MODELLING THE IMPACT OF GENETIC TESTING ON INSURANCE — EARLY-ONSET ALZHEIMER'S DISEASE AND OTHER SINGLE-GENE DISORDERS

By

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I hereby declare that the work presented in this thesis was carried out by myself at Heriot-Watt University, Edinburgh, except where due acknowledgement is made, and has not been submitted for any other degree.

Eng Hock Gui (Candidate)

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Date

For my wife, Pearl

Contents

Acknowledgements **xv**

Abstract **xvii**

Introduction **1**

1 GENETICS AND INSURANCE **3**
1.1 Basics of Genetics 4
1.1.1 DNA 4
1.1.2 Chromosomes and Genes 5
1.1.3 The Genetic Code 5
1.1.4 Duplication of DNA 6
1.2 Human Inheritance and Diseases 6
1.2.1 Cell Division and Reproduction 7
1.2.2 Alleles 7
1.2.3 Phenotype and Penetrance 8
1.2.4 Gene Mutations 8
1.2.5 Mendel's Laws and Genetic Disorders 11
1.2.6 Genetic Testing 15
1.3 Genetic Information and Insurance 16
1.3.1 Genetic Testing and Implications for Insurance 17
1.3.2 Genetic Testing and Insurance in the UK 19
1.3.3 Genetic Testing and Insurance in Other Countries 23
1.4 Research Works in Genetics and Insurance 30
1.4.1 Actuarial Research 30
1.5 Epidemiology of Genetic Diseases 34
1.5.1 Epidemiological Data 34
1.5.2 Epidemiological Studies and Survival Analysis 35
1.5.3 Pedigrees 35

2 EARLY-ONSET ALZHEIMER'S DISEASE **37**
2.1 Alzheimer's Disease 37
2.1.1 Disease Etiology 38
2.1.2 Natural History and Management of AD 39
2.2 The Genetics of Early-onset Alzheimer's Disease 40
2.2.1 Databases of Pedigrees with Mutations in the EOAD Genes . 41
2.2.2 The Presenilin-1 Gene 43

2.2.3 The Presenilin-2 Gene . . . 43
2.2.4 The Amyloid Precursor Protein Gene . . . 43
2.3 EOAD Gene Mutations . . . 44
2.3.1 Mutations in the Presenilin-1 Gene . . . 44
2.3.2 Mutations in the Presenilin-2 Gene . . . 44
2.3.3 Mutations in the Amyloid Precursor Protein Gene . . . 45
2.4 The Epidemiology of EOAD . . . 45
2.4.1 The Epidemiological Literature . . . 45
2.4.2 EOAD Genes and Insurance Applications . . . 46

3 A NELSON-AALEN ESTIMATE OF THE INCIDENCE RATES OF EARLY-ONSET ALZHEIMER'S DISEASE 47
3.1 Introduction . . . 47
3.1.1 Estimating Rates of Onset of Single-Gene Disorders . . . 47
3.1.2 Nelson-Aalen Estimates . . . 48
3.1.3 Estimating Rates of Onset of Early-Onset Alzheimer's Disease 49
3.2 Pedigree Analysis . . . 49
3.2.1 Pedigrees and Mutation Probabilities . . . 49
3.2.2 Definition of Risk Groups . . . 51
3.2.3 The Life Table Method . . . 53
3.3 An Analysis of the Life Table Method . . . 54
3.3.1 Conditioning on Currently Known Information . . . 54
3.3.2 Conditioning Retrospectively on Observed Cases . . . 55
3.3.3 Newcombe's Estimates . . . 56
3.3.4 Information From Events Other Than Onset . . . 57
3.3.5 A Corollary: What Information Should Pedigrees Include? . . 59
3.4 A Modified Nelson-Aalen Estimate . . . 60
3.4.1 The Nelson-Aalen Estimate . . . 60
3.4.2 A Modified Nelson-Aalen Estimate . . . 62
3.4.3 A Diagnostic Check for the Inclusion of Censored Observations 65
3.4.4 Allowing for Genetic Testing . . . 66
3.4.5 Allowing for Unaffected Relatives . . . 68
3.4.6 Remarks . . . 70
3.5 Summary . . . 70

4 ESTIMATES OF THE INCIDENCE RATES OF EARLY-ONSET ALZHEIMER'S DISEASE ASSOCIATED WITH THE PSEN-1 GENE 71
4.1 Estimates of Incidence Rates . . . 71
4.1.1 Choice of Estimator . . . 71
4.1.2 Approximations Used With Pedigrees . . . 72
4.1.3 Smoothing Method . . . 75
4.1.4 Bootstrap Confidence Intervals . . . 79
4.1.5 Results . . . 79
4.1.6 Possible Ascertainment Bias . . . 82
4.2 Extrapolating Rates of Onset of EOAD Associated with PSEN-1 Mutations . . . 84

4.3 Estimating Mortality Rates After Onset of EOAD 86
4.4 Estimating Mutation Frequencies 88
4.5 Summary 90

5 EARLY-ONSET ALZHEIMER'S DISEASE AND CRITICAL ILLNESS INSURANCE 92
5.1 Introduction 92
5.1.1 Insurance Questions 92
5.1.2 Genetic Testing for EOAD 93
5.2 Premium Ratings for Critical Illness Insurance 94
5.2.1 Critical Illness Insurance 94
5.2.2 Transition Intensities in the Critical Illness Insurance Model . 94
5.2.3 Differential Equations Associated with the Model 94
5.2.4 Premiums Based on Known PSEN-1 Mutations 96
5.2.5 Premiums Based on Family History of EOAD 98
5.3 The Potential Cost of Adverse Selection in Critical Illness Insurance . 100
5.3.1 Genetic Information, Moratoria and Adverse Selection 100
5.3.2 Parameterisation 103
5.3.3 Computation 105
5.3.4 Moratoria and Underwriting Classes 107
5.3.5 Moratoria on Genetic Test Results 107
5.3.6 A Moratorium on Genetic Test Results and Family History . . 109
5.3.7 Adverse Selection Extending to Higher Sums Assured 111
5.3.8 The Rate of Genetic Testing 111
5.4 Summary 111
5.4.1 Premium Ratings 112
5.4.2 Adverse Selection 113

6 EARLY-ONSET ALZHEIMER'S DISEASE AND LIFE INSURANCE 114
6.1 A Model of EOAD and Life Insurance 114
6.1.1 The Model 114
6.1.2 Parameterisation 117
6.2 Premium Ratings for Life Insurance 117
6.2.1 Life Insurance Premiums Based on Known PSEN-1 Mutations 117
6.2.2 Life Insurance Premiums Based on Family History of EOAD . 120
6.3 The Potential Costs of Adverse Selection in Life Insurance 120
6.3.1 Moratoria and Underwriting Classes 120
6.3.2 Moratoria on Genetic Test Results 120
6.3.3 Moratorium on All Genetic Test Results and Family History . 121
6.3.4 Adverse Selection Extending to Higher Sums Assured 121
6.3.5 Increasing the Rate of Genetic Testing 123
6.4 Summary 123
6.4.1 Premium Ratings 123
6.4.2 Adverse Selection 123

7 ESTIMATE OF THE INCIDENCE RATES OF EARLY-ONSET ALZHEIMER'S DISEASE ASSOCIATED WITH THE PSEN-2 and APP GENES 125
7.1 Introduction . . . 125
7.2 Estimates of Incidence Rates . . . 126
7.2.1 Bootstrap Confidence Intervals . . . 127
7.3 Results . . . 127
7.3.1 Comparing the Rates Due to Mutations in the PSEN-2 and APP Genes . . . 130
7.4 Summary . . . 131

8 MULTIPLE ENDOCRINE NEOPLASIA TYPE 2 133
8.1 Introduction . . . 133
8.1.1 Medullary Thyroid Carcinoma . . . 136
8.1.2 Phaeochromocytoma . . . 139
8.1.3 Hyperparathyroidism . . . 140
8.2 The RET proto-oncogene . . . 141
8.2.1 RET proto-oncogene mutations . . . 142
8.2.2 Prevalence and age-related penetrance . . . 142
8.2.3 Genotype-phenotype correlation . . . 143
8.3 Genetic and biochemical screening . . . 145
8.4 Insurance Implications . . . 145
8.5 Summary . . . 147

9 HEREDITARY HAEMOCHROMATOSIS 149
9.1 Introduction . . . 149
9.1.1 Clinical Features . . . 150
9.1.2 Insurance and Health Cost Implications . . . 151
9.2 The Haemochromatosis Gene . . . 152
9.2.1 HFE gene mutations . . . 152
9.2.2 Phenotypic expressions . . . 154
9.2.3 Prevalence and penetrance . . . 155
9.3 Management of HHC . . . 157
9.3.1 Treatment . . . 157
9.3.2 Survival Rates . . . 158
9.4 Testing and population screening for HHC . . . 159
9.4.1 Liver Biopsy . . . 160
9.4.2 Genetic Testing . . . 160
9.5 Implications for Insurance . . . 160
9.5.1 Implications of Population Screening . . . 162
9.6 Summary . . . 162

10 CONCLUSIONS 164
10.1 Novel Estimates of Rates of Onset of EOAD . . . 165
10.2 Novel Negative Conclusions on MEN2 and HHC . . . 166
10.3 Epidemiology and Models . . . 167
10.4 Premium Ratings . . . 167

10.5 Adverse Selection 168
10.6 Implications for Policy 168
10.7 Further Research 169

A Presenilin-1 gene mutations **171**

B Presenilin-2 gene mutations **178**

C Amyloid precursor protein gene mutations **180**

D Pedigree database of presenilin-1 gene mutations **183**

E Pedigree database of presenilin-2 gene mutations **214**

F Pedigree database of amyloid precursor protein gene mutations **219**

G The Critical Illness Insurance Model **230**

References **233**

List of Tables

1.1 Key to the single letter and 3-letter codes for amino acids. 6
1.2 Life insurance and the main types of genetic disorder. Source: Harper (1997). 18
1.3 Conditions and genetic tests recommended by the ABI as relevant for insurance purposes 20
2.4 French family SAL 513 with PSEN-1 gene mutation Leu113Pro, extracted from Appendix D. 42
4.5 Optimal bandwidths for biweight kernel smoothing. 78
4.6 Peto-Wilcoxon test comparing the survival curves of the three different age-at-onset groups. 87
5.7 Level net premiums for level CI cover with known PSEN-1 mutations, as a percentage of the standard level premiums. Rates of onset of EOAD are 100%, 50% and 25% of those observed. 97
5.8 Level net premiums for level CI cover for persons with family histories of EOAD known to be associated with PSEN-1 mutations, as a percentage of the standard level premiums. Rates of onset of EOAD are 100%, 50% and 25% of those observed. 99
5.9 Possible underwriting classes with three sub-populations: $i = 1$ not at risk of EOAD; $i = 2$ at risk of EOAD but not PSEN-1 mutation carriers; $i = 3$ at risk of EOAD and PSEN-1 mutation carriers. (T) denotes persons who have had a genetic test and (U) denotes persons who have not. 107
5.10 Percentage increases in premium rates for CI cover, arising from moderate and severe adverse selections following a moratorium on the use of genetic test results, with family history underwriting allowed, for a market operating between ages 20 and 60. 108
5.11 Percentage increases in premium rates for CI cover, arising from severe adverse selection following a moratorium on the use of genetic test results, with family history underwriting allowed, for a market operating between ages 20 and 60. EOAD rates of onset 50% and 25% of those observed. 108
5.12 Percentage increases in standard premium rates for CI cover, arising from new underwriting classes, moderate and severe adverse selections following a moratorium on the use of genetic test results and family history, for a market operating between ages 20 and 60. Rates of onset of EOAD 100%, 50% and 25% of those observed. 110

5.13 Percentage increases in CI premium rates arising from severe adverse selection following a moratorium on the use of genetic test results, with family history underwriting allowed, for a market operating between ages 20 and 60. Rate of genetic testing 0.02 per annum. 112
6.14 Level net premiums for level life cover with known PSEN-1 mutations, as a percentage of the standard level premiums. 118
6.15 Level net premiums for level life cover for persons with family histories of known PSEN-1 mutations, as a percentage of the standard level premiums. 119
6.16 Percentage increases in life insurance premium rates arising from moderate and severe adverse selections, following a moratorium on the use of genetic test results, with family history underwriting allowed, for a market operating between ages 20 and 60. 121
6.17 Percentage increases in life insurance premium rates arising from severe adverse selection following a moratorium on the use of genetic test results, with family history underwriting allowed, for a market operating between ages 20 and 60. EOAD rates of onset 50% and 25% of those observed. 122
6.18 Percentage increases in standard life insurance premium rates arising from new underwriting classes and severe adverse selection following a moratorium on the use of genetic test results and family history, for a market operating between ages 20 and 60. 122
8.19 Subtypes of multiple endocrine neoplasia syndromes, with percentages of patients with the clinical symptoms. Source: Thakker (1998). 135
8.20 Characteristics of medullary thyroid carcinoma. Source: Lewinski et al. (2000). 136
8.21 Diagnosis and cure rates of MEN2. Source: Goretzki et al. (1998). . . 138
8.22 RET proto-oncogene mutations. Source: Human Gene Mutation Database. 141
8.23 Summary of RET proto-oncogene mutations. Source: Randolph (2000). 142
8.24 Stratified levels for MTC risks according to the mutated codon on the RET proto-oncogene. Level 3 is the most severe. Adapted from Brandi et al. (2001). 144
9.25 HFE genotypes as percentage composition (with 95% confidence intervals) of HHC probands in a review by Hanson et al. (2001) (2,229 probands in Europe and 2,929 globally). '++' denotes mutation in both copies of the gene, '+−' denotes mutation in one copy, and '−−' denotes normal gene copies. 153
9.26 HFE gene mutations showing nucleotide change, location within the gene, adapted from Pointon et al. (2000). 154
9.27 HFE genotype frequencies in white subjects, predominantly of northern European heritage, as given in Bradley et al. (1998). 155
9.28 HFE genotype frequencies (per 1,000) in the general population, as given in Hanson et al. (2001); with 95% confidence intervals. 156
9.29 Ratings for life insurance as given in Brackenridge and Elder (1998) . 161
B.30 Mutations in the PSEN-2 gene 179
C.31 Mutations in the APP gene 181

G.32 28-Day mortality rates ($q_x^h = 1 - p_x^h$) following heart attack. Based on Dinani et al. (2000). 231

List of Figures

2.1 Pedigree diagram of French family SAL 513 with PSEN-1 gene mutation Leu113Pro, pedigree information based on Table 2.4. Squares are males, circles are females, and a slash denotes death. Affected individuals are shown as filled squares/circles. The age at onset or oldest observed age free of AD is shown, age at death is given in round brackets, and current age of affected shown in square brackets. An asterisk means that a person has been tested and does carry a mutation, a dagger that he/she has been tested and does not carry a mutation. By convention siblings are listed left-to-right in birth order. 42

3.2 A hypothetical example of a pedigree. 50

3.3 A two state model of mortality 61

3.4 A model of the incidence of Alzheimer's disease where an individual may have an EOAD mutation (State 0, +ve) or may not have an EOAD mutation (State 1, −ve). 63

3.5 $\Lambda(x)$, and six simulated estimates of $\hat{\Lambda}(x)$ with sample size 30, for a hypothetical intensity $\mu_{02}(x) = (-x^4 + 85x^3 - 25x^2) \times 10^{-7}$ and $p = 1/2$, with random censoring. 65

3.6 A Markov model of transfers between states representing the Mendelian probability (at birth) of having a mutation, and genetic testing. 67

3.7 A Markov model of transfers between states representing probability at birth of having a mutation. For the parent and siblings to be 'at risk' means it is not known whether or not any of them have a mutation. Transition from State 0 to State 1 represents learning that the parent or a sibling does have a mutation; this fixes p (usually at 1/2). 69

4.8 Pedigree of the family with the Leu282Arg PSEN-1 mutation (Aldudo et al., 1998), see Appendix A. Squares are males, circles are females, and a slash denotes death. Affected individuals are shown as filled squares/circles. The age at onset or oldest observed age free of AD is shown, and the age at death is given in brackets. By convention siblings are listed left-to-right in birth order. 72

4.9 A hypothetical sibship in which the ages of unaffected lives are not known. The oldest sibling is known to be age 59. 74

4.10 Estimated exposure times for all persons in the $p = 1/2$ risk group. Each line represents the time spent in the risk group by a single individual. The estimated maximum exposure times are on the left (276 lives), and minimum exposure times on the right (264 lives). Exposures ending with onset of EOAD are indicated by a triangle. . . 76
4.11 Estimated exposure times for men, maximum exposure times are on the left (72 lives), and minimum exposure times on the right (64 lives). Exposures ending with onset of EOAD are indicated by a triangle. . . 77
4.12 Estimated exposure times for women, maximum exposure times are on the left (81 lives), and minimum exposure times on the right (79 lives). Exposures ending with onset of EOAD are indicated by a triangle. 77
4.13 Estimated risk function, G(b), for use in determining the optimal bandwidth for the PSEN-1 mutation data. 79
4.14 Modified Nelson-Aalen estimates of $\int_0^x \lambda(t,\mu)\mu_{02}(t)dt$ for all persons, men and women, in families with PSEN-1 mutations. The smoothed versions are shown as dashed lines. Note different scales. 80
4.15 Estimated incidence rates of EOAD among men and women with PSEN-1 mutations, combined and separately, with approximate 95% confidence limits. Note different scales. 81
4.16 Probabilities of surviving free of EOAD among persons with PSEN-1 mutations, with approximate 95% confidence limits. 83
4.17 Estimated and smoothed/extrapolated incidence rates (100%, 50% and 25% of those estimated from the data with maximum possible exposures) of EOAD associated with PSEN-1 mutations. 85
4.18 Nelson-Aalen estimates of the duration-dependent integrated hazard of death after onset of EOAD, and approximate 95% confidence intervals, for persons with PSEN-1 mutations. Ages at onset 20–39, 40–49, 50–60 and 20–49. The graduated estimate for AAO 20–49 is also shown. 87
4.19 Comparing the Nelson-Aalen estimates of the duration-dependent integrated hazard of death after onset of EOAD with the cumulative population mortality rates from the English Life Tables No. 15 (ELT15). We use male cumulative mortality rates for comparison as these are higher than the female cumulative mortality rates. 89
5.20 A model for EOAD and critical illness insurance. 95
5.21 A Markov model of genetic testing, insurance purchase and CI insurance events for a person in the i^{th} risk subpopulation. 101
5.22 A Markov model of a CI insurance market allowing for a family history of EOAD and genetic testing. 102
6.23 A semi-Markov model of genetic testing, insurance purchase and life insurance events for a person in the i^{th} subpopulation. z is duration since onset of EOAD. 115

7.24 Estimated exposure times for all persons in the $p = 1/2$ risk group. Each line represents the time spent in the risk group by a single individual. The estimated exposure times due to PSEN-2 gene mutation are on the left (60 lives), and the estimated exposure times due to APP gene mutation are on the right (34 lives). Exposures ending with onset of EOAD are indicated by a triangle. 126
7.25 Estimated risk function, G(b), for use in determining the optimal bandwidth for the PSEN-2 and APP mutation data. 127
7.26 Estimated incidence rates of EOAD with PSEN-2 mutations, with approximate 95% confidence limits. 128
7.27 Estimated incidence rates of EOAD with APP mutations, with approximate 95% confidence limits. 128
7.28 Probabilities of surviving free of EOAD among persons with PSEN-2 mutations, with approximate 95% confidence limits. 129
7.29 Probabilities of surviving free of EOAD among persons with APP mutations, with approximate 95% confidence limits. 130

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Abstract

The recent advance of genetics has brought with it many questions, among which are the implications for insurance. The public worries about the misuse of personal information by insurers, especially information regarding an individual's susceptibility to serious inherited disorders which may be brought to light by genetic testing; while the insurance industry is wary of the cost of possible adverse selection if insurers are denied access to genetic information. Under the new molecular light thrown on the susceptibility, onset, progression and treatment of genetic diseases, this thesis looks into the effect genetic information will have on insurance, from both the perspective of the insured and the insurer.

We develop a non-parametric method based on the Nelson-Aalen method to estimate the rates of onset of early-onset Alzheimer's disease (EOAD) associated with the presenilin-1 (PSEN-1) gene mutations, using pedigree data gathered from published reports on the mutations. Mortality rates after onset are also estimated.

We then use multi-state models, for critical illness (CI) and life insurance, to estimate the change in premium rating for an applicant with a family history or a known mutation associated with the disease, and the cost of adverse selection to the insurer under various moratoria on the use of genetic test results and family history. CI insurance premium increases implied by known PSEN-1 mutations or a family history of PSEN-1 mutations are extremely high, but life insurance premium increases are only outside the limits currently offered under the most pessimistic set of assumptions. For both CI and life insurance, older people in at-risk families who have not had a genetic test can be offered very much better terms than if they were known PSEN-1 mutation carriers. The cost of adverse selection appears to be negligible except in the case of small markets, extreme behaviour on the part of

'adverse selectors' and high rates of onset of EOAD.

The rates of onset of EOAD due to mutations in the presenilin-2 gene and the amyloid precursor protein gene are also estimated. These rates are not applied to insurance models due to insufficient data.

We derive novel negative conclusions about the implications for insurance of multiple endocrine neoplasia type 2 and hereditary haemochromatosis. The etiology, epidemiology, natural history and clinical management of each of these two single-gene disorders are reviewed. The possibility of early detection together with effective intervention and treatment mean these two disorders are unlikely to be of significance for insurance.

We also provide detailed lists of the family studies in which mutations in the three genes associated with EOAD have been found, with comprehensive databases for the published pedigree information.

Introduction

We begin by reviewing some basic facts of human inheritance and genetic testing in Chapter 1. The issues of genetic information and insurance are then looked into from both the U.K. and the international perspectives. We review actuarial research work on the implications of genetic information in insurance. The importance of relevant epidemiological data for the multi-state models used in these research studies is also discussed.

In chapter 2 we introduce the genetics of Early-onset Alzheimer's Disease (EOAD). EOAD is a devastating neurodegenerative disease characterised by rapid decline in cognitive functions, leading to death within a few years after disease onset. EOAD is inherited in an autosomal dominant manner and occurs before age 65. The two presenilin genes and the amyloid precursor protein (APP) genes are the three major genes found to date which are responsible for EOAD.

From survival data gathered from pedigree information in published papers, a modified Nelson-Aalen method is developed in Chapter 3 and then applied in Chapter 4 to estimate the rates of onset of EOAD due to PSEN-1 gene mutations. In Chapter 5 these rates are applied in a Markov model of EOAD and critical illness insurance purchase to study the effects that genetic testing or family history would have on premium ratings. Mortality rates after onset of EOAD due to PSEN-1 gene mutations are also estimated from the pedigree data and applied in a semi-Markov model of EOAD and life insurance purchase, in Chapter 6.

In Chapter 7, we apply the method described in Chapter 3 to pedigree data collected from families with a history of mutations in both APP and PSEN-2 to estimate the rates of onset of EOAD due to mutations in these two genes. Due to the small sample sizes, these estimates are not sufficiently reliable to be applied to

insurance models.

The epidemiology of multiple endocrine neoplasia type II is presented in Chapter 8, together with the importance of genetic and biochemical screening for members of at-risk families. We provide an evidence-based conclusion of the likely insignificance of this uncommon disorder for insurance, contrary to the U.K. industry's initial assumptions.

Hereditary haemochromatosis is the commonest genetic disorder in white populations. This iron metabolism disorder can often lead to death after vital organs are affected. The disease etiology is reviewed in Chapter 9, and we present another case where genetic testing for mutations in the gene associated with a relatively common disease is not likely to have any implications for insurance.

In Chapter 10, we conclude this thesis with a comprehensive review of the work done in the preceding chapters and suggest areas for future research.

Appendices A, B, and C summarise the family studies in which the PSEN-1, PSEN-2 and APP gene mutations, respectively, have been found. Appendices D, E, and F provide the databases of the pedigree information collected from published papers on the mutations of these genes.

Appendix G details the model for critical illness (CI) insurance based on medical studies and population data (provided in Gutiérrez and Macdonald (2003)) which is employed as part of our model for EOAD and CI insurance in Chapter 5

Chapter 1

GENETICS AND INSURANCE

> We are like trees: we must create new leaves, new directions, in order to grow.
>
> Ann Van Tassell

A historical moment for our continuous endeavour into scientific discovery happened at the turn of this new century. The human genome has been sequenced separately and independently by scientists at Celera Genomics and by the Human Genome Project undertaken by a publicly funded consortium of laboratories. The two groups used very different strategies to complete the sequencing, succeeding after years of intense efforts. The sequencing involves the identification of almost three billion base pairs that make up the 23 pairs of chromosomes of the human genome. Unravelling the human genome is one of the most important projects scientists have ever undertaken.

The complete human genome sequence will facilitate the identification of genes that contribute to disease. The success of these two major projects signals the beginning of a new enhanced integration of biology and medicine, with far reaching social implications. We now have a powerful tool to unlock the secrets of our genetic codes, giving new insights into human diseases. More accurate diagnostic testing and potential clinical intervention for treatment and possibly prevention of many hereditary diseases are now becoming possible with a better understanding of the relationship between human genes and diseases.

1.1 Basics of Genetics

In order to appreciate the impact that genetic information may have on insurance, we must begin by reviewing some basic facts about genetics. Fischer and Berberich (1999) provide an introduction to genetics for non-specialists with an insurance background; readers with no previous knowledge of genetics might find it useful. For definitive treatments, useful for pursuing further research in genetics and insurance, see Pasternak (1999) and Strachan and Read (1999).

The cell is the smallest unit of life. Within each cell, the nucleus is a membrane-bound compartment which isolates the genetic material from the rest of the cell. Genes which form the basic units of hereditary material transmitted from one generation to the next (Section 1.2.1) are specific segments of the long molecules of deoxyribonucleic acid (DNA) located in the cell nucleus.

The human genome, the set of all of the genetic material of the human body, consists of huge amounts of DNA. DNA contains within its structure all the genetic information necessary to make a human body functional. Recently, it has been estimated that the human genome contains about $30,000$–$40,000$ genes (Venter et al., 2001).

1.1.1 DNA

The chemical constituents of DNA are nucleotide bases, a sugar called deoxyribose, and phosphate groups. Nucleotide bases include two types of purine: adenine (A) and guanine (G), and two types of pyrimidine: thymine (T) and cytosine (C). The nucleotide bases form part of a subunit of DNA known as the nucleotide. The beginning of a strand of a DNA molecule is known as the 5' end and the end of the strand as the 3' end. The 5' and 3' terms refer to the position of the nucleotide bases relative to the sugar molecule in the DNA backbone. Two strands of joined nucleotides run in opposite directions to make up the DNA double helix. Within the double helix, a purine always lies opposite a pyramidine and vice versa. Thus, in the normal setting, only guanine and cytosine or adenine and thymine can be located opposite to each other and form a complementary base pair (G-C or A-T).

1.1.2 Chromosomes and Genes

The DNA, in which genes are encoded, makes up a number of rod-shaped structures called chromosomes in the nucleus of each cell. Except for the reproductive (germline) cells, all cells in the body are known as somatic cells. There are 23 pairs of chromosomes in each somatic cell in the human body. Of these chromosomes, 22 pairs are similar in males and females. These pairs of autosomes (chromosomes that are not sex chromosomes) are numbered from the largest (chromosome 1) to the smallest (chromosome 22). The sex chromosomes make up the 23^{rd} pair, a pair of X chromosomes in females, and a pair comprising of a X chromosome and a Y chromosome in males.

Genes are sequences of base pairs that encode information for the synthesis of all the proteins and other molecules that make up the structure of the body (bones, muscles etc) and that control all biochemical processes of tissues and cells in the body. They can range in size from less than 100 base pairs to several million base pairs.

1.1.3 The Genetic Code

The typical human gene has a complex internal structure made up of exons which contains coding information for proteins. These exons are separated by introns which are non-coding regions. The biological properties of introns are still poorly understood. In addition to exons and introns, genes also contain regions that are important in determining how actively protein is to be synthesised from them.

The order of nucleotide bases along a DNA strand is known as the sequence. The genetic information is encoded in the sequence of the base pairs. A sequence of three base pairs represents a code word, codon, for an amino acid. Amino acids are the basic structural units of proteins, the building blocks of the human body. The codon sequence then gives rise to a corresponding sequence of amino acids, forming the specific gene product. Table 1.1 lists the 20 amino acids. There are also start codons, which indicate the beginning of the coding region, and stop codons, which indicate the end of the coding region.

Table 1.1: Key to the single letter and 3-letter codes for amino acids.

1-letter code	3-letter code	Amino Acid
A	Ala	Alanine
C	Cys	Cysteine
D	Asp	Aspartic Acid
E	Glu	Glutamic Acid
F	Phe	Phenylalanine
G	Gly	Glycine
H	His	Histidine
I	Ile	Isolucine
K	Lys	Lysine
L	Leu	Leucine
M	Met	Methionine
N	Asn	Asparagine
P	Pro	Proline
Q	Gln	Glutamine
R	Arg	Arginine
S	Ser	Serine
T	Thr	Threonine
V	Val	Valine
W	Trp	Tryptophan
Y	Try	Tyrosine

1.1.4 Duplication of DNA

Genes create exact duplicates of themselves each time a cell divides. This happens during development of the embryo and during repair/replacement of dead or damaged cells throughout life. Since the adult develops from the fertilised egg by cell division, all cells have the same set of genes. Copies of these genes are passed from parents to offspring, creating patterns of inheritance. One copy of each gene from each parent is passed on to the offspring. This underlies the mechanisms of various type of inherited disease, namely autosomal dominant, autosomal recessive and X-linked type diseases (see Section 1.2.5).

1.2 Human Inheritance and Diseases

In this section, we look at the basics of cell reproduction and describe how errors which occur during cell divisions can lead to various types of somatic and inherited diseases.

1.2.1 Cell Division and Reproduction

In order to appreciate the mechanisms of inherited diseases, we need to understand the method by which hereditary material in the human genome is transmitted from cell to cell during cell divisions and from generation to generation.

There are two types of cell divisions in the human body:

(a) Somatic cell division — somatic cells descend from the fertilised egg (zygote) through a divisional process known as mitosis, by which the body grows, differentiates, and effects tissue regeneration. During mitosis, an identical set of chromosomes is distributed to each of the two daughter cells produced from division of the mother cell.

(b) Germline cell division — meiosis occurs only in cells of the germline. The reproductive cells, gametes, are produced from meiosis with only 23 chromosomes each instead of the usual 23 pairs: one of each of the 22 kind of autosomes and either an X or a Y chromosome. Besides halving the number of chromosomes, there is shuffling of the genetic material during meiosis, an important mechanism to ensure genetic variation when genetic information is passed from one generation to the next.

Details of mitosis and meiosis are available from any standard text of human biology (see Strachan and Read (1999)).

1.2.2 Alleles

One member of each pair of chromosomes is inherited from the father, the other from the mother. Members of a pair of chromosomes carry matching genetic information, having the same genes in identical sequence. At any specific locus, however, there may be either identical or slightly different forms of the same gene, called alleles. An allele that is very common in a population is referred to as wild type while less common alleles are referred to as mutant alleles.

An individual is said to be homozygous at a gene locus if there are identical alleles at the locus, and heterozygous if the two alleles are different at that locus. A compound heterozygote is a genotype (or the individual with the genotype) in

which two different mutant alleles of the same gene are present. An example is the compound heterozygous genotype with the C282Y and H63D mutations in the haemochromatosis gene associated with hereditary haemochromatosis in Chapter 9.

1.2.3 Phenotype and Penetrance

Genotype is the composition of all, or a subset of, the alleles possessed by an individual. A phenotype is any measurable characteristic or distinctive trait possessed by an individual, as a result of gene products determined by the individual's genotype. Differences in environmental conditions or in genetic backgrounds may cause individuals that are genetically identical at a particular locus to exhibit different phenotypes.

The penetrance is a measure of the degree to which individuals with a particular genotype exhibit the corresponding phenotype. A genotype is said to possess full penetrance if the carrier will definitely exhibit the associated phenotype, such as the complete penetrance of the gene for blue/brown eyes. Other genotypes are associated with incomplete penetrance, the apolipoprotein E gene that predisposes late-onset Alzheimer's disease being an example. Also, a trait, although penetrant, may vary in its level of expression. Cystic fibrosis associated with the cystic fibrosis transmembrance conductance regulator gene has variable expressivity, meaning that the symptoms may be present in milder or more severe forms.

1.2.4 Gene Mutations

A mutation occurs when there is a change in the nucleotide sequence or arrangement of DNA. A mutation might arise due to:

- spontaneous errors occuring during normal cellular activities, primarily DNA replication and repair; or
- exposure to a mutagenic agent or environment such as
  - chemicals which interact with DNA to create base changes,
  - ionising radiation such as X-rays which results in deletions or insertions of DNA, and

- non-ionising radiation such as ultra-violet light which causes adjacent thymines on one DNA strand to bond together.

Corresponding to the site where the DNA sequence changes, the amino acid sequence in the gene product may become altered. Details on mutations in the human genes can be obtained from basic texts on human genetics, like Strachan and Read (1999). Note that only mutations that occur in germline cells can be passed to offspring.

The basic types of mutations are:

- point mutation — a change in a very small segment of DNA, involving a single nucleotide or nucleotide pair
  - base substitution
    (a) transition — substitution of one purine for another purine or one pyrimidine for another pyrimidine
    (b) transversion — substitution of one purine for a pyrimidine or vice versa
  - deletion — deletion of a nucleotide or nucleotide pair
  - insertion — insertion of a nucleotide or nucleotide pair
- gross mutation — large scale changes involving from a few nucleotides of DNA to megabases of DNA that encompass the entire gene, the entire chromosome, or sets of chromosomes
  - gross deletion — deletion of a large number of nucleotides
  - gross insertion — insertion of a large number of nucleotides
  - chromosomal rearrangement — changing the location of a piece of DNA within the genome, resulting in large structural changes in genes and possibly changing the expression of genes
    (a) translocation — movement of DNA to a nonhomologous chromosome, usually in an exchange between two such chromosomes

(b) inversion — movement of DNA within the same chromosome with a 180° rotation of the affected material (i.e. a reversal of the sequence)

Mutations are also classified according to their effects on the coding of proteins and on the gene function as a whole:

- effect on protein
  (a) silent — change in a codon that leaves the amino acid coded for unchanged
  (b) nonsense — change in a amino acid coding codon to a stop codon, resulting in premature amino acid chain termination during translation
  (c) missense — change in a codon that changes the amino acid coded for to a different amino acid, changing the primary sequence of the amino acid chain and altering the function of the protein
  (d) neutral — change in a codon such that the different amino acid specified behaves similarly to the original one and does not alter the function of the protein
  (e) frameshift — a shift of the reading frame caused by a deletion or insertion of one or more (but not multiples of 3) nucleotides, creating numerous missense and nonsense codons downstream of the location where the mutaton occurs
- effect on gene function
  (a) loss-of-function — a mutation that results in a lack of gene function, and is recessive in nature. A mutation is said to be recessive if both alleles at a single gene locus need to be mutated before there can be an expression of the associated phenotypic effect.
  (b) gain-of-function — a mutation that results in a new or different kind of gene function, and is dominant in nature. A mutation is dominant if a single mutated copy of the gene pair is sufficient for the associated phenotype to be expressed.

1.2.5 Mendel's Laws and Genetic Disorders

Genetic factors are important in determining an individual's health from birth. Approximately 5% of newborn babies carry with them significant genetic conditions as they enter the new world (Sudbery, 2002) while the genetic constitution we inherited from our parents influences our susceptibility to many of the common diseases of later life.

The patterns of transmission of units of genetic information from one generation to the next are determined by the conceptual framework established by Gregor Mendel. Mendel published the findings of his genetic experiments on the garden pea in 1866 and laid the foundation of modern genetics. The law of segregation states that each parent contains two copies of a unit of inheritance (i.e. a gene) for each trait, one of which is transmitted through a gamete to the offspring. The law of independent assortment states that the segregation of one gene pair occurs independently of any other gene pair. However, the second Mendel's law is true only for genes which are not inherited together on the same chromosome.

Gene mutations and abnormalities in chromosome number or structure can lead to various types of inherited and somatic disorders. Some of these medical disorders are quite common, such as Down syndrome. Chromosomal changes during somatic cell division are involved in the initiation and progression of many types of cancer.

Genetic disorders include:

- single-gene (monogenic) disorders in which the disease is caused by one or a pair of mutant alleles at a single gene locus;
- multi-gene (or multifactorial) disorders in which variation in multiple genes (which may be mutations or commonly occurring alleles) lead to the disorder, often with a contributing effect from exposure to other environmental factors like lifestyle, pollution and infections; and
- chromosome disorders where the clinical condition is caused by an abnormal chromosome constitution in which there is a rearrangement of chromosomal material or an addition/deletion of a whole chromosome or parts of a chromosome.

Gene Functions and Monogenic Disorders

Possible loss or gain of gene function may arise due to a mutation (Section 1.2.4). If the half-normal amount of gene product from the normal allele in heterozygotes is sufficient to perform its designated function, the mutant allele is recessive. Hence both copies of the alleles at the gene locus need to be mutated before the associated (recessive) disorder can be expressed. A mutation carrier, an individual with only one mutated recessive allele, will not exhibit the associated disease but is capable of transmitting the disease to offspring.

If the mutant allele causes disease regardless of whether there is a normally functioning wild type allele, the associated disease is dominant. One normal copy of the gene is insufficient to prevent the disorder if:

- more than half of the normal gene product is required to prevent the disorder;
- an abnormal protein is produced by the mutant allele which interferes with the protein function of normal allele, hence causing an abnormal phenotype;
- there is a gain in function where protein produced by the mutant allele is enhanced in one or more of its normal properties or become toxic to the cell through acquisition of a new property; or
- the loss of function of one copy of an autosomal gene increases the predisposition to cancer, thus resulting in pedigrees with dominantly inherited cancer.

Monogenic Disorders

Single-gene disorders are rare genetic disorders which follow the Mendelian pattern of inheritance, hence they are also known as Mendelian disorders. Although they are rare individually, as a group, monogenic disorders are responsible for a significant proportion of disease and death. For the general population, the lifetime risk from these disorders is about 2% (Nussbaum et al., 2001) but this includes many inherited diseases of childhood. They range in severity and differ in the modes of inheritance within families. Each mode of inheritance exhibits obvious and characteristic Mendelian pedigree patterns:

- autosomal dominant inheritance: a single defective allele of the gene pair on an autosome is sufficient to cause the disorder
  - the phenotype usually appears in every generation, each affected person having an affected parent
  - individuals with abnormal alleles manifest the disease and have a 50% chance to transmit it
  - pedigrees have approximately equal numbers of affected males and females
  - there is transmission from affected males or females, with approximately equal numbers of affected or unaffected offspring
  - unaffected individuals are without abnormal alleles and so do not transmit the disease
- autosomal recessive inheritance: two defective alleles at the same gene locus on an autosome are needed to cause the disorder
  - pedigrees exhibit a horizontal pattern, i.e. disease is normally expressed among the sibship of the proband (the individual being studied), but not in parents, the affected's offspring or other relatives
  - pedigrees have approximately equal numbers of affected males and females
  - parents of an affected child are carriers of mutant alleles
  - there may be consanguinity in pedigrees, that is, a marriage between first cousins, especially if the mutant allele responsible for the condition is rare in the population
  - the recurrence risk for each sibling of the proband is 1/4
- X-linked recessive inheritance: recessive disorders that are carried by the X chromosome
  - males, who have only one X chromosome, are more susceptible than women who have two X chromosomes

  - lack of male-to-male transmission as males must transmit their Y chromosome to sons
  - the mutated allele of an affected male is transmitted to all his daughters, hence any of his daughters' sons has a 50% chance of inheriting the disease
  - sons of carrier females have a 50% chance to be affected while daughters have a 50% chance to be a carrier but no chance of being affected
  - heterozygous females are usually unaffected but some may express mild disease manifestation

- X-linked dominant inheritance: rare dominant disorders that are carried by the X chromosome
  - presence of the abnormal allele usually produces a severe phenotype with lethality, where the affected males do not survive and are presented as spontaneous abortion (Wilson, 2000)
  - affected males with normal mates have no affected sons and no normal daughters
  - both male and female offspring of affected females have a 50% chance of inheriting the phenotype

Multifactorial Disorders

Many common disorders of adult life and a number of developmental disorders resulting in congenital malformations are multifactorial. Multifactorial disease is often the result of a combination of small variations in genes that produce or predispose to a serious defect, usually with contributions from environmental factors. These disorders tend to recur in families and it is estimated that from about 5% of the pediatric population to more than 60% of the general population suffer from multifactorial conditions (Nussbaum et al., 2001).

Chromosome Disorders

Chromosome disorders which arise from chromosomal mutations are not common as a group, affecting about 7 per 1,000 liveborn infants and they account for about

50% of all spontaneous first-trimester abortions (Nussbaum et al., 2001). Down syndrome (for example) is a specific chromosome disorder caused by an extra copy of chromosome 21.

Age-related Penetrance of Mendelian Disorders

The expression of a monogenic disorder depends on many factors and may not show a strict Mendelian pedigree pattern described in the earlier paragraphs. An important case is the age-related penetrance of 'late-onset' diseases.

Genetic conditions may be congenital, i.e. present at birth, or be manifested later in life. The age at onset of a disorder can range over decades, with the conditions of some genetic disorders appearing only in the fourth, fifth or sixth decades of life.

Age-dependent penetrance may result over a period of time from cumulative tissue damage caused by the gene product of the mutated alleles. Delayed onset may be caused by slow accumulation of a deleterious substance such as Aβ_{42} or Aβ_{43} in early-onset Alzheimer's disease, mutant huntingtin in Huntington's disease and cysts in adult polycystic kidney disease. The 'late-onset' may also be caused by a mutation in a gene for DNA repair, such as those in the BRCA1 and BRCA2 genes in breast and ovarian cancer. The clinical features marking these 'late-onset' disorders may not be evident until a particular threshold of tissue damage or cell death is reached.

Depending on the disease, the penetrance of the mutation may become 100% as the person carrying the mutation reaches a particular age, or it may be incomplete with some mutation carriers remaining asymptomatic at very old ages.

1.2.6 Genetic Testing

The introduction of genetic tests for disease raises concerns about many issues, from the psychological impact of knowing one's own genetic susceptibility to an incurable disease, to the potential for discrimination in access to insurance and long-term care. Once a mutation has been detected in an affected individual, accurate testing is possible for the same mutation in other family members. Unless the family having the particular mutation has fairly narrow ranges for the onset ages and duration of

survival after onset, a positive test does not necessarily give a good indication of the severity of disease nor provide an accurate onset age for the mutation carrier.

Genetic disorders differ in onset and progress, and the severity of the symptoms. Detection of a mutation associated with a rare but highly penetrant (that is, with a high chance of expressing the associated disease) monogenic disease in an individual will imply that the individual has a high chance of developing the disease. However, if the associated genetic disease is multifactorial, a genetic test can at most show an increase in propensity of the individual to the disease.

Genetic testing is the analysis of a specific gene, its product or function, or other DNA and chromosome analysis, to detect or exclude an alteration likely to be associated with a genetic disorder (Sudbery, 2002). The types of genetic testing available are:

- biochemical analysis where change in the level of a specific gene product or a characteristic disturbance of metabolism can be detected to indicate an inherited change in a gene; and
- direct analysis of the heritable genetic material to detect change in DNA or chromosome into which it is packaged.

This definition of genetic testing (GAIC, 2000) excludes diagnosis based on clinical examinations or other established non-genetic investigations (like biochemical tests for cholesterol).

1.3 Genetic Information and Insurance

Genetic information refers to information derived from knowledge regarding an individual's chromosomes and genes. The usage of genetic information is a complex issue accompanying the developments in genetics (Zimmern, 2001).

The following types of information are classified as genetic information:

- chromosome or DNA based diagnostic test results;
- results of specific biochemical tests which can indicate an inherited change in a gene; and

- information that can be used to infer the possible presence of specific genetic variation or changes influenced by genetic variation such as:
  - family history of an hereditary disease,
  - clinical diagnosis of an hereditary disease, and
  - imaging and chemical test results indicating the expression of an hereditary disease.

1.3.1 Genetic Testing and Implications for Insurance

The predictive power of genetic tests can have consequences in many non-clinical circumstances. The use of genetic information in insurance has generated numerous debates and concerns. Like using other medical and family history information, an insurance company might like to consider a genetic test result for underwriting. Underwriting is the process of assessing a risk or proposal for insurance, resulting in accepting or rejecting the risk and setting the premium rate payable if the insurer is taking up the proposal. The availability of genetic information may enable certain diseases to be predicted and foretell an individual's risk of a particular genetic disorder. This can have important consequences for the insurance industry.

The insurance industry is based on the principles of equity (people with similar health or similar life expectancies should pay equal premiums while those having worse health or lower life expectancies should pay higher premiums for life or health insurance policies), mutuality (the pooling of similar risks and the achievement of broad equity among persons in an insured risk pool) and actuarial fairness. It works on the basis of a mutual risk pool in which members contribute according to the risk they bring to the pool. The insurer underwrites to classify each applicant either into the normal risk group paying the standard premium or into a higher risk (substandard risk) group paying a rated-up premium. In some countries, applicants may be classified as 'superfit' and offered a premium lower than standard (called 'preferred lives underwriting'). This practice has not spread to the U.K. The applicant may also be deemed uninsurable if the insurer thinks that the risk involved in accepting the applicant into the risk pool is too high. The risk depends on both the likelihood

of claiming and the size of the claim.

Adverse selection in insurance happens when unknown to the insurer, the at-risk individual selects against the insurance company by purchasing a policy at a higher than average sum assured or is more likely to buy insurance than an average person. This can cause considerable problems to the insurer as it destabilises the equity principle. An individual may have knowledge about his or her predisposition to a certain disease after undergoing a genetic test. If this genetic information is not shared with the insurer during the process of underwriting, then adverse selection occurs. Harper (1997) outlines the main categories of genetic disease discussed in Section 1.2.5 and the extent to which adverse selection in life insurance is likely to be of significance (Table 1.2).

Table 1.2: Life insurance and the main types of genetic disorder. Source: Harper (1997).

Category of genetic disorder	Relevance to life insurance
Autosomal dominant	Important with late-onset and progressive course. Little relevance for those with early onset.
Autosomal recessive	Little relevance. Genetic risks largely confined to sibs. Often early onset. Numerous healthy carriers.
X-linked	Risks mainly to male relatives; serious disorders usually have early onset.
Multifactorial	Common; genetic testing of uncertain significance at present, but likely to be of importance in future.
Chromosomal abnormalities	Usually early onset, not progressive, carriers normally healthy.

Family history is also used in underwriting. An individual has a family history of a certain critical inherited disease (like breast cancer) if one or more of the individual's family members carries the disease. Existence of family history often results in a rated-up premium for critical illness and life policies. Depending on the number of affected family members and severity of the disease associated with the family, there may be cases where the insurer deems the applicant to be of too high a risk to be insured.

1.3.2 Genetic Testing and Insurance in the UK

In its 1995 comprehensive report on human genetics (HCSTC, 1995), the House of Commons Science and Technology Select Committee recommended that the insurance industry should try to ensure that their commercial interests do not conflict with medical interests in genetic testing. The report covered an extensive range of issues arising from the developments in genetics including genetic research in the U.K., clinical and industrial implications, the potential for discrimination and human rights abuses, the need for a government body to monitor developments and offer advice to the government.

Responding to this report, the Human Genetics Advisory Commission (HGAC) was set up by the government in December 1996 as a non-statutory advisory body to advise the government on the issues arising from developments in human genetics that were expected to have wide social, ethical and economical consequences. In its 1997 report "The Implications of Genetic Testing for Insurance" (HGAC, 1997), HGAC recommended the insurance industry should introduce a two year moratorium on requiring the disclosure of genetic test results as there was a lack of quantifiable evidence on the subject. The report recommended the establishment of a mechanism to evaluate the actuarial and scientific evidence in support of the use of specific genetic tests for insurance products.

The Code of Practice on Genetic Testing was put in place in December 1997 by the Association of British Insurers (ABI) (ABI, 1997). ABI members will only take into account genetic tests that are considered actuarially sound by the independent expert advisory body. The three basic principles established in the Code of Practice for insurers with regard to the use of genetic tests were:

- insurers should not require applicants to undergo a genetic test to obtain insurance;
- an applicant with a relevant genetic test result may be required to declare it to the insurer; and
- insurers would observe a self-imposed moratorium on the use of genetic test results for life assurance up to £100,000 linked to a mortgage.

In November 1998, acting under the advice of their genetics advisor Sandy A. Raeburn, Professor of Clinical Genetics at the University of Nottingham, the ABI issued a list of ten tests for seven genetic conditions which they recommended to be relevant for insurance purpose. The list is shown in Table 1.3 (www.geneticsinsuranceforum.org.uk/Criteria/specific.asp). Adult polycystic kidney disease was originally in the list but later dropped because it is usually detected by ultrasound scanning rather than genetic testing.

Table 1.3: Conditions and genetic tests recommended by the ABI as relevant for insurance purposes

Condition	Gene(s) tested for
Early onset familial Alzheimer's disease	APP, PSEN-1, PSEN-2
Familial adenomatosis polyposis	APC
Hereditary breast and ovarian cancer	BRCA1, BRCA2
Hereditary motor and sensory neuropathy	PMP22
Huntington's disease	HD
Multiple endocrine neoplasia type 2	RET
Myotonic dystrophy	MDPK

Also in response to the 1997 HGAC report, the government set up the Genetics and Insurance Committee (GAIC) in April 1999 as a non-statutory, independent advisory body. Its role is to assess the use of genetic test results by insurers in setting premiums, on actuarial and other scientific grounds. GAIC is also responsible for reporting to the government on the subsequent level of compliance by the industry with its recommendations. Applications for approval to use genetic test results for insurance underwriting are sent to GAIC for approval against a set of criteria of assessment, namely,

- scientific relevance: the genetic test should be technically reliable and accurately reflect the genetic information;
- clinical relevance: a positive result in the genetic test should have implications for the health of the individual; and
- actuarial relevance: the health implications should contribute a significant difference to the chance of a claim under the proposed insurance product.

In October 2000, GAIC approved the use of genetic tests for Huntington's disease for use in life insurance, acknowledging the reliability and relevance of the genetic test for this hereditary disease.

Currently, the diseases under consideration by GAIC for use by the insurance industry in life (except for Huntington's disease), critical illness, income protection and long-term care (except for hereditary breast and ovarian cancer) insurance are:

- Huntington's disease,
- early onset Alzheimer's disease associated with mutations in the amyloid precursor protein and the presenilin 1 genes, and
- hereditary breast and ovarian cancer associated with the BRCA1 and the BRCA2 genes.

The Human Genetics Commission (HGC) was established in May 1999 by the U.K. Government as an independent advisory body that helps to identify and maximise benefits from advances in human genetics. The membership of HGC includes people from a wide range of backgrounds, representing the diverse interests of different groups. Its remit is to address broad ethical, legal and social implications that may arise. HGC takes over the role of HGAC which it subsumed. In December 2000, HGC published "Whose hands on your genes?" (HGC, 2000), a public consultation document discussing the storage, protection and use of genetic information.

Following a request from the ministers to include in their consultation wider social and ethical issues arising from usage of genetic data by insurers, HGC published "Inside information — balancing interests in the use of personal genetic data" in May 2002 (HGC, 2002). The later report concludes that "society needs to achieve the right balance between an individual's interest in privacy and the interests of others in benefiting from the use of personal genetic information for medicine and research". A recommendation was made to the government to draw up legislation to prevent genetic discrimination in employment, insurance and other areas. Other recommendations included taking steps to safeguard genetic research databases, continuing the funding of independent research on genetics and family history and, reviewing the evidence which the insurance industry uses to justify the use of family

history to set insurance premiums when GAIC judges applications for approval to use genetic test results for insurance underwriting. The extension of the moratorium on the use of genetic test results in insurance to the use of family history information was not recommended by the report.

The Code of Practice established by the ABI requires its member companies to use only those tests that have been submitted to GAIC and subsequently approved for use in insurance underwriting. Any tests that were not submitted to GAIC by December 2000 are to be withdrawn. The Code also requires members to agree to re-assess affected policies back to the day the ABI first recommended using the genetic tests (1^{st} November, 1998) if GAIC later decides that a test is not relevant. However, there appeared to be inconsistency in the interpretation by some insurers of the GAIC application procedure. Some insurers would consider the results from all the ten tests for seven conditions as listed by the ABI (Table 1.3), even prior to submission of the application for the tests and the subsequent approval by GAIC (HGC, 2002). This misinterpretation has been cleared up by the ABI with its member insurers since.

In October 2001, the United Kingdom (UK) government reached an agreement with the ABI to impose a five-year moratorium on the use of genetic test results. The moratorium will apply to life insurance policies up to a value of £500,000, to critical illness, long term care and income protection policies up to a value of £300,000. These respective limits will be reviewed in three years. For policies above these limits, insurers may only use results of tests approved by GAIC.

Following recommendations in the House of Commons Science and Technology Committee 2001 report on Genetics and Insurance (HCSTC, 2001), GAIC was suspended in April 2001. The reconstituted GAIC was back in action in September 2002, with a new membership and expanded remit (www.doh.gov.uk/genetics/gaic/index.htm). Its terms of reference include:

- to develop and publish criteria for the evaluation of specific genetic tests, their application to particular conditions and their reliability and relevance to particular types of insurance;

- to evaluate particular genetic tests against the criteria set out and to bring to

public attention its findings; and

- to report to the Department of Trade and Industry, Health and Treasury ministers on proposals received by GAIC from insurers and the subsequent level of compliance by the industry with GAIC recommendations.

As part of its new remit, GAIC provides an independent review of how insurers use genetic tests. It provides independent scrutiny of compliance by the insurers with the ABI Code of Practice and the terms of the 5-year moratorium set up in October 2001 on the use of genetic test results. GAIC will consider complaints from insurance applicants on the handling of their insurance application by the insurers under the moratorium, after the complaints have failed to be resolved by the insurers or by the ABI. GAIC also reports annually to the Department of Trade and Industry, Health and Treasury ministers on compliance by insurers with the ABI Code of Practice and the moratorium.

In November 1998, the Faculty of Actuaries and the Institute of Actuaries initiated setting up of the UK Forum for Genetics and Insurance (UKFGI), of which the ABI, the British Society for Human Genetics, the Genetics Interest Group, the Royal Society and the Wellcome Trust were founder members. UKFGI provides information on the ABI code of practice, its criteria for genetic tests to be used for insurance purposes and other issues related to genetic testing and insurance. The forum seeks to "analyse the implications of advances in genetic knowledge for insurance in all forms and to serve the public interest by reporting its findings" (www.ukfgi.org.uk).

1.3.3 Genetic Testing and Insurance in Other Countries

In Austria, Belgium, Denmark, France, Norway and the Netherlands, the use of genetic information for any business purpose is not allowed. Besides the UK, Finland, France, Germany, Sweden, Switzerland, and the Netherlands have imposed moratoria on the use of genetic information by insurers.

Committees and advisory groups in many countries published reports to advise policy makers to protect individuals against genetic discrimination by insurers and

employers (ESHG, 2001). For example:

- Danish Council of Ethics — Protection of Sensitive Personal Information (1992);
- National Consultative Ethics Committee in France — Opinion and Recommendations on Genetics and Medicine: from Prediction to Prevention (1995);
- Italian Committee on Bioethics — Orientamenti bioetici per i test genetici (1999);
- Norwegian Biotechnology Advisory Board — The Use of Genetic Information about Healthy People by Insurance Companies (1997);
- Swiss Academy of Medical Sciences — Medical-ethical Guidelines for Genetic Investigations in Humans (1993); and
- Health Council of the Netherlands — Heredity, Science and Society: On the Possibility and Limits of Genetic Testing and Gene Therapy (1999).

Australia

In Australia, the *Medicare* scheme provides universal health care insurance, though an increasing number of people are taking out private health insurance (30% of the population in 1997, McGleenan (2001)). Hence the issue of genetic testing and insurance is mainly applicable to life and other insurance products. However, the Australian insurance industry does not encourage its members to require applicants to undergo genetic testing (LISA, 1997).

The Disability Discrimination Act (1992) prevents Australian insurers from discriminating against applicants on the ground of disability, but there is a provision within the Act which allows insurers to discriminate on the basis of genetic information if the discrimination is based on actuarial or statistical grounds (Crosbie, 2000). The Genetic Privacy and Non-discrimination Bill (1998) prohibits insurers from requesting genetic information or requiring insurance applicants to undergo genetic analysis.

Prior to the Privacy Act, applicants were under a legal obligation to provide any existing genetic test results to the insurers and the insurers were legally entitled to acquire such results. The Privacy Act which came into force in December 2001, addresses the need for higher protection for 'sensitive information', which includes personal genetic information (Doble, 2001).

Austria

The Gene Technology Act (1994) in Austria imposes conditions requiring strong informed consent of an individual prior to a genetic test being carried out (www.gentechnik.gv.at/gentechnik/B1_orientierung/gen_10084.html). Employers and insurers are forbidden from obtaining and/or making use of results of genetic tests of their present or prospective employees, policyholders or insurance applicants (McGleenan, 2001).

Belgium

The Belgian Law on Terresterial Insurance Contracts (1992) forbids the transmission of genetic information during an insurance application, even if the information is to the advantage of the insurance applicant (ESHG, 2001). Any predictive tests which may be indicative of future state of health are not to be used during a medical examination for insurance purposes (McGleenan, 2001).

Canada

In Canada, there is no legislation which addresses the issue of the use of genetic information by insurers (Crosbie, 2000). The Canadian focus on genetic testing and use of genetic results is mainly in the clinical research and forensic areas.

Denmark

The Danish Council of Ethics recommends very strict control on the use of medical records and recommends legislation to ensure an individual's rights and control over sensitive personal information. There is no law at present to prevent insurers

from requesting health information, including information on blood samples (ESHG, 2001).

Finland

There is currently no legislation to govern the use of genetic tests by insurers in Finland. However, the Finnish Federation of Insurance Companies has indicated that it is not their policy to request or use genetic test information (McGleenan, 2001). The Personal Data Act (1999) gives individuals the rights to access personal information held about them.

France

A 5-year moratorium on the use of genetic information in insurance was imposed by the Federation Francaise des Societies d'Assurances in 1994, and subsequently extended till 2004 (ESHG, 2001). The National Consultative Commission was created to address the issue of application of genetic test results for medical purposes (McGleenan, 2001).

Germany

In Germany, there are no specific legal regulations on the use of genetic information by insurers although the Federal government has recently set up a body to investigate the laws and ethics of modern medicine, including the effect of use of genetic information in insurance (Crosbie, 2000). A moratorium was introduced in 1988, and renewed in 1999, by the insurance companies on the use of new and past genetic test results in insurance (McGleenan, 2001).

Greece

There is no legislation to date concerning the use of genetic information in insurance. The insurance industry has implemented a voluntary code of conduct requiring insurers not to request genetic testing for insurance purposes.

Iceland

There is no legislation in Iceland prohibiting insurers from using genetic information for insurance purposes. A bill to encourage genetic testing for use in medical research for public benefit has been presented.

Ireland

In Ireland, there are no regulations in place regarding genetic testing. Discrimination on the grounds of genetic status is prohibited in health insurance by law (ESHG, 2001). The Irish Insurance Federation proposed to implement a code of practice to forbid insurers from requiring applicants to undertake a genetic test to obtain life insurance or disclosing results of genetic tests taken after a policy has come into force, though any test results known at the time of application must be declared.

Israel

Genetic testing is not allowed in Israel by the Science Parliament Committee. However, the Law on Protection of Personal Genetic Information (2000) is in place to prohibit insurers from requesting genetic testing, though insurers are permitted to ask whether applicants had a genetic test (from a list of diseases determined by the Minister of Health) in the last 3 years for a policy with a high sum assured not linked to a mortgage (ESHG, 2001).

Italy

In Italy, there is no legislation on the use of genetic information for insurance purposes. The Law n.675 (1996) deals with the privacy of medical information and the Italian Committee on Bioethics recommends that genetic information be treated as general medical information thus not allowing insurers to acquire or use this genetic information without consent (ESHG, 2001).

The Netherlands

In the Netherlands, the Medical Examination Act (1998) applies to medical examinations for life insurance, a civil pension, and a civil occupational disability insurance

contract (McGleenan, 2001). The Act strengthens the legal position of persons undergoing medical examinations. It prohibits the use by insurers of presymptomatic or susceptibility genetic testing for serious, untreatable disorders. Applicants (if asymptomatic of the disease) and the applicant's relatives are not to be questioned about hereditary conditions and any genetic test results unless the sum to be insured exceeds a certain set limit. There is a moratorium in place on the use of existing genetic test results for life and disability insurance applications up to certain limits. Insurers are also not allowed to request applicants to take genetic tests for any applications (ESHG, 2001).

Norway

The Act Relating to the Application of Biotechnology in Medicine (1994) in Norway requires genetic testing to be undertaken only for medical diagnostic or therapeutic purposes. Requesting, receiving, retaining or using of genetic information relating to a third party is prohibited (McGleenan, 2001).

Portugal

Though there is no specific legislation concerning genetic testing and insurance in Portugal, there are guidelines published by the Ministry of Health on the confidentiality and privacy of genetic information (ESHG, 2001).

Spain

The Spanish Constitution forbids any type of discrimination on grounds of any personal or social circumstance or condition. The Organic Law regulating the automated processing and protection of personal data (1999) serves to protect personal health data, including genetic information .

Sweden

In Sweden, an agreement was set up in 1999 between the Swedish government and the Swedish Insurance Federation (SIF) to govern the use of genetic information by insurers (Crosbie, 2000). Insurers are not to require applicants to undergo genetic

tests when taking out policies or extending existing ones. Also, the applicant need not declare undergoing a genetic test or submit the result of such test. Insurers in the Federation are not permitted to take into account the family history of the applicant. The SIF's voluntary code set up in 1998 has a similar effect as the agreement. The Law 114 (1991) on the Use of Certain Gene Technologies requires authorisation from the National Board of Health and Welfare before DNA testing can be carried out (ESHG, 2001). The use of genetic information other than for medical purposes is prohibited.

Switzerland

Under the Insurance Contract Act, applicants have to provide information to insurers which might influence the contract. However, Article 119 (1992) of the Swiss Federal Constitution states that an individual's genetic information may be used only with his or her consent, or on the basis of a legal prescription. A bill on Genetic Investigations in Humans (1998) was presented in 1998 to prevent insurers from demanding presymptomatic or prenatal investigation as a condition of insurance.

The United States

The health care system in the United States (US) is mostly dependent on private health insurance. As such, legislation at both state and federal level focuses mainly on the prohibition of genetic discrimination in health insurance (Crosbie, 2000). At the federal level, the Health Insurance Portability and Accountability Act (1996) which applies to employer-based and commercial group health insurance, deals with the issue of genetic discrimination in insurance. The Americans with Disabilities Act (1996) allows genetic discrimination in insurance only if it is actuarially justifiable. There are many bills at state level which deal with the use of genetic information by insurers, and many states have enacted legislation in the areas of genetic discrimination in insurance (McGleenan, 2001).

1.4 Research Works in Genetics and Insurance

With the advances made in human genetics, there has been a growing debate on the potential effect of a dramatic increase in genetic testing for adult-onset diseases on insurance. Surprisingly, until the mid-1990's, this heated and often emotional discussion was conducted in the absence of any quantitative evidence whatsoever (Harper, 1997).

Fogarty (1999), Zick et al. (2000) and Daykin et al. (2003) are some of the recent reports attempting to better inform the public, the insurance industry and the policy makers on the issues surrounding genetics and insurance. Fogarty (1999) examines the issues surrounding predictive genetic testing for Alzheimer's disease and the use of test results in determining insurance premiums and eligibility. Zick et al. (2000) assesses the potential for adverse selection in the life insurance market when tested individuals know their genetic test results but the insurers do not, with the conclusion that women tested positive for a BRCA1 gene mutation do not purchase more life insurance than those who have not had a genetic test. The Genetics Group within the Faculty and Institute of Actuaries looks into the implications of advances in genetics for all actuarial areas (Daykin et al., 2003).

1.4.1 Actuarial Research

The actuarial profession in the U.K. held a joint meeting on 'Human Genetics: Uncertainties and the Financial Implications Ahead' with the Royal Society of London in September 1996. There were contributions from the actuarial profession as well as from the medical, legal, social and other scientific communities. In one of the first reports on genetics and insurance with quantitative support, Macdonald presented a paper on the effects genetic information would have on insurance (Macdonald, 1997).

All the models used in quantitative actuarial research to date are multiple-state models. This is because single-gene disorders can be represented by a small number of discrete populations. Multiple-state models are parameterised by their intensities and the information needed for this must come primarily from genetic epidemiology

(Section 1.5).

Multiple-state models have been used in the modelling of genetic disorders for insurance, both with 'top-down' and 'bottom-up' approaches. With the models, we are able to investigate the premium increase for an individual with the gene mutation causing the disorder, and for an individual with a family history of the disease. Given the population frequencies of each gene mutation, the cost of adverse selection in the insurance market can be studied under the existence of any moratorium on genetic test results and/or family history. Multifactorial disorders have not been modelled yet except in 'top-down' models.

'Top-down' models

A 'top-down' approach makes extreme adverse assumptions about the risk associated with the gene mutation or group of mutations, the extent of adverse selection by persons at risk and the incidence of genetic testing. Such models do not require detailed epidemiology of individual disorders but only results reflecting the non-significance of adverse selection can be reached (Daykin et al., 2003).

Macdonald (1997) and Macdonald (1999) conclude that multifactorial disorders are not likely to be of significance for life insurance as the premium increases caused by adverse selection under very extreme assumptions are insignificant. Only the tendency to take up unusually large amounts of insurance has much impact on the costs of adverse selecting. Similar conclusions were reached in Macdonald (2003b), modelling an entire class of single-gene disorders.

'Bottom-up' approach of modelling specific disorders

In the 'bottom-up' approach, each genetic disorder is modelled to obtain the cost of adverse selection due to the disorder. This approach can provide estimates of the cost of adverse selection but problems with parameterisation of the model due to the scarcity of epidemiological data need to be overcome (Daykin et al., 2003).

Macdonald and Pritchard (Macdonald and Pritchard, 2000, 2001; Pritchard, 2002) developed a mathematical model for Alzheimer's disease attributable to the different apolipoprotein E genotypes, to estimate the costs of disability and adverse

selection in long-term care insurance. A similar model was also used by Warren et al. (1999) to model Alzheimer's disease in long-term care.

Gutiérrez and Macdonald (2002a) review the literature on the epidemiology of Huntington's Disease (HD), a highly penetrant and dominantly inherited fatal neurological disorder. The paper estimates the rates of onset, the mortality rate after onset, and the distribution of CAG trinucleotide repeat lengths in the population. The number of times the CAG trinucleotide is repeated in the HD gene has a strong effect on the phenotypic expresson of this genetic disorder. In an earlier paper, Smith (1998) concluded that persons at risk of Huntington's disease may be offered life insurance at lower cost than previouly thought possible.

Macdonald et al. (2003a) and Wekwete (2002) model the family history of breast cancer and ovarian cancer and estimate the probabilities that a female applicant for insurance has BRCA1 or BRCA2 gene mutation given knowledge (complete or incomplete) of her family history. The implications of breast/ovarian cancer due to mutations in the BRCA1 and BRCA2 genes on life insurance were also studied by Subramanian et al. (2000) and Lemaire et al. (2000).

Macdonald and Yang (2003a) provide an atlas for penetrance of highly penetrant genetic disorders with tables of premiums for critical illness insurance in the presence of these disorders presented in Macdonald and Yang (2003b).

This thesis (Chapter 3 and Chapter 4) adds to the list of 'bottom-up' quantitative research, estimating from published pedigree data the age specific penetrance function of early onset Alzheimer's disease due to mutations in the presenilin-1 gene (results of which are also in Gui and Macdonald (2002b)).

Extension of moratoria to family history as well as genetic test results

Using the estimates derived in Gutiérrez and Macdonald (2002a), Gutiérrez and Macdonald (2002b) study the critical illness and life insurance markets, in relation to genetic test results for HD that disclose the CAG repeat length. The paper also considers the possible adverse selection costs under the various moratoria on the use of genetic information, including family history. Gutiérrez and Macdonald (2002b) point out that restricting disclosure of genetic information could deprive insurers

of information needed for risk management even if the information is not used in underwriting.

Gutiérrez and Macdonald (2003) estimate the rates of kidney failure from adult polycystic kidney disease and uses a multi-state model for critical illness insurance to study the extra premiums needed in the presence of an associated mutation and in the presence of family history of the disease, and the possible costs from adverse selection if there are moratoria on genetic test results and/or family history.

The costs of critical illness insurance and the effect of adverse selection due to breast cancer and ovarian cancer are investigated in Macdonald et al. (2003b).

Chapter 5 and Chapter 6 of this thesis use multi-state models to estimate the cost of adverse selection in critical illness insurance and in life insurance respectively, if insurers were unable to use genetic test or family history information in respect of EOAD associated with presenilin-1 gene mutations.

Reviews on the current state of actuarial research in genetics and insurance are available in Macdonald (2002), Macdonald (2003a) and Daykin et al. (2003).

The Genetics and Insurance Research Centre

During the moratorium period, research on the medical, actuarial and social aspects of the use of genetic test results in insurance will be carried out to develop a long-term policy to replace the moratorium. One such research programme is being carried out at the Genetics and Insurance Research Centre (GIRC) at Heriot-Watt University in the UK of which this project is a part. GIRC was set up in 1999 to develop mathematical and actuarial models to estimate the costs of genetic information to individuals buying insurance and to insurers and other service providers. Though funding is provided by the ABI, GIRC is completely autonomous and independent. Its work is published in the public domain and is overseen by a steering committee comprising geneticists, actuaries and representatives from genetic interest groups.

1.5 Epidemiology of Genetic Diseases

Genetic epidemiology is the study of the etiology, distribution, and control of disease in groups of relatives and of inherited causes of disease in populations. With the success of the human genome project and rapid advancement in the understanding of our genetic makeup, research in disease etiology has placed increasing importance on the genetic causes.

1.5.1 Epidemiological Data

Epidemiology of a genetic disease such as the prevalence of the gene mutations involved, the penetrance as a function of age, and survival rates after onset of the diseases, are required before we can model the disease for insurance application. These data are extremely rare in the current medical and scientific literature.

The data on the distribution of disease provided by descriptive epidemiology are usually based on time (different periods of time), place (geographical differences), and person (age, sex differences). The main outcomes of epidemiological studies of a disease are:

- prevalence — the number of cases within a defined population at a given point in time, age specific rates may sometime be presented (Alloul et al., 1998);
- incidence — the number of new cases developing over period of time (usually of one year);
- mortality — age specific mortality rates from disease-related deaths;
- mean/median ages of onset;
- survival rates at specific time intervals after disease onset (often Kaplan-Meier estimates);
- penetrance estimates at one or a few ages (often Kaplan-Meier estimates);
- relative risks — the ratio of the risk of disease in those with the genetic risk factor to the risk of disease in those without the factor;

- odds ratios — estimates of the relative odds of onset; and
- allele frequencies — of genes associated with the disease.

1.5.2 Epidemiological Studies and Survival Analysis

Here, we make a distinction between genetic epidemiology and survival analysis.

Genetic epidemiology explores the relationship between genetic characteristics that may be influenced by environmental exposures and the distribution of disease among relatives and within the general population. The subject makes inferences primarily from statistical analysis of the distribution of disease or other traits among family members, and more recently, from studies into the molecular mechanisms for variation in the disease among families and populations, using new knowledge in molecular biology and genetics.

Survival analysis is the study and interpretation of time-to-event data from a sample, such as ages of onset and death of the affected in the sample. Both parametric and nonparametric methods have been developed to estimate age specific hazard and survival functions. Hosmer and Lemeshow (1999); Hougaard (2000); Klein and Moeschberger (1997); Therneau and Grambsch (2000) provide a good introduction the subject. In Chapter 3 and Chapter 4, we make use of tools from survival analysis to estimate the rates of onset of EOAD due to PSEN-1 gene mutations, from pedigree information in published papers.

1.5.3 Pedigrees

The patterns of inheritance of a trait within families are reflected in the family trees known as pedigrees (see Section 2.2.1 for an example of a pedigree). Pedigrees are important experimental data for human geneticists. In some studies of human diseases, many different pedigrees had to be assembled. In others, a large single multigeneration pedigree can provide sufficient genetic information.

Our study involves collecting a sufficient number of pedigrees with a history of EOAD to enable analysis of the onset and survival times. Published reports on EOAD are mostly biochemical in nature though occasionally, family pedigree data

with ages at onset and death may be given in papers reporting novel mutations. It was from these published reports with pedigree information that we were able to carry out our estimation of the penetrance and survival rates after onset of early-onset Alzheimer's disease. We present a method of estimating these rates in the next chapters.

Chapter 2

EARLY-ONSET ALZHEIMER'S DISEASE

2.1 Alzheimer's Disease

Dementia is a chronic disorder which leads to serious impairment of the daily functioning and quality of life. Globally, about 10% of persons older than 70 years have dementia (Nussbaum et al., 2001). Alzheimer's Disease (AD) is the most common cause, accounting for 50–80% of all diagnosed cases of dementia (Cras, 2001; Pasternak, 1999). Clinically characterised by a gradual and progressive deterioration of intellectual capabilities, memory, personality and judgement, AD is a major health problem in many countries.

AD was first described by Alois Alzheimer (1864–1915), a gifted German neurologist, to a small group of researchers in 1906. He first examined a senile 51-year-old woman with an unusual form of amnesia. The patient died 4 years later and on examining her brain in the autopsy, Dr. Alzheimer observed odd tangles and persistent plaques.

The Alzheimer's Society (http://www.alzheimer's.org.uk) estimates that over 700,000 people in the UK have dementia. Of these, approximately 55.6% have AD and the annual cost of treatment and care of AD patients is around £5.5 billion (Newton, 1998). These numbers are expected to rise rapidly over the next 25 years as the population ages. Globally, the number of people with dementia stands at

around 20 millions and is expected to double by the year 2025 (Newton, 1998).

Research into AD has gained significant ground in the past two decades. With growing knowledge on AD, we will eventually be able to develop more effective drugs to slow the progression or even prevent the emergence of this devastating disease.

2.1.1 Disease Etiology

AD is a complicated and heterogeneous disorder, a part of which is genetic in etiology and is classified as familial AD (FAD). FAD is further classified into late- and early-onset forms, depending on whether the onset age is after or before age 65. Early-onset FAD constitutes about 5–10% of all AD cases, and occurs as a well-defined, fully penetrant autosomal dominant inheritance (van Duijn et al., 1991a). Late-onset FAD cases comprise 15–25% of all AD patients, while the remainder of AD patients have sporadic AD (Nussbaum et al., 2001). Lippa et al. (2000) investigates the influence of genetic factors on age at onset and age at death among patients with dominantly inherited AD.

Mutations in the amyloid precursor protein (APP), presenilin-1 (PSEN-1) and presenilin-2 (PSEN-2) genes are associated with the early-onset autosomal dominant AD. These are discussed in Section 2.2. The $\epsilon 4$ allele at the apolipoprotein E gene (APOE) locus on chromosome 19 has also been implicated in the early-onset form of AD (van Duijn et al., 1994).

However, the $\epsilon 4$ allele is more commonly associated with increased susceptibility to late-onset familial and sporadic AD (Farrer, 2001), accounting for about 50% of late-onset AD (Lendon and Craddock, 2001). Its implications for long-term care insurance or costs have been discussed by Macdonald and Pritchard (2000, 2001) and by Warren et al. (1999).

There is significant evidence of genetic linkage of AD to susceptibility gene(s) on chromosome 10 (Bertram et al., 2000; Lendon and Craddock, 2001). Inheritance of a polymorphism in the A2M gene on chromosome 12 which encodes alpha-2 macroglobulin, a large multifunctional protein, has been shown to increase the risk of late-onset AD (Blacker et al., 1998).

Diagnosis of AD can only be definite after post-mortem examination (Cras, 2001).

Histological study of autopsied brains of AD patients reveals three distinctive neuropathological features (Pasternak, 1999) which have become the diagnostic hallmarks of AD:

- very significant neuronal loses within the cerebral cortex and degeneration of neuronal connection between the cerebral cortex neurones and the cortical neurons;
- presence of dense spherical structures, 20–200 μm in diameter, called senile plaques (SP); and
- aggregations of very small fibres (neurofibrillary tangles, NFT) accumulate within the cell bodies and the dendritic processes (branching processes of the cell body of neurone which make contact with other neurones and carry nerve impulses from them to the cell body) of the cerebral neurones.

Current evidence suggests that the neuronal dysfunction and death observed in AD are caused by defects of β-amyloid precursor protein metabolism (Cras, 2001).

2.1.2 Natural History and Management of AD

AD is characterised by the progressive loss of cognitive function. This includes short-term memory, language, abstract reasoning, visual perception, visual-spatial function and concentration. Cognitive decline often begins with subtle episodes of forgetfulness; anxiety and frustration follow, leading to rigidity, speech problems, incontinence and the patient becoming bedridden. AD Patients may also experience agitation, social withdrawal, hallucinations, seizures and myoclonus (a sudden spasm of the muscles which is a major feature of some progressive neurological illnesses with extensive degeneration of the brain cells). Death often follows from cardiovascular disease, bronchitis and pneumonia, though it is widely recognised that cause of death among dementia patients does not differ much from those without dementia (Beard et al., 1996). Deaths are also attributable to the terminal complications of AD, consisting of a progressive vegetative state, malnutrition, and dehydration culminating in cardiorespiratory arrest (Heyman et al., 1987).

For AD patients with later onset, at age 65 years or later, the disease duration varies from 8 to 20 years. In contrast, AD patients diagnosed before age 65 years have a more rapid disease course, and death often occurs within 5 to 10 years from the time of diagnosis (Pasternak, 1999).

At present there are no curative therapies available for AD and treatments today are mainly symptomatic (Cras, 2001). Treatment is focussed on the amelioration of associated behavioral and neurological problems, using drugs for agitation, depression and insomnia. If treated early in the course of the disease, a fraction of AD patients respond to drugs that increase cholinergic (relating to nerve fibres that release a neurotransmitting chemical acetylcholine, or to nerve receptors at which acetylcholine acts to pass on messages from nerve fibres) activity, modestly slowing the rate of cognitive decline. This has become the standard therapy in clinical practice (Cras, 2001). A diverse range of treatment options is now being researched into for AD, a disease which until very recently was considered incurable.

2.2 The Genetics of Early-onset Alzheimer's Disease

Early-onset Alzheimer's disease (EOAD) is an autosomal dominant form of AD occurring before age 65. Whereas AD after that age is relatively common, EOAD is rare. There may be as many as 20,000 people affected with young onset dementia, a large proportion of which is in the form of EOAD (Harvey, 1998). Sometimes EOAD runs in families, with a pattern of inheritance suggesting that one or more autosomal dominant genes are responsible. Three genes, amyloid precursor protein (APP), presenilin-1 (PSEN-1) and presenilin-2 (PSEN-2) have been confirmed as causing EOAD. PSEN-1 is the major subject of this study.

APP and PSEN-1 gene mutations account for 10–15% and 20–70% of EOAD, respectively (Campion et al., 1999). They are highly penetrant; the absence of AD by age 60 among confirmed carriers is rare. PSEN-2 gene mutations are very rare. The ages at onset of EOAD also vary (PSEN-1 25–60, APP 40–65 and PSEN-2 45–84 (Campion et al., 1999)). It is quite possible that other genes with mutations

leading to EOAD will be found.

Pathogenic mutations of these genes are usually missense mutations in which an error at a single DNA base causes an incorrect amino acid to be substituted in the protein produced by the gene. These genes are involved in producing the β amyloid peptide, that has 40 or more amino acids, and is found in the amyloid plaques in the brains of both sporadic and familial AD patients. The dominant hypothesis for AD (the 'amyloid cascade hypothesis') suggests that overproduction of, or failure to clear, the long forms of the peptide is crucial for disease pathogenesis (Funato et al., 1999; Hardy, 1997). Mutated genes produce Aβ_{42} or Aβ_{43} rather than the less pathogenic Aβ_{40} (Younkin et al., 1996; Czech et al., 2000). Iwatsubo (1998) suggests that mutations in the presenilin genes cause AD by fostering the production and deposition of Aβ_{42}. See St. George-Hyslop (2000) for a review of the molecular genetics of AD.

2.2.1 Databases of Pedigrees with Mutations in the EOAD Genes

Appendices A, B and C summarise the family studies in which PSEN-1, PSEN-2 and APP mutations have been found, respectively. Appendices D, E and F provide the database of pedigrees of families with mutations in each of the three EOAD genes. It is hoped that this database will serve as useful starting point for analysis into the onset, duration and other studies of the early onset Alzheimer's disease due to mutations in the three genes. Family pedigree diagrams can be easily constructed from the database.

We illustrate the use of the database with an example. Table 2.4 shows the pedigree SAL513 extracted from the database (Appendix A) of the pedigrees with PSEN-1 gene mutations. See Appendix A for an explanation of the coding used. We 'construct' the pedigree diagram of SAL513 using the information in the database, as shown in Figure 2.2.1.

Table 2.4: French family SAL 513 with PSEN-1 gene mutation Leu113Pro, extracted from Appendix D.

ID	Sex	AAO	Age censored (at death)	Comments	Reference
113LP.A1.0001	2	?	(?)	Family SAL 513, French	Raux et al. (2000b)
113LP.a1.0001	1		(?)		
113LP.A2.0101	1		(?)		
113LP.A2.0102	2	38	(44)		
113LP.A2.0103	2	45	(56)		
113LP.a2.0103	1		(?)		
113LP.A3.0301	2		67	-/-	
113LP.A3.0302	2	50	65	+/-	
113LP.A3.0303	2	39	(50)		
113LP.a3.0303	1		(?)		
113LP.A4.0301	2	40	43	+/-	

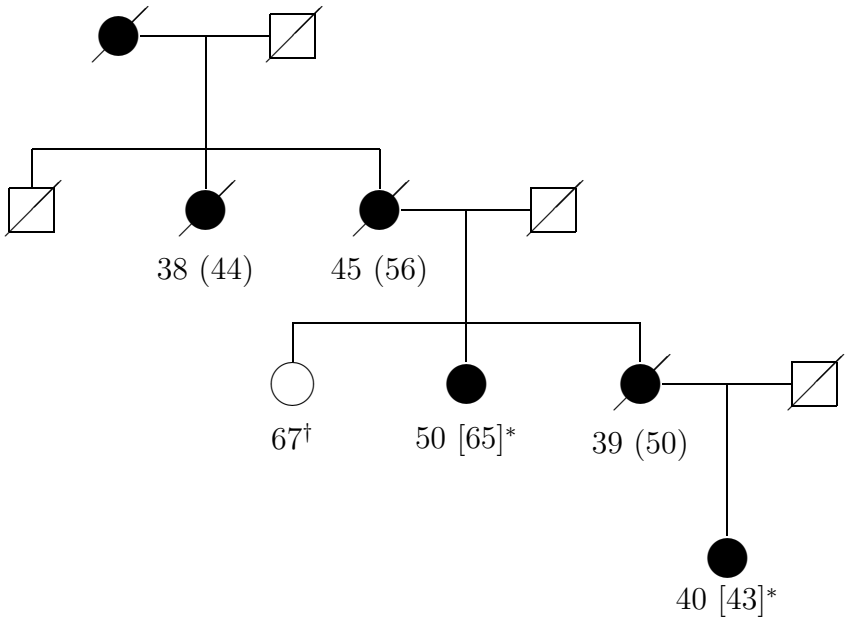

Figure 2.1: Pedigree diagram of French family SAL 513 with PSEN-1 gene mutation Leu113Pro, pedigree information based on Table 2.4. Squares are males, circles are females, and a slash denotes death. Affected individuals are shown as filled squares/circles. The age at onset or oldest observed age free of AD is shown, age at death is given in round brackets, and current age of affected shown in square brackets. An asterisk means that a person has been tested and does carry a mutation, a dagger that he/she has been tested and does not carry a mutation. By convention siblings are listed left-to-right in birth order.

2.2.2 The Presenilin-1 Gene

Also known as S182, the PSEN-1 gene was localised on chromosome 14 (location 14q24) in 1992 but could only be isolated in 1995 (Sherrington et al., 1995). It is highly conserved in evolution, so mutations are rare. The coding region comprises 10 exons, numbered 3–12, and encodes a transmembrane protein that is produced at low level in many different cell types, and is almost homogeneously expressed in the brain and in peripheral tissues (St. George-Hyslop, 2000; Czech et al., 2000).

2.2.3 The Presenilin-2 Gene

The PSEN-2 gene product is highly homologous to the PSEN-1 gene product; they show about 67% amino acid sequence similarity, both are membrane proteins and are expressed in neurons of the brain and a wide variety of other types of cells and tissues including the heart, pancreas and lungs. Located on 1q31-q42, PSEN-2 includes 10 coding exons, coding a polypeptide with 448 amino acids (St. George-Hyslop, 2000; Czech et al., 2000). It is expressed maximally in cardiac muscle, skeletal muscle and the pancreas.

2.2.4 The Amyloid Precursor Protein Gene

The APP gene was the first AD susceptibility gene to be identified, and is located at 21q21.3–q22. It has a variety of rôles including promotion of cell survival and neurite outgrowth. It has 19 exons and encodes a single large transmembrane domain precursor protein of about 770 amino acids (St. George-Hyslop, 2000).

The precursor protein undergoes alternative splicing to produce three peptides. One of these, containing 695 amino acids, is expressed highly in neurons, undergoes axonal transport, and is cleaved to produce the Aβ peptide (St. George-Hyslop, 2000).

2.3 EOAD Gene Mutations

2.3.1 Mutations in the Presenilin-1 Gene

To date, nearly 100 different mutations causing EOAD have been found. PSEN-1 mutations are usually associated with very aggressive EOAD, with duration of dementia ranging from about 2 to 23 years and mean duration of 8.2 $\pm$ 4.1 years (Appendix D, 133 subjects). In studies with fewer subjects, mean duration of 11.5 $\pm$ 5.6 years (Ishii et al., 2001; 23 subjects) and 4.5 $\pm$ 0.7 years (Russo et al., 2000; 11 subjects) were reported. We note that these averages were estimated from only observed onset cases with documented duration from onset to death, and hence biased. The lower ages at onset are around 30 though Wisniewski et al. (1998) has reported an individual in a Polish EOAD family with onset at 24.

There are rare survivors with a mutation at sufficiently high ages to suggest incomplete penetrance. The few isolated cases could be sporadic rather than inherited mutations. Overall, however, mutations appear to be highly penetrant before the age of about 60; Rogaeva et al. (2001) reported that 90% of those with PSEN-1 mutations were affected by age 60. But note that this 'observation' of high penetrance is not based on any epidemiological model in which the penetrance has been estimated but on unsystematic reporting of observation of families in which EOAD has been found.

This degree of genetic heterogeneity, plus the shared environment of each family studied, could lead to systematic differences in age at onset in respect of different families or mutations. The data are as yet inconclusive, though it is possible that some measure such as mean age at onset within a family might emerge as a covariate in any larger studies in future.

Appendix A summarises the family studies in which PSEN-1 mutations have been found.

2.3.2 Mutations in the Presenilin-2 Gene

Like PSEN-1 mutations, PSEN-2 mutations increase the secretion of long-tailed Aβ peptides. The phenotype associated with PSEN-2 mutations is, however, much

more variable, and the range of age of onset is between 40 and 88 years of age in heterozygous carriers E. At ages over about 65, it may be unclear whether AD is attributable to a PSEN-2 mutation or is sporadic.

There are very few reported PSEN-2 mutations, confined to several families in a Volga-German study (Bird et al., 1988; Levy-Lahad et al., 1995a,b; Nochlin et al., 1998), three Italian families (Finckh et al., 2000a,b; Hardy et al., 1991; Rogaev et al., 1995; Sherrington et al., 1996) and a German family (Finckh et al., 2000b), as well as two isolated cases. The Volga-German families, who all have the same mutation, account for about 85% of all observed cases.

Appendix B summarises the family studies in which PSEN-2 mutations have been found.

2.3.3 Mutations in the Amyloid Precursor Protein Gene

Not all APP mutations are clearly pathogenic. The French family with a double mutation (Ala713Thr and a silent change at Val715) reported by Carter et al. (1992) has one affected person out of seven (in two generations) with the mutation, but this is unusual. Like PSEN-1, there are a few isolated cases. A large proportion of the APP gene mutations are at codon 717. These APP717 mutations account for less than 3.6% of all EOAD cases, at a 95% confidence level (van Duijn et al., 1991b).

Appendix C summarises the family studies in which APP mutations have been found.

2.4 The Epidemiology of EOAD

2.4.1 The Epidemiological Literature

The genetic epidemiology of EOAD is sparse (Dartigues and Letenneur, 2000), and there is a lack of informative community-based studies. The genetic epidemiology of AD described by Dartigues and Letenneur (2000) is almost entirely related to the ApoE gene.

No rates of onset of EOAD have been published in the literature of genetic epidemiology. Most of the epidemiological studies on AD include both EOAD and

the senile form of the disease, as separation by age of onset is not supported by epidemiological data (Rocca et al., 1986). There are very few estimates of EOAD prevalence and little is known about the mutation frequencies of these three genes. (Despite this, EOAD is included in the list of disorders regarded as significant for insurance by the ABI.)

2.4.2 EOAD Genes and Insurance Applications

For each of the EOAD genes, the following needs to be known before any actuarial studies can be carried out into insurance applications:

(a) mutation frequencies,

(b) onset rates of the gene mutation as a function of age,

(c) survival rates after onset of EOAD, and possibly

(d) rates of progression of dementia through several stages.

As mentioned in Section 1.5 these parameters are either sparse or absent in the current epidemiology literature for EOAD.

In Chapter 4, a modified Nelson-Aalen estimate is used to estimate the incidence rates of EOAD in respect of PSEN-1 mutations, based on pedigrees published in the medical genetics literature. From the same sources, rates of mortality after onset are estimated. These estimates of incidence rates in respect of EOAD gene mutations are novel. Chapter 7 estimates the incidence rates of EOAD due to mutations in the PSEN-2 and APP genes.

Chapter 3

A NELSON-AALEN ESTIMATE OF THE INCIDENCE RATES OF EARLY-ONSET ALZHEIMER'S DISEASE

3.1 Introduction

This chapter and the next form parts of a joint work already published (Gui and Macdonald, 2002b).

3.1.1 Estimating Rates of Onset of Single-Gene Disorders

Among the human diseases caused by single-gene disorders are some whose sporadic occurrence (that is, in the absence of a gene mutation) is rare or unknown. In these cases, age-related rates of onset can be estimated using the life table method of Newcombe (1981), following Elandt-Johnson (1973). Before the introduction of DNA-based genetic testing, members of affected families could only be confirmed as mutation carriers once onset had occurred. The longer someone survived disease-free, therefore, the more likely it was that they did not carry the mutation, and observation of non-carriers would inevitably be censored. Some early estimates of rates of onset simply excluded these censored cases, but Newcombe (1981) pointed

out that this was biased; his method properly allowed for them. His estimates were obtained in a deterministic setting, in which their statistical properties were not directly available.

If a (reliable) genetic test is available, asymptomatic members of affected families can be: untested and at risk of being a carrier; tested and known to be a carrier; or tested and known not to be a carrier. One of the aims of this study is to extend Newcombe's method to allow for these new risk groups.

An important question is how to make use of information gained about risk status; this may change throughout a person's lifetime as their own and their relatives' life histories reveal information. A key feature of Newcombe's method is that all the information available at the time of the study is used to assign people to the same risk groups throughout their lives; in effect, making the best use of the latest available information.

In Section 3.3 we use a simple probabilistic model to study how information acquired at different times might be used in non-parametric estimates of rates of onset, *via* conditional expectations or probabilities of onset. We show that, perhaps surprisingly, information acquired at any age x should not be used in estimating rates of onset at earlier ages. Intuitively, it might seem that its use should lead to better estimates, but in a probabilistic setting this is seen to be untrue.

3.1.2 Nelson-Aalen Estimates

When there are a number of distinct risk groups, individuals may have to be assigned to different groups at different times, depending on the information that has by then emerged. In Section 3.4 we specify a model that allows for this, in a discrete-state continuous-time setting, and obtain Nelson-Aalen type estimates for certain functions of the transition intensity of interest, along with approximate confidence intervals. Further, in the simplest case we find that the function estimated is bounded above, unlike the usual integrated hazard, providing a diagnostic check for the inclusion of censored observations or possibly ascertainment bias.

The Nelson-Aalen approach is a non-parametric estimate of the cumulative intensity (or force of mortality), also known as the integrated hazard in statistics

(Therneau and Grambsch, 2000). The Nelson-Aalen estimator is remarkably easy to compute and as it is non-parametric, we do not need any prior knowledge of the underlying distribution of the "life-length" random variable. The theory of the Nelson-Aalen estimate is based on counting processes and a major benefit derived from formulating a survival analysis based on the latter is that many results from martingale theory may be used (see Section 3.4.1). Andersen et al. (1993) derives the Nelson-Aalen estimator as a non-parametric maximum likelihood estimator of the integrated hazard function for a univariate counting process which makes the estimator more appealing.

For actuarial applications, we think in terms of a continuous-time, finite-state stochastic process model (see Macdonald (1997, 1999); Subramanian et al. (2000)) in which some of the transitions represent onset of EOAD; the rates of onset are then the transition intensities in the model.

3.1.3 Estimating Rates of Onset of Early-Onset Alzheimer's Disease

We use the methods described in Section 3.4 to estimate rates of onset of EOAD associated with PSEN-1 mutations (published data on PSEN-2 and APP mutations are not extensive enough to support a similar analysis). Many of the articles on PSEN-1 mutations that we use (summarised in Appendix A) include usable pedigrees, but few give all the times of entry to and exit from all relevant risk groups, especially for censored cases, so we have had to make some approximations, described in Section 4.1.2. The details of the estimation are in the remaining sections of Chapter 4.

3.2 Pedigree Analysis

3.2.1 Pedigrees and Mutation Probabilities

Figure 3.2 gives a hypothetical example of a pedigree. The father in this example did not have a genetic test, but EOAD is so rare that we can reasonably assume that

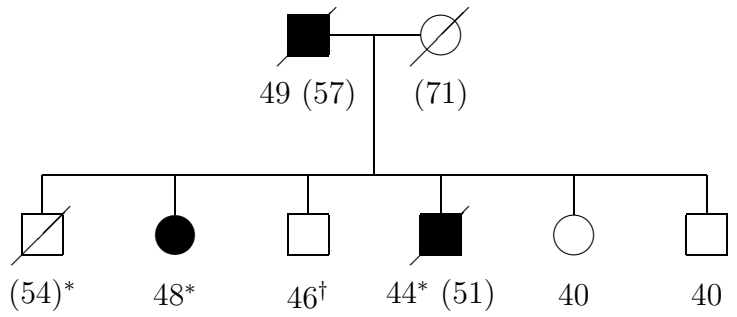

Figure 3.2: A hypothetical example of a pedigree.

he did carry the mutation. Of the second generation, the first, second and fourth lives have been tested and have a mutation; the third life has been tested and has no mutation; and the fifth and sixth lives have not been tested and are at risk of having the mutation. The probabilities that they have a mutation depend on the available information. By Mendel's laws, these probabilities would appear to be 1/2 each, but this may have to be modified in complicated ways. For example, denote the father F and the fifth child C.

(a) Survival free of EOAD reduces the probability that someone at risk has a mutation, ultimately to zero if the mutation is fully penetrant. Let $p(x)$ be the probability that a mutation carrier is free of EOAD at age x. Then the probability that an at-risk individual who is free of EOAD at age x is a carrier (ignoring all other decrements) is $p(x)/(1+p(x))$, which is the Mendelian 1/2 at age 0.

(b) F's carrier status was not known when C was born; only when his condition appeared later on. If one of F's parents had had EOAD then, when C was born, the Mendelian probability of her having a mutation would be 1/4, not 1/2, but again this would be modified by survival. For example, if C was born when F was age 25, C's mutation probability at age x, while F was healthy (again ignoring all other decrements), would be:

$$\frac{0.25p(x)p(x+25)}{0.5+0.25p(x+25)+0.25p(x)p(x+25)}. \tag{3.1}$$

(c) Even this may fail to use all the available information. While F is healthy, the survival of C's siblings free of symptoms (and before having had a genetic test) also decreases the probability that C carries a mutation. See Newcombe (1981) for an example of these calculations.

Complications (b) and (c) above arise only when the carrier status of F and all of C's siblings is uncertain. As soon as any one of them develops EOAD, and can be assumed to have the mutation, C's mutation probability reverts to $p(x)/(1 + p(x))$. Alternatively, if C were to have a (100% accurate) genetic test, her mutation probability would then change to 0 or 1. Similarly, as long as F remains free of EOAD, his mutation probability depends upon the continuing freedom from EOAD of all his children.

We ignored other decrements above (death from other causes or loss to follow-up) which would, in practice, introduce censoring mechanisms.

3.2.2 Definition of Risk Groups

At any time, a family member is in one of four risk groups:

(a) *Group 1: Mutation known to be absent.* As a result of a genetic test, taken by the person or an ancestor, the mutation probability is 0 (assuming the test to be accurate).

(b) *Group 2: Mutation known to be present.* Either a genetic test has revealed a mutation, or EOAD has occurred. EOAD is rare enough that, within affected families, its presence may be assumed to indicate the presence of a gene mutation, though strictly a genetic test would be necessary to confirm it. This assumption could not be made in the case of a condition that commonly occurred for other reasons (for example, breast cancer).

(c) *Group 3: Parent or any sibling known to have the mutation.* The mutation probability is $p(x)/(1 + p(x))$. This depends only on the age of the individual concerned, it does not depend explicitly on the details of the family.

(d) *Group 4: Parent and siblings at risk but free of EOAD.* The mutation probability is complicated and depends explicitly on the details of the family; Equation (3.1) is the simplest case.

We wish to estimate age-related rates of onset of EOAD. It is clear that the risk groups defined above will enter the analysis somehow. For example, consider simple occurrence/exposure rates. The numerators present no problems, but the exposures will have to allow for the different risk groups. An intuitive approach is to weight each person's contribution to the exposure at age x by the probability that they have the mutation. Strictly, we should say the *conditional* probability that they have the mutation, since it depends on the data. A key question is this: for a person at risk at age x, what information should we use to condition the probability that they have the mutation?

An example will show why the question arises. Consider an only child who is age 10 when her mother suffers EOAD, and who suffers it herself at age 40, dying at age 50. How does she contribute to the exposure at age 20? We could use this life history in two ways:

(a) She was in risk group 4 for ten years, risk group 3 for thirty years and risk group 2 for ten years. At age 20, *based only on what was known at that time* she had the mutation with probability $p(20)/(1 + p(20))$, which is therefore her contribution to the exposure.

(b) By the time the analysis is carried out, after her death, it is known that she had had EOAD so she was, in fact, in risk group 2 throughout her life. She therefore contributes one full year to the exposure at age 20.

The latter is the basis of the 'life table method' of Newcombe (1981). Intuitively, it seems sensible to condition on all the information available at the time of the study, and to use this 'best knowledge' to assign each person to one risk group throughout their life. However, this leads to problems in interpreting the resulting occurrence/exposure rates.

3.2.3 The Life Table Method

Based on Elandt-Johnson (1973), Newcombe (1981) introduced a modified life table analysis for Huntington's disease (HD) to allow for risk pools like Groups 3 and 4 above (this work predated the discovery of the HD gene). Previous analyses had estimated occurrence/exposure rates based only on affected persons (risk group 2 above) which were clearly biased, especially at older ages, because the omission of censored observations understated the true numbers at risk. Newcombe's estimate added terms to the exposure to allow for censored observations of at-risk individuals. Harper and Newcombe (1992) tabulated probabilities of being a carrier, given age and family history, that are used in counselling for people at risk of HD.

Four groups were distinguished; obligate carriers with mutation probability 1, and at-risk individuals with Mendelian mutation probability 0.5, 0.25 or 0.125, depending on the last generation affected. Suppose that A_x persons suffered onset of HD at age x, and observation of N_x lifetimes was censored at age x. For each of these, the mutation probability was calculated allowing for all the information available at the time of the study, including what was known about relatives; call this R_x^i in respect of the i^{th} life censored at age x. The exposure to risk, during each full year of observation, in respect of lives censored at age x was taken to be $\sum_{i=1}^{i=N_x} R_x^i$, and the effective total (initial-type) exposure at age x was:

$$E_x = \sum_{y \geq x} A_y + \sum_{y > x} \sum_{i=1}^{i=N_y} R_y^i + \frac{1}{2} \sum_{i=1}^{i=N_x} R_x^i. \tag{3.2}$$

Because of the appearance of rates of onset in the R_x^i, it was impossible to estimate one-year probabilities as A_x/E_x in the usual way; the system of 71 non-linear equations was solved by iteration.

This method seems intuitively reasonable, but it was not derived from any underlying probabilistic model, and its properties are hard to find for that reason as well as because of its inherent complexity. Confidence limits were not available, for example. A simulation experiment showed that the mean age at onset was biased slightly upwards; the bias was statistically but not practically significant.

3.3 An Analysis of the Life Table Method

Occurrence/exposure rates arise very naturally as moment estimates in the context of probabilistic models for censored data. Put simply, we proceed from the model specification to an equation of the form:

$$\text{E[No. of Events} \mid \text{Information]} = \text{P[Event]} \times E \tag{3.3}$$

where E is some quantity that is known from the given information. As the notation suggests, E can often be interpreted as an intuitive 'exposure to risk', hence the name 'occurrence/exposure rates' for the resulting moment estimates. In most simple cases, moment and likelihood estimates coincide (we concentrate on moment estimates, because that is the simplest interpretation of the Nelson-Aalen estimate we use later).

In Elandt-Johnson (1973) and Newcombe (1981) no probabilistic model was specified explicitly, and expected values were implicitly replaced by proportions. Here we use a simple probabilistic model, that includes the key features of Newcombe's estimation procedure, to pose some questions about the conditional expectations that may underlie Equations (3.2) and (3.3).

Suppose we begin with a sample of N independent lives who, at birth, each have a mutation with probability 1/2. A person with the mutation, healthy at age x, has probability q_x of suffering onset of the disorder by age $x+1$. Let $\mathbf{X}_1, \mathbf{X}_2, \ldots$ be the number of cases of onset during the first year of life, second year of life and so on. We observe all cases of onset until some fixed age T, when observation ceases. Onset of the disorder is the only decrement, so the only cause of censoring is by remaining unaffected at age T. The problem is to estimate the q_x at integer ages x.

3.3.1 Conditioning on Currently Known Information

First, we can write down the conditional expectations, assuming only that we know what happened up to the time (or age) for which a rate is being estimated; we denote information known at age x by $\mathcal{F}_x$:

$$\mathrm{E}[\mathbf{X}_1|\mathcal{F}_0] = \frac{1}{2}Nq_0 \tag{3.4}$$

$$\mathrm{E}[\mathbf{X}_2|\mathcal{F}_1] = (N-\mathbf{X}_1)\frac{(1-q_0)}{1+(1-q_0)}q_1 \tag{3.5}$$

$$\mathrm{E}[\mathbf{X}_3|\mathcal{F}_2] = (N-\mathbf{X}_1-\mathbf{X}_2)\frac{(1-q_0)(1-q_1)}{1+(1-q_0)(1-q_1)}q_2 \quad \text{etc.} \tag{3.6}$$

This is exactly what would be done in a conventional survival analysis. Censored cases and cases of onset alike are included in the exposure, and there is no bias arising from the omission of censored cases.

3.3.2 Conditioning Retrospectively on Observed Cases

Newcombe (1981) takes advantage of the fact that the analysis is retrospective, and is carried out at time T. By that time, $\mathbf{X}^* = \mathbf{X}_1 + \mathbf{X}_2 + \ldots + \mathbf{X}_T$ individuals have been identified as mutation carriers, and $(N - \mathbf{X}^*)$ may or may not be. This information is used to split the sample population in two throughout the analysis:

(a) the $\mathbf{X}^*$ known to be mutation carriers; and

(b) the $N - \mathbf{X}^*$ not known to be mutation carriers, each of whom is a mutation carrier with probability $P/(1+P)$, where:

$$P = (1-q_0)(1-q_1)\ldots(1-q_{T-1}). \tag{3.7}$$

Note that knowing $\mathbf{X}^*$ is not the same as knowing $\mathbf{X}_1, \mathbf{X}_2, \ldots, \mathbf{X}_T$ separately.

Conditional expected values of $\mathbf{X}_1, \mathbf{X}_2, \ldots$ are then found using this additional information; here we denote the information at age x by $\mathcal{F}^*_x$. Note that $\mathrm{E}[\mathbf{X}^*|\mathcal{F}_0] = N(1-P)/2$, while $\mathrm{E}[\mathbf{X}^*|\mathcal{F}^*_0] = \mathbf{X}^*$.

$$\mathrm{E}[\mathbf{X}_1|\mathcal{F}^*_0] = \mathbf{X}^*\frac{q_0}{1-(1-q_0)(1-q_1)\ldots(1-q_{T-1})} \tag{3.8}$$

$$\mathrm{E}[\mathbf{X}_2|\mathcal{F}^*_1] = (\mathbf{X}^*-\mathbf{X}_1)\frac{q_1}{1-(1-q_1)(1-q_2)\ldots(1-q_{T-1})} \tag{3.9}$$

$$\mathrm{E}[\mathbf{X}_3|\mathcal{F}^*_2] = (\mathbf{X}^*-\mathbf{X}_1-\mathbf{X}_2)\frac{q_2}{1-(1-q_2)(1-q_3)\ldots(1-q_{T-1})} \quad \text{etc.} \tag{3.10}$$

We derive Equation (3.9) as an example. Let $\mathbf{X}_j^i$ be the indicator of onset of the disorder during the j^{th} year of life of the i^{th} person. That is, $\mathbf{X}_j^i = 1$ if the i^{th} person suffers onset between ages $j-1$ and j, and $\mathbf{X}_j^i = 0$ otherwise. Then $\mathbf{X}_j = \sum_{i=1}^{i=N} \mathbf{X}_j^i$. Further, define $\mathcal{C}$ to be the set of indices corresponding to the $\mathbf{X}^*$ identified mutation carriers, and let $\mathcal{U}$ be the set of indices corresponding to censored observations. That is, $i \in \mathcal{C}$ if the i^{th} life suffered onset, and $i \in \mathcal{U}$ otherwise. Then:

$$\begin{aligned}
\mathrm{E}[\mathbf{X}_2|\mathcal{F}_1^*] &= \sum_{i=1}^{i=N} \mathrm{E}[\mathbf{X}_2^i|\mathcal{F}_1^*] && (3.11)\\
&= \sum_{i=1}^{i=N} \mathrm{P}[\mathbf{X}_2^i = 1|\mathcal{F}_1^*] && (3.12)\\
&= \sum_{\substack{i\in\mathcal{C}\\ \mathbf{X}_1^i=0}} \mathrm{P}[\mathbf{X}_2^i = 1|i \in \mathcal{C}, \mathbf{X}_1^i = 0] + \sum_{\substack{i\in\mathcal{U}\\ \mathbf{X}_1^i=0}} \mathrm{P}[\mathbf{X}_2^i = 1|i \in \mathcal{U}, \mathbf{X}_1^i = 0] && (3.13)\\
&= (\mathbf{X}^* - \mathbf{X}_1)\frac{q_1}{1-(1-q_1)(1-q_2)\ldots(1-q_{T-1})}. && (3.14)
\end{aligned}$$

In going from Equation (3.12) to Equation (3.13) we split the summation between sets of indices that are known given $\mathcal{F}_1^*$, and then the second sum clearly disappears because $\mathrm{P}[\mathbf{X}_2^i = 1|i \in \mathcal{U}, \mathbf{X}_1^i = 0] = \mathrm{P}[\mathbf{X}_2^i = 1|i \in \mathcal{U}] = 0$, by definition of $\mathcal{U}$.

This approach apparently yields a system of T equations in T unknowns, which we might try to solve. Unfortunately $\mathrm{E}[\mathbf{X}_T|\mathcal{F}_{T-1}^*] = \mathbf{X}_T$, so we must have $q_{T-1} = 1$. The system of equations from Equation (3.8) to Equation (3.10) is thus reduced to:

$$\begin{aligned}
\mathrm{E}[\mathbf{X}_1|\mathcal{F}_0^*] &= \mathbf{X}^* q_0 && (3.15)\\
\mathrm{E}[\mathbf{X}_2|\mathcal{F}_1^*] &= (\mathbf{X}^* - \mathbf{X}_1)q_1 && (3.16)\\
\mathrm{E}[\mathbf{X}_3|\mathcal{F}_2^*] &= (\mathbf{X}^* - \mathbf{X}_1 - \mathbf{X}_2)q_2 \quad \text{etc.} && (3.17)
\end{aligned}$$

Note that these estimates are the same as those obtained by ignoring censored observations, that Newcombe (1981) observed to be biased.

Essentially, this is because we have conditioned on the very statistic we need for estimation. Any attempt to write down a conditional likelihood, conditioning on $\mathcal{C}$ and $\mathcal{U}$, will suffer similar problems.

3.3.3 Newcombe's Estimates

The exposures in Newcombe's estimates are different; they are:

$$E_0 = \mathbf{X}^* + (N - \mathbf{X}^*)\frac{P}{1+P} \tag{3.18}$$

$$E_1 = (\mathbf{X}^* - \mathbf{X}_1) + (N - \mathbf{X}^*)\frac{P}{1+P} \tag{3.19}$$

$$E_2 = (\mathbf{X}^* - \mathbf{X}_1 - \mathbf{X}_2) + (N - \mathbf{X}^*)\frac{P}{1+P} \quad \text{etc.} \tag{3.20}$$

These correspond to Equations (3.2), except that here, censoring occurs only at one fixed age. As can be seen from Section 3.3.2, they are not the conditional expectations, given the information used by Newcombe (1981), and the resulting estimates are not moment estimates (or conditional likelihood estimates). Nevertheless, they are consistent with moment estimates in the sense that $\mathrm{E}[E_0|\mathcal{F}_0]q_0 = \mathrm{E}[\mathbf{X}_1|\mathcal{F}_0]$, $\mathrm{E}[E_1|\mathcal{F}_1]q_1 = \mathrm{E}[\mathbf{X}_2|\mathcal{F}_1]$ and so on (as can easily be checked) so for reasonably large samples, they should be quite similar. In a probabilistic framework, however, conditioning on information that includes the very events being studied fails. The absence of a probabilistic framework also means that the properties of the Newcombe's estimator cannot be studied directly.

3.3.4 Information From Events Other Than Onset

Information about a person's genotype can be revealed by events other than they themselves suffering onset of the disorder. Onset in relatives, or genetic tests taken by the person or their relatives, can alter their risk status. How should people be assigned to risk groups in the light of these events? For example:

(a) Consider identical twin brothers, at risk 1/2 of being carriers. One suffers onset at age 40. As we saw in Section 3.3.2, we cannot then assign him to the 'known carrier' risk group at earlier ages, but can we so assign his brother?

(b) Consider someone age 30 who takes a genetic test that shows they are a carrier. This is not the same event as that whose rate of occurrence we wish to estimate, so can we assign that person to the 'known carrier' risk group at earlier ages? And can we use this information when assigning their relatives (for example, children) to risk groups?

It should be clear that the answer to (a) above is no. The event whose rate of occurrence is being estimated cannot appear in the information set used in conditional expectations or probabilities. This is perhaps most obvious if we consider the likelihood, which would be the conditional *joint* probability of the observed events befalling both brothers; we cannot condition on different information in respect of each.

The answer to (b) above is also no; however we try to condition on the information revealed by an event before it has happened, analysis like that in Section 3.3.2 shows this to be flawed. The reason is the same, that conditioning on a *future* event that implies that onset will not occur before that time means that onset occurs *now* with probability zero. We cannot even retrieve matters by choosing to 'forget' some of the information that we so inconveniently know: for example, if the problem is that the age at which a genetic test was taken is known, can we not simply 'forget' that piece of information, and then assign tested individuals to a 'known status' risk group throughout their lives? Denote this information at age x by $\mathcal{F}_x^\dagger$ and consider (for example):

$$\mathrm{E}[\mathbf{X}_2|\mathcal{F}_1^\dagger] = \sum_{i=1}^{i=N} \mathrm{P}[\mathbf{X}_2^i = 1|\mathcal{F}_1^\dagger]. \tag{3.21}$$

Suppose the i^{th} life is known to have had a positive test *before onset*, but when is unknown. Let the unknown time of the test be $\mathbf{T}^i$. Then:

$$\mathrm{P}[\mathbf{X}_2^i = 1|\mathcal{F}_1^\dagger] = \mathrm{P}[\mathbf{T}^i \leq 1]q_1 + \mathrm{P}[\mathbf{T}^i > 1] \times 0 \tag{3.22}$$

and:

(a) we have effectively removed a proportion of the at-risk population, leading to the same sort of biased estimate as if only observed cases of onset were included; and

(b) we have had to introduce age-related probabilities of taking a genetic test.

For our simple probabilistic model to work, the estimates of rates of onset at age x can only be conditioned on information known at age x. The acquisition of

information in the model is represented by observation of events, that is, the onset of the disease. For example, we should not condition on 'knowing' the genotype from an event that happens after age x, but by observing the event that revealed it. Any attempt to estimate probabilities of onset at age x conditioned on knowledge of mutation carrier status will fail as the estimation should be properly based on conditional probabilities:

$$\mathrm{P}[\text{ Onset at age } x | \text{ Onset observed at } x+t \text{ }]$$

which are either 0 or 1. Similar argument applies to knowledge gained from events other than onset in the individual concerned.

In a probabilistic setting, every attempt to use knowledge obtained at future ages to improve estimates of rates of onset at past ages is foiled because, conditioning on that information, we know that onset did not occur. And, although we have considered conditional expectations and moment estimates, the same will be true of conditional probabilities and likelihood estimates. For an interesting discussion of conditioning on missing or unobserved information (called 'data coarsening') see Heitjan (1994).

In this section we have omitted any complications, but it is clear that we should not assign individuals retrospectively to one risk group throughout their lives, but allow them to be in different risk groups at different ages. This leads naturally to continuous-time discrete-state stochastic process models. In Section 3.4.1 we will specify such a model in which a person age x is assigned to a risk group using only the information available at age x, and we will derive a modified version of the Nelson-Aalen estimate.

3.3.5 A Corollary: What Information Should Pedigrees Include?

This conclusion has an important corollary, concerning the information that ought to be included in pedigrees. A person moves from one risk group to another either when they have a genetic test, or when a relative has a genetic test or suffers onset of EOAD. Therefore:

(a) the age at which an asymptomatic person has a genetic test; and

(b) the affected parent's age at the birth of each child

must be recorded as part of the pedigree; for epidemiological purposes it is not enough just to know a test result, or the unconnected ages of family members when events befall them.

3.4 A Modified Nelson-Aalen Estimate

From now on, we will often refer to the rate of onset as a transition intensity (or just intensity), denoted $\mu(x)$ as a function of age x, adding subscripts in models involving more than one intensity. It is a natural target for estimation because it is a key quantity in many actuarial applications. Equivalently, we can estimate any simple function of $\mu(x)$. One such function is the integrated intensity $\int_0^x \mu(t)dt$, for which there is a natural estimate, the Nelson-Aalen estimate. This has nice statistical properties, but for our purposes its advantage is that it can be generalised to allow for uncertainty about genotype.

In Section 3.4.1 we introduce the Nelson-Aalen estimate, then we modify it in stages:

- in Sections 3.4.2 and 3.4.3 we allow for an unaffected person with Mendelian probability p at birth of having a mutation;
- in Section 3.4.4 we allow for genetic testing; and
- in Section 3.4.5 we allow for (or rather, are defeated by) the information contributed by unaffected relatives.

3.4.1 The Nelson-Aalen Estimate

Here we introduce, non-rigorously, the Nelson-Aalen estimate. A fuller, but still heuristic, introduction to counting processes can be found in Macdonald (1996); see Fleming and Harrington (1991) or Andersen et al. (1993) for a proper treatment.

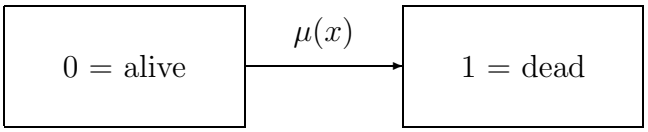

Figure 3.3: A two state model of mortality

Suppose we observe M lives, each of whose survival can be represented by the continuous-time model in Figure 3.3. The state space is $\mathcal{S} = \{0, 1\}$, and at age x the state occupied by the i^{th} person is denoted $\mathbf{S}^i(x)$, $\mathbf{N}^i(x)$ is the number of transitions from alive to dead by age x (either 0 or 1), and $\mathbf{Y}^i(x)$ indicates presence in the alive state just before age x ($\mathbf{Y}^i(x) = 1$ if the life is alive just before age x, and is 0 otherwise). $F^i = \{\mathcal{F}^i_x\}_{x\geq 0}$ is the natural filtration of $\mathbf{N}^i(x)$. The compensated process $\mathbf{M}^i(x) = \mathbf{N}^i(x) - \int_0^x \mathbf{Y}^i(t)\mu(t)dt$ is a F^i-martingale, and $\int_0^x \mathbf{Y}^i(t)\mu(t)dt$ is the F^i-compensator of $\mathbf{N}^i(x)$.

Sum these quantities over the M lives ($\mathbf{N}(x) = \sum_{i=1}^M \mathbf{N}^i(x)$ and so on, absence of the superscript i denoting such sums) and let $F = \{\mathcal{F}_x\}_{x\geq 0}$ be the natural filtration. $\mathbf{M}(x)$ is a F-martingale and, if $\mathbf{H}(x)$ is a predictable process adapted to F, the stochastic integral $\int_0^x \mathbf{H}(t)d\mathbf{M}(t) = \int_0^x \mathbf{H}(t)d\mathbf{N}(t) - \int_0^x \mathbf{H}(t)\mathbf{Y}(t)\mu(t)dt$ is also a F-martingale, zero at $x = 0$. Define $\mathbf{J}(x) = \mathbf{I}_{\{\mathbf{Y}(x)>0\}}$, with the convention that $\mathbf{Y}(x) = 0 \Rightarrow \mathbf{J}(x)/\mathbf{Y}(x) = 0$, and take $\mathbf{H}(x) = \mathbf{J}(x)/\mathbf{Y}(x)$. Then:

$$\mathrm{E}\left[\int_0^x \frac{\mathbf{J}(t)}{\mathbf{Y}(t)} d\mathbf{N}(t)\right] = \mathrm{E}\left[\int_0^x \mathbf{J}(t)\mu(t)dt\right] \approx \int_0^x \mu(t)dt. \tag{3.23}$$

$\hat{\Lambda}(x) = \int_0^x \mathbf{J}(t)\mathbf{Y}^{-1}(t)d\mathbf{N}(t)$ is the Nelson-Aalen estimate of $\int_0^x \mu(t)dt$. In words: at age x, $\mathbf{Y}(x)$ lives are at risk. If one dies, the estimate increases by $1/\mathbf{Y}(x)$, provided $\mathbf{Y}(x) > 0$. $\mathbf{J}(x)$ takes care of the possibility that $\mathbf{Y}(x) = 0$. In between observed death times, the estimate is level. Equation (3.23) shows that $\hat{\Lambda}(x)$ is 'almost' unbiased, the bias arising from the possibility that no lives remain under observation.

The variance of the Nelson-Aalen estimate can be estimated reasonably well by:

$$\mathrm{Var}[\hat{\Lambda}] \approx \int_0^x \frac{\mathbf{J}(t)(\mathbf{Y}(t) - \Delta\mathbf{N}(t))}{(\mathbf{Y}(t))^3} d\mathbf{N}(t) \tag{3.24}$$

(Andersen et al., 1993), where $\Delta\mathbf{N}(t)$ is the jump in $\mathbf{N}(t)$ at time t, leading to pointwise confidence intervals. However, in Section 3.4.2 we estimate a more complicated function of the intensity, and we will use the so-called 'Weird Bootstrap' (Andersen et al., 1993) as follow:

(a) At each jump time of $\mathbf{N}(x)$, fix the numbers at risk at their observed values $\mathbf{Y}(x)$.

(b) Simulate the number of deaths at the jump times, as a Binomial$(\mathbf{Y}(x), d\mathbf{N}(x)/\mathbf{Y}(x))$ random variable.

(c) Calculate a simulated Nelson-Aalen estimate, and solve for the intensity if desired.

(d) Over many simulations, the distribution of $\int_0^x \hat{\mu}(t)dt$ or $\hat{\mu}(x)$ is built up, from which pointwise confidence intervals can be found directly.

The indicators $\mathbf{Y}^i(x)$ and $\mathbf{Y}(x)$ can allow for many censoring schemes. In this case the natural filtration is $\mathcal{F}_x^i = \sigma(\mathbf{N}^i(t), \mathbf{Y}^i(t) : t \leq x)$, but for simplicity we ignore such censoring in what follows.

3.4.2 A Modified Nelson-Aalen Estimate

Figure 3.4 shows a model representing the onset of AD, with two starting states: State 0 (has mutation) and State 1 (no mutation). The state space is now $\mathcal{S} = \{0, 1, 2\}$. Therefore:

(a) $\mu_{02}(x)$ is the incidence rate that we wish to estimate; and

(b) $\mu_{12}(x)$ is the incidence rate of sporadic EOAD, assumed known (often zero).

We suppose that the person has not had a genetic test, so we do not know in which state they start (at birth), but we know the Mendelian probability p that, at

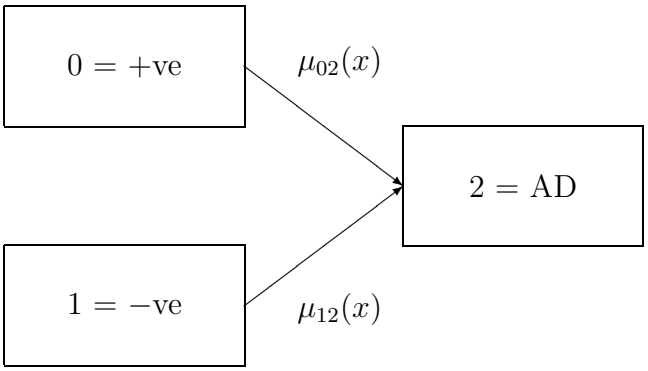

Figure 3.4: A model of the incidence of Alzheimer's disease where an individual may have an EOAD mutation (State 0, +ve) or may not have an EOAD mutation (State 1, −ve).

birth, they are in State 0, and $1-p$ that they are in State 1, for example because an ancestor is a known mutation carrier (Groups 3 and 4 in Section 3.2.2).

Here, we modify the Nelson-Aalen estimate, and show that it estimates a function of $\mu_{02}(x)$, more complicated than $\int_0^x \mu_{02}(t)dt$, but capable of numerical solution.

In obvious notation, the model for the i^{th} life history is the multivariate counting process $(\mathbf{N}^i_{02}(x), \mathbf{N}^i_{12}(x))$ and indicators $(\mathbf{Y}^i_0(x), \mathbf{Y}^i_1(x))$. However, we cannot observe these separately, but only $\mathbf{N}^i(x) = \mathbf{N}^i_{02}(x) + \mathbf{N}^i_{12}(x)$ and $\mathbf{Y}^i(x) = \mathbf{Y}^i_0(x) + \mathbf{Y}^i_1(x)$, so our information is:

(a) p, the Mendelian probability of carrying a mutation; and

(b) the filtration $G^i = \{\mathcal{G}^i_x\}_{x\geq 0}$, where $\mathcal{G}^i_x = \sigma(\mathbf{N}^i(t) : t \leq x)$; we observe whether or not AD has appeared by age x.

It is easily checked that:

$$\mathbf{A}^i_{\mathcal{G}}(x) = \int_0^x \mathbf{Y}^i(t) \frac{p\exp(-\int_0^t \mu_{02}(s)ds)\mu_{02}(t) + (1-p)\exp(-\int_0^t \mu_{12}(s)ds)\mu_{12}(t)}{p\exp(-\int_0^t \mu_{02}(s)ds) + (1-p)\exp(-\int_0^t \mu_{12}(s)ds)} dt \tag{3.25}$$

is the G^i-compensator of $\mathbf{N}^i(x)$. Since $\mu_{02}(x)$ represents a highly penetrant disorder, and $\mu_{12}(x)$ a rare sporadic event, $\mu_{02}(x) \gg \mu_{12}(x)$, and we approximate $\mu_{12}(x) \approx 0$. Then:

$$\mathbf{A}^i_{\mathcal{G}}(x) \approx \int_0^x \mathbf{Y}^i(t) \frac{p \exp(-\int_0^t \mu_{02}(s)ds)\mu_{02}(t)}{p \exp(-\int_0^t \mu_{02}(s)ds) + (1-p)} dt = \int_0^x \mathbf{Y}^i(t)\lambda(t,\mu)\mu_{02}(t)dt \quad (3.26)$$

which we take as the definition of $\lambda(t,\mu)$. (We define $\lambda(t,\mu)$ for notational convenience only; it is a function of $\mu_{02}(s)$ for all $s \leq t$.). Hence we interpret $\lambda(x,\mu)\mu_{02}(x)$ as the intensity in the model in Figure 3.3 where the counting process is the observable $\mathbf{N}$. Now sum over all lives ($\mathbf{N}(x) = \sum_{i=1}^M \mathbf{N}^i(x)$ and so on) and define $\mathbf{J}(x) = \mathbf{I}_{\{\mathbf{Y}(x)>0\}}$ as before, then:

$$\hat{\Lambda}(x) = \int_0^x \frac{\mathbf{J}(t)}{\mathbf{Y}(t)} d\mathbf{N}(t) \quad (3.27)$$

is an 'almost' unbiased estimate of $\int_0^x \lambda(t,\mu)\mu_{02}(t)dt$. The obvious procedure is then: estimate $\hat{\Lambda}(x)$, let $\tilde{\Lambda}(x)$ be a smoothed version of it, and estimate $\hat{\mu}_{02}(x)$ by solving:

$$\frac{d\tilde{\Lambda}(x)}{dx} = \lambda(x,\mu)\mu_{02}(x) \quad (3.28)$$

numerically. Alternatively, note that:

$$\hat{\Gamma}(x) = \int_0^x \frac{\mathbf{J}(t)}{\mathbf{Y}(t)\lambda(t,\mu)} d\mathbf{N}(t) \quad (3.29)$$

estimates $\int_0^x \mu_{02}(t)dt$, which we could solve by iteration (rather as Newcombe (1981) did). We may take:

$$\int_0^x \frac{\mathbf{J}(t)(\mathbf{Y}(t) - \Delta\mathbf{N}(t))}{(\mathbf{Y}(t))^3} d\mathbf{N}(t) \qquad \text{and} \qquad \int_0^x \frac{\mathbf{J}(t)(\mathbf{Y}(t) - \Delta\mathbf{N}(t))}{\lambda(x,\mu)^2(\mathbf{Y}(t))^3} d\mathbf{N}(t) \quad (3.30)$$

to estimate $\mathrm{Var}[\hat{\Lambda}(x)]$ and $\mathrm{Var}[\hat{\Gamma}(x)]$, respectively (see Andersen et al. (1993) Section IV.1). The 'Weird Bootstrap' (Section 3.4.1) can be used exactly as before to find confidence intervals for $\mu_{02}(x)$; at each event time we have a risk set containing an unknown true number of lives with a mutation, but by using the same Binomial distribution we correctly re-sample from the observations.

Figure 3.5: $\Lambda(x)$, and six simulated estimates of $\hat{\Lambda}(x)$ with sample size 30, for a hypothetical intensity $\mu_{02}(x) = (-x^4 + 85x^3 - 25x^2) \times 10^{-7}$ and $p = 1/2$, with random censoring.

3.4.3 A Diagnostic Check for the Inclusion of Censored Observations

Let $\Lambda(x)$ be the solution of Equation (3.28), based on the 'true' intensity $\mu_{02}(x)$. The 'true' version of Equation (3.28) can be put in the form:

$$\frac{d}{dx}f(x) + c(x)f(x) = \frac{p-1}{p}c(x) \tag{3.31}$$

where $c(x) = \Lambda'(x)$ and $f(x) = \exp(-\int_0^x \mu_{02}(t)dt)$. Solving this linear ODE, we see that any solution of Equation (3.28) with $f(0) = 1$ and $\Lambda(0) = 0$ satisfies:

$$\exp\left(-\int_0^x \mu_{02}(t)dt\right) = \frac{1}{p}\left(e^{-\Lambda(x)} - (1-p)\right), \tag{3.32}$$

which means that $\Lambda(x)$ cannot exceed $-\log(1-p)$. In practice, $\hat{\Lambda}(x)$ can exceed $-\log(1-p)$, in which case $\hat{\mu}_{02}(x)$ explodes to infinity. If $p = 1/2$, $-\log(1-p)$ is only 0.693. Figure 3.5 shows the true $\Lambda(x)$, and six simulated estimates of $\hat{\Lambda}(x)$ between ages 0–60 (sample size 30, all observed from age 0, with random censoring taking place from age 20, heavier near the younger ages), for $p = 1/2$ and a hypothetical intensity $\mu_{02}(x) = (-x^4 + 85x^3 - 25x^2) \times 10^{-7}$ that reaches about 0.5 at age 60, so

penetrance is close to 100%. Two of the simulated estimates exceed the bound. This is quite predictable at older ages, where the exposure is small; however the exposure may be understated for other reasons. If $\hat{\Lambda}(x)$ exceeds its bound at a rather early age, where exposures are still reasonable, we should suspect that some censored cases have been excluded from the data, perhaps because vital information such as age at censoring has not been recorded, or because only families with large numbers of affected members have been studied (the latter is called 'ascertainment bias' and is a major feature of genetic epidemiology). This may provide a useful diagnostic check.

Intuitively, with 100% penetrance, we expect the proportion of the at-risk individuals surviving, $exp(-\hat{\Lambda}(x))$, to approach $(1-p)$. If $p = 1/2$, we will have the theoretical bound of $\hat{\Lambda}(x)$ as $\log 2$. Note that here we assume 100% penetrance and $p = 1/2$. Under different assumptions, this bound will vary.

Equation (3.32) extends to a heterogeneous model, in which different rates of onset may be associated with different mutations. Suppose there are two mutations, that an 'at-risk' person carries with probabilities p_1 and p_2, respectively ($p_1+p_2 = p$). The associated rates of onset are $\mu^1_{02}(x)$ and $\mu^2_{02}(x)$, respectively. The form of $\Lambda(x)$ is found by modifying Equation (3.25) in the obvious way, and in place of Equation (3.32) we obtain:

$$p_1 \exp\left(-\int_0^x \mu^1_{02}(t)dt\right) + p_2 \exp\left(-\int_0^x \mu^2_{02}(t)dt\right) = \frac{(1-p)^{-1} - e^{\Lambda(x)}}{(1-p)^{-1}e^{\Lambda(x)}}. \qquad (3.33)$$

We remark that the common life-table assumption of an upper limit ω to lifetimes implies that $\mu(x)$ explodes at $x = \omega$. In ordinary survival analysis this is unproblematic, because $\int_0^x \mu(t)dt$ need not be bounded, but here the bound on $\Lambda(x)$ may present a fundamental limit to inference if penetrance is high and data are sparse.

3.4.4 Allowing for Genetic Testing

Genetic testing is easily included by adding transitions into 'tested' states to the model in Figure 3.4, but we use a slightly different approach which is easier to extend later. Figure 3.6 shows a Markov model representing the information gained from a

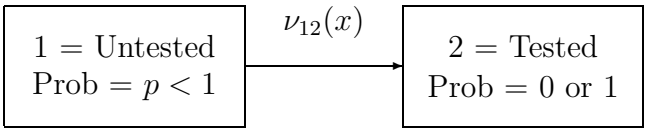

Figure 3.6: A Markov model of transfers between states representing the Mendelian probability (at birth) of having a mutation, and genetic testing.

test. At birth, the Mendelian probability of having a mutation is $p < 1$, but after testing the probability of having a mutation is either 0 or 1. The state space of this model is $\mathcal{P} = \{1, 2\}$, and the state occupied at age x by the i^{th} life is the process $\mathbf{P}^i(x)$. Combining the two models, we work with the state space $\mathcal{S} \times \mathcal{P}$, and the state occupied at age x is the process $(\mathbf{S}^i(x), \mathbf{P}^i(x))$. Our counting processes are now $\mathbf{N}^i_{jk,l}(x)$ and $\mathbf{N}^i_{j,kl}(x)$ representing jumps from state (j, l) to (k, l), and from state (j, k) to (j, l), respectively, and the indicator of presence in state (j, k) is denoted $\mathbf{Y}^i_{j,k}(x)$.

All that we are interested in is that $\mathbf{P}^i(x)$ is observable; we are not interested in the intensity in Figure 3.6, even though it could conceivably depend on $\mu_{02}(x)$ because the act of deciding to be tested may be influenced by a person's family history which depends, in a complicated way, on $\mu_{02}(x)$. As $\mu_{02}(x)$ increases, that is, when there is a higher incidence of AD from individuals with EOAD mutations, we are likely to have a lower rate of genetic testing. This is because the untested population with EOAD mutations, which contributes significantly to the testing rate, would then be depleted at a higher rate. The processes we can observe are $\mathbf{N}^i_1(x) = \mathbf{N}^i_{02,1}(x) + \mathbf{N}^i_{12,1}(x)$ and $\mathbf{N}^i_{02,2}(x)$. Define $\mathbf{Y}^i_1(x) = \mathbf{Y}^i_{0,1}(x) + \mathbf{Y}^i_{1,1}(x)$, and let G^i be the natural filtration generated by the observable processes. Assuming $\mu_{12}(x) \approx 0$, $\mathbf{N}^i_1(x)$ has G^i-compensator $\int_0^x \mathbf{Y}_1{}^i(t)\lambda(t, \mu)\mu_{02}(t)dt$, while $\mathbf{N}^i_{02,2}(x)$ has G^i-compensator $\int_0^x \mathbf{Y}^i_{0,2}(t)\mu_{02}(t)dt$.

Sum over all M lives, dropping the i superscripts, and define $\mathbf{J}_1(x)$ and $\mathbf{J}_{0,2}(x)$ in the same way as before. Then:

$$\hat{\Lambda}(x) = \int_0^x \frac{\mathbf{J}_1(t)}{\mathbf{Y}_1(t)} d\mathbf{N}_1(t) + \int_0^x \frac{\mathbf{J}_{0,2}(t)}{\mathbf{Y}_{0,2}(t)} d\mathbf{N}_{02,2}(t) \tag{3.34}$$

is a Nelson-Aalen-type estimate of $\int_0^x (1+\lambda(t,\mu))\mu_{02}(t)dt$, or:

$$\hat{\Gamma}(x) = \int_0^x \frac{\mathbf{J}_1(t)}{\mathbf{Y}_1(t)\lambda(t,\mu)} d\mathbf{N}_1(t) + \int_0^x \frac{\mathbf{J}_{0,2}(t)}{\mathbf{Y}_{0,2}(t)} d\mathbf{N}_{02,2}(t) \tag{3.35}$$

is a Nelson-Aalen-type estimate of $2\int_0^x \mu_{02}(t)dt$, and we can proceed as before.

By orthogonality of the (compensated) components of a multivariate counting process:

$$\mathrm{Var}[\hat{\Lambda}(x)] \approx \int_0^x \frac{\mathbf{J}_1(t)(\mathbf{Y}_1(t) - \Delta\mathbf{N}_1(t))}{(\mathbf{Y}_1(t))^3} d\mathbf{N}_1(t) + \int_0^x \frac{\mathbf{J}_{0,2}(t)(\mathbf{Y}_{0,2}(t) - \Delta\mathbf{N}_{02,2}(t))}{(\mathbf{Y}_{0,2}(t))^3} d\mathbf{N}_{02,2}(t)$$

(we omit $\mathrm{Var}[\hat{\Gamma}(x)]$). For confidence intervals of $\mu_{02}(x)$, we can use the Weird Bootstrap, simulating onset of EOAD separately among those who have or have not been tested.

In practice, if either risk group is rather small, it might be better to omit it, because Equation (3.35) suggests that any cases of onset in that group will be extremely influential.

3.4.5 Allowing for Unaffected Relatives

Figure 3.7 extends the model of Figure 3.6 to allow for the subject to be born before the carrier status of the at-risk parent or any siblings is known (State 0). (This was called risk group 4 in Section 3.2.2.) As soon as the parent or any sibling is known to have a mutation, the subject's mutation probability at birth is fixed, usually at $p = 0.5$ (State 1). Alternatively, the subject could be tested first. The state space now is $\mathcal{S} \times \mathcal{P}$, where $\mathcal{P} = \{0, 1, 2\}$.

Note that $\nu_{01}(x)$ will be a function of $\mu_{02}(t)$ (in general, at all ages $t \leq x$) since that transition represents onset of EOAD in a relative. However, we need not try to estimate $\nu_{01}(x)$; all that matters is that the transition is observable.

Having no affected relatives is the least tractable part of the model. In previous sections, the observable counting process components, in respect of the i^{th} life, had compensators $\int_0^x \mathbf{Y}_1{}^i(t)\lambda(t,\mu)\mu_{02}(t)dt$ and $\int_0^x \mathbf{Y}_{0,2}^i(t)\mu_{02}(t)dt$ in which the integrands took the general form:

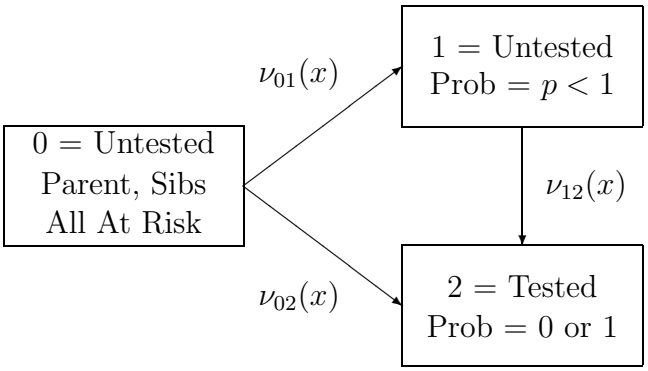

Figure 3.7: A Markov model of transfers between states representing probability at birth of having a mutation. For the parent and siblings to be 'at risk' means it is not known whether or not any of them have a mutation. Transition from State 0 to State 1 represents learning that the parent or a sibling does have a mutation; this fixes p (usually at 1/2).

$$\text{Indicator} \times \text{Function of age and } \mu_{02}(t). \tag{3.37}$$

The key point is that the second term was the same for all lives in the risk group; the compensator depending on the circumstances of the i^{th} life only through the indicator. This is no longer true if the subject has only unaffected parents and siblings, or in general no affected relatives in any number of generations. The compensator can still be put in the form of Equation (3.37), but now the second term will in general be a different function, say $\lambda^i(\mu)$, for each life, depending on the relatives' ages as well. As an estimate we get (in the obvious notation):

$$\hat{\Lambda}(x) = \int_0^x \frac{\mathbf{J}_1(t)}{\mathbf{Y}_1(t)} d\mathbf{N}_1(t) + \int_0^x \frac{\mathbf{J}_{0,2}(t)}{\mathbf{Y}_{0,2}(t)} d\mathbf{N}_{02,2}(t) + \sum_{i=1}^{i=M} \int_0^x \frac{\mathbf{J}_0^i(t)}{\mathbf{Y}_0^i(t)} d\mathbf{N}_0^i(t) \tag{3.38}$$

(we omit $\hat{\Gamma}(x)$) in which the third term is unhelpful, and the Nelson-Aalen methodology breaks down. The simplest solution is to exclude time spent in State 0 of Figure 3.7, and use the estimate of Section 3.4.4, at the cost of not using all of the data. This will not lead to bias: the compensators leading to Equation (3.34) are not changed by anything in this section, so the estimate has the same statistical properties as before. The form of Newcombe's (1981) estimate did allow this

information to be used.

3.4.6 Remarks

(a) The fundamental difference between this approach and the life table method of Newcombe (1981) is in the conditioning. We condition (probabilities of) events that may befall a person age x on information known at age x, not on information acquired later, whereas Newcombe (1981) conditions on the last known risk status at the time of the investigation. Some statistical properties of the Nelson-Aalen-type estimates are available, while those of the life table estimates appear not to be.

(b) This method requires that the time spent in different risk groups can be observed or approximated; therefore, in future, the ages at which genetic tests were taken will be a relevant part of the pedigree.

(c) It might be thought that, in time, complete families will have genetic tests, so that non-carriers can be excluded without bias. However, the uptake of genetic tests is quite low (Meiser and Dunn, 2000; Steinbart et al., 2001; Taylor, 1994), in respect of severe untreatable disorders, so this is only likely to happen once effective treatments are available. Epidemiologists might have to deal with mixtures of risk groups for some time to come.

3.5 Summary

In this chapter, we described how pedigrees can provide data from which rates of onset of various risk groups can be estimated. We then reviewed the life table method used in Newcombe (1981) and derived a modified Nelson-Aalen estimate to estimate the hazard rates of single-gene disorders. Also, we suggested a method to diagnose the presence of ascertainment bias from the Nelson-Aalen estimates calculated from collected pedigree information.

Chapter 4

ESTIMATES OF THE INCIDENCE RATES OF EARLY-ONSET ALZHEIMER'S DISEASE ASSOCIATED WITH THE PSEN-1 GENE

4.1 Estimates of Incidence Rates

In Chapter 3, we derived a modified Nelson-Aalen estimate to estimate the hazard rates of single-gene disorders. In this chapter, we will apply this estimate to the pedigree data gathered from available literature to estimate the incidence rates and the mortality rates after onset of EOAD associated with the PSEN-1 gene.

4.1.1 Choice of Estimator

In practically all of the families with history of EOAD studied, some genetic tests have been carried out, suggesting Equations (3.34) or (3.35) as estimates. No information is given on when tests were taken, but we can assume that all tests were very recent, so almost no time has been spent in the tested state. Therefore, we

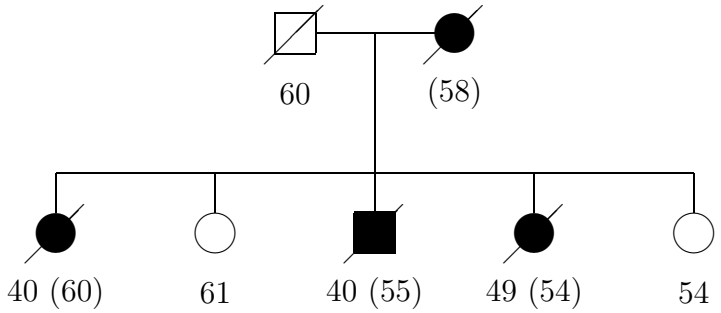

Figure 4.8: Pedigree of the family with the Leu282Arg PSEN-1 mutation (Aldudo et al., 1998), see Appendix A. Squares are males, circles are females, and a slash denotes death. Affected individuals are shown as filled squares/circles. The age at onset or oldest observed age free of AD is shown, and the age at death is given in brackets. By convention siblings are listed left-to-right in birth order.

can drop the second terms in Equation (3.34) or Equation (3.35). Should genetic testing become more widespread, the second term in Equation (3.34) or Equation (3.35) will begin to contribute.

4.1.2 Approximations Used With Pedigrees

First, we have to discard any incomplete sibships in pedigrees, since only complete sibships can be regarded as random samples of mutated and wild-type alleles, based on the appropriate Mendelian probabilities. Using this approach may raise the problem of ignoring any ascertainment bias present in the data. Most published pedigrees give complete sibships in respect of more recent generations but not older generations.

We need two items of information, in respect of each life included; unfortunately neither is always straightforward. They are:

(a) The age at which each person entered the risk group (entered State (0,1) or (1,1) in the model, which being unknown) which is their age when their parent or first sibling contracted EOAD. (In fact, we found only one example in which a sibling contracted EOAD before the parent (who had died young) but this was excluded for other reasons.) This, however, is not usually known from the pedigree, because we do not know the parent's age when each of their children

was born. This datum may well exist in the full pedigree, but it is not usually published.

(b) The age at onset of EOAD, or the age at censoring in other cases. The problem here is that the ages at censoring or death of unaffected siblings are often not given, even when complete sibships are shown.

Here, we explain the approximations we have used, making all possible use of the information that is in the pedigrees. We shall see that the effect of (a) above should be small, but that (b) is more serious.

First, we assume that the affected parent's age at the birth of his or her children is 30 years, on average. Given the parent's age at onset, this allows us to approximate the ages at which their children entered the $p = 1/2$ risk group. For example, Figure 4.8 shows a pedigree of a family with the Leu282Arg PSEN-1 mutation (Aldudo et al., 1998), see Appendix A. The average age of onset in this family is 43 years (Aldudo et al., 1998). If the average age at childbirth is 30 years, then the average age of a child when their parent suffers onset is 13 years. We use this (in this pedigree) whenever the exact age is unknown, or cannot be better approximated. We proceed as follows:

(a) The mother is excluded since her age at onset is unknown and she may not be part of a complete sibship.

(b) We assume the first, third and fourth children were 13 when the mother suffered onset.

(c) We can do slightly better with the two surviving children. Their average age is about 58 years, so we suppose their mother suffered onset $58 - (43 - 30) = 45$ years ago. Then the second child was 16 and the fifth child 9 at that time.

Despite some sweeping assumptions, this approach is not likely to affect the estimation significantly. The reason is that ages at onset are roughly in the range 30–60 years. Unless child-bearing extends very far on either side of age 30, there should be few cases in which the true age on entering the relevant risk group is within this range. Therefore:

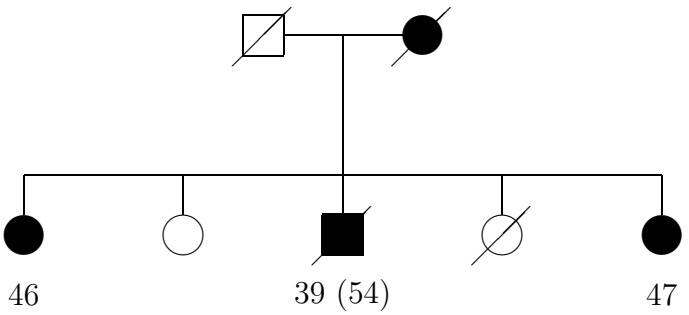

Figure 4.9: A hypothetical sibship in which the ages of unaffected lives are not known. The oldest sibling is known to be age 59.

(a) most errors will occur at ages with no, or few, observed cases of onset (so it might be unsuitable for use with diseases that occur before age 20, say); and

(b) any errors will tend to occur at ages where the exposures are greatest, and therefore their effect will be minimal.

Next, if the ages of unaffected siblings are not known, we use the convention that they are listed in birth order to estimate highest and lowest ages at which censoring might have occurred. Estimates based on these extremes then define a feasible region for $\hat{\mu}_{02}(x)$. For example, consider the hypothetical sibship shown in Figure 4.9. There are two unaffected sisters, one still alive.

(a) The older must be at least 55 (say), since her younger brother died at age 54, but she cannot be older than about 58, since her older sister is alive at age 59.

(b) The younger could have died in infancy, so may never have entered the $p = 1/2$ risk group. At the other extreme, she could be just about two years younger than her unaffected sister, and have died recently. So the highest and lowest possible ages at censoring are about 56 and 0 respectively.

In a few cases, extra information (such as the age at onset of an affected child of a sibling) helps to refine these bounds, and we are not interested in the exact age at censoring if it is above 60 anyway. We had to exclude many sibships for which even these crude calculations could not be made. Figures 4.10, 4.11 and 4.12 show the approximate maximum and minimum exposure times in the $p = 1/2$ risk group,

for males and females combined and separately. Note that the combined samples include some siblings whose sex was not identified in the pedigrees.

The need to use approximate bounds on the exposures is a significant weakness of this analysis, but one that could only be overcome with access to original pedigree data. We suggest that this is an important area for consideration in future research.

4.1.3 Smoothing Method

We have six samples: males and females combined and separately, each with minimum and maximum estimated exposures in the $p = 1/2$ risk group. We estimate $\hat{\Lambda}(x)$ for each, then smooth them using a biweight-kernel method, and Equation (3.28) is then solved numerically. (Smoothing is also helpful because the ages of onset show clustering at some quinquennial ages, suggesting approximations in the data.) Kernel smoothing is natural since it exploits the stochastic integral framework of Nelson-Aalen estimators, and it is quite robust to the choice of kernel. See Andersen et al. (1993) for details, including choice of bandwidth and treatment of extreme ages.

A kernel-smoothed estimate $\tilde{\Lambda}(x)$ with bandwidth b is a weighted average of $\hat{\Lambda}(y)$ for $y \in [x - b, x + b]$. The weights are provided by the kernel, which is just a symmetric function on $[-b, b]$ integrating to 1. The biweight kernel is given on $[-1, 1]$ by:

$$K(t) = \frac{15}{16}(1 - t^2)^2 \tag{4.39}$$

and it is zero outside $[-1, 1]$ It gives progressively heavier weight to points close to 0 in the interval $[-1, 1]$. We scale the kernel by the bandwidth b, so that:

$$\tilde{\Lambda}(x) = \frac{1}{b} \int_{-\infty}^{\infty} K\left(\frac{x - u}{b}\right) \hat{\Lambda}(u) du. \tag{4.40}$$

Let x_L and x_U be the extreme ages. For $x_L < x < x_L + b$, we use an asymmetric kernel, K_q(t). Letting $q = x/b$, then on $[-1, q]$ we have $K_q(t) = K(t)(\alpha + \beta t)$, where

$$\alpha = \frac{64(8 - 24q + 48q^2 - 45q^3 + 15q^4)}{(1 + q)^5(81 - 168q + 126q^2 - 40q^3 + 5q^4)} \tag{4.41}$$

Figure 4.10: Estimated exposure times for all persons in the $p = 1/2$ risk group. Each line represents the time spent in the risk group by a single individual. The estimated maximum exposure times are on the left (276 lives), and minimum exposure times on the right (264 lives). Exposures ending with onset of EOAD are indicated by a triangle.

Figure 4.11: Estimated exposure times for men, maximum exposure times are on the left (72 lives), and minimum exposure times on the right (64 lives). Exposures ending with onset of EOAD are indicated by a triangle.

Figure 4.12: Estimated exposure times for women, maximum exposure times are on the left (81 lives), and minimum exposure times on the right (79 lives). Exposures ending with onset of EOAD are indicated by a triangle.

Table 4.5: Optimal bandwidths for biweight kernel smoothing.

	Maximum Exposures			Minimum Exposures		
Sex	No. of Lives	τ_U	Optimal Bandwidth	No. of Lives	τ_U	Optimal Bandwidth
Combined	276	60	4.5 years	264	60	4.5 years
Male	72	56	2.3 years	64	56	2.2 years
Female	81	56	2.2 years	79	56	2.3 years

and:

$$\beta = \frac{1120(1-q)^3}{(1+q)^5(81-168q+126q^2-40q^3+5q^4)}. \tag{4.42}$$

For $x_U - b < x < x_U$, we let $q = (x_U - x)/b$ and replace t with $-t$ in $K_q(t)$. Note that we are not interested in ages over about 60, since later onset is probably not EOAD, but the data include cases of onset at higher ages; therefore the adjustment at the upper age limit does not affect the results reported here.

The bandwidth b is chosen to minimise the mean integrated squared error (MISE) of $\lambda(x,\mu)\mu_{02}(x)$ over a suitable range τ_L to τ_U (we use $\tau_U < x_U$ since we are not interested in ages over about 60). For convenience write $\lambda(x,\mu)\mu_{02}(x) = \alpha(x)$. We have:

$$\text{MISE}(b) = \text{E}\left[\int_{\tau_L}^{\tau_U} [\hat{\alpha}(u) - \alpha(u)]^2 du\right]. \tag{4.43}$$

Klein and Moeschberger (1997) show that it suffices to minimise

$$G(b) = \sum_{i=1}^{J-1} (\frac{u_{i+1}-u_i}{2})[\tilde{\alpha}^2(u_i) + \tilde{\alpha}^2(u_{i+1})] - 2b^{-1}\left[\sum_{i\neq j} K(\frac{t_i - t_j}{b})\Delta\hat{\Lambda}(t_i)\Delta\hat{\Lambda}(t_j)\right] \tag{4.44}$$

where the first sum is evaluated at J suitable points $\tau_L = u_1 < u_2 < ... < u_J = \tau_U$, and the second sum at the jump-times of $\hat{\Lambda}(x)$. Figure 4.13 shows $G(b)$ for the six samples, and Table 4.5 shows the results.

Figure 4.14 shows the the unsmoothed $\hat{\Lambda}(x)$ and smoothed $\tilde{\Lambda}(x)$ for men and

Figure 4.13: Estimated risk function, G(b), for use in determining the optimal bandwidth for the PSEN-1 mutation data.

women, combined and separately, using the maximum and minimum estimated exposures for each. In all cases, $\hat{\Lambda}(x)$ exceeds its theoretical bound of $\log 2$ (Section 3.4.3) by about age 50, so we shall be unable to estimate $\mu_{02}(x)$ beyond that age.

4.1.4 Bootstrap Confidence Intervals

For approximate confidence limits, we generate 500 random samples of onset based on the observed exposures and onsets at each age (the 'Weird Bootstrap', see Section 3.4.1). For each of these samples, the intensity is calculated as before, and at each age the 25^{th} and 475^{th} samples give an approximate 95% confidence interval for $\hat{\mu}_x^{02}$.

4.1.5 Results

Figure 4.15 shows the resulting estimates of $\mu_{02}(x)$. This has several features:

- Although estimates are obtained up to about age 50 (when $\hat{\Lambda}(x)$ exceeds $\log 2$) their behaviour changes at about age 45.
- The confidence limits are limited to shorter age ranges than the estimates,

Figure 4.14: Modified Nelson-Aalen estimates of $\int_0^x \lambda(t,\mu)\mu_{02}(t)dt$ for all persons, men and women, in families with PSEN-1 mutations. The smoothed versions are shown as dashed lines. Note different scales.

Figure 4.15: Estimated incidence rates of EOAD among men and women with PSEN-1 mutations, combined and separately, with approximate 95% confidence limits. Note different scales.

because in each case, among the 500 simulated experiences there were some in which $\hat{\Lambda}(x)$ exceeded $\log 2$ at a lower age than in the actual sample.

- The estimates in respect of males and females show some unevenness that may be evidence of clustering at certain ages, but those for the combined sample seem to be well-smoothed.

- The general features of all the estimates are the same; unevenness of the smaller samples aside, $\mu_{02}(x)$ reaches about 0.1–0.2 by age 45.

For practical use, it would probably be best not to use these intensities directly, but to use them as a guide in choosing some simpler, smoother function that may be extrapolated to age 60 (say). We do this in Section 4.2.

Probabilities of survival free of EOAD ($\exp(-\int_0^x \mu_{02}(t)dt)$) are shown in Figure 4.16, with bootstrapped 95% confidence limits. What is perhaps most significant is that in all cases, these survival probabilities are very low (< 0.5) by about age 45, so our inability to obtain good estimates beyond that age may be of little practical significance. That is, of course, a consequence of the high penetrance of PSEN-1 mutations.

4.1.6 Possible Ascertainment Bias

It may be be more likely for families with larger numbers of members affected with EOAD associated with the PSEN-1 gene mutations to be ascertained compared with families with smaller numbers of affected members. At one extreme, it would be very unlikely for families carrying PSEN-1 gene mutations, but without any of the members affected, to be ascertained. This will introduce ascertainment bias into the pedigree data from which the incidence rates of EOAD are estimated.

The estimates shown in Figure 4.15 can be obtained only for ages up to about 50, after which, $\hat{\mu}_{02}(x)$ explodes to infinity as $\hat{\Lambda}(x)$ can exceed its bound $-\log(1-p)$ (Section 3.4.3). From Figure 4.10, we see that the exposures are still reasonable at these ages (> 50 for all persons in the $p = 1/2$ risk group). One possibility is that $p > 1/2$ in the ascertained sample, because of ascertainment bias, so our assumed

Figure 4.16: Probabilities of surviving free of EOAD among persons with PSEN-1 mutations, with approximate 95% confidence limits.

bound of $\log 2$ is in fact too low. A possible subject of future research would be the estimation of p and hence a correction for ascertainment bias.

4.2 Extrapolating Rates of Onset of EOAD Associated with PSEN-1 Mutations

Figure 4.15 shows the estimated rates of onset in respect of known PSEN-1 mutation carriers, with minimum and maximum possible exposures. Due to the possibility of ascertainment bias as mentioned in Section 3.4.3, our estimated rates of onset are likely to be higher than the actual rates. Hence for application, we use the lower estimate. We note, also, that the ABI, in making applications to GAIC to be allowed to use certain genetic test results, adopted the practice of underestimating rates of onset when in doubt (Daykin et al., 2003).

The lower estimate has to be smoothed and extrapolated to age 60. We can ignore the fact that the incidence rates will become infinitely high for ages beyond 60 by extrapolating, because the age range applicable in the insurance market is below 60 years. Then, it is necessary to consider the strong possibility that these are too high, because they are based on families selected for high incidence of EOAD, and are not based on prospective population studies. Other studies into AD (Macdonald and Pritchard, 2000, 2001) and breast and ovarian cancer (Macdonald et al., 2003a,b) reduced the observed rates of onset by 50% and 75% to allow for this, and we will do likewise here.

Given the limited information available, we carried out the smoothing and extrapolation by fitting the following piecewise linear function (with quadratic smoothing at the corners) to the estimate, fitting ages 20–45 and extrapolating to age 60:

Figure 4.17: Estimated and smoothed/extrapolated incidence rates (100%, 50% and 25% of those estimated from the data with maximum possible exposures) of EOAD associated with PSEN-1 mutations.

$$\mu_x^{fitted} = \begin{cases} 0.0 & \text{if } x < 20.0, \\ f1(x) & \text{if } 20.0 \leq x < 28.0, \\ (29.0 - x)f1(x) + (x - 28.0)f2(x) & \text{if } 28.0 \leq x < 29.0, \\ f2(x) & \text{if } 29.0 \leq x < 38.0, \\ (39.0 - x)f2(x) + (x - 38.0)f3(x) & \text{if } 38.0 \leq x < 39.0, \\ f3(x) & \text{if } x \geq 39.0, \end{cases} \tag{4.45}$$

where $f1 = -0.0112324 + 0.000553792x$, $f2 = -0.205248 + 0.00735054x$, and $f3 = -0.602651 + 0.0177141x$. Note that the results are not too sensitive to the extrapolation to age 60; rates of onset are so high up to age 46 that about 80% of mutation carriers will have EOAD by then (Section 4.1.5). It is these fitted rates of onset that we will reduce by 50% and 75% as a sensitivity analysis for possible ascertainment bias. Figure 4.17 shows the estimated and smoothed/extrapolated incidence rates (of those estimated from the data with maximum possible exposures) of EOAD associated with PSEN-1 mutations.

4.3 Estimating Mortality Rates After Onset of EOAD

Survival data are available from the same sources as were used to estimate rates of onset, namely published pedigrees. These estimated rates are based only on PSEN-1 families. There is evidence that survival rates do depend on the gene in which the mutation occurs. Carriers of PSEN-1 mutations follow a much more aggressive course of AD after onset, with average disease duration of 4.5 years, than do persons with APP mutations (12.5 years), PSEN-2 mutations (11.0 years) or with sporadic AD (8.8 years) (Russo et al., 2000; Bird et al., 1996).

Age at death after onset is one of the most carefully reported items of information in any pedigree, in the sense that it is rarely missing, though it might often be hard to establish accurately. The problems described in Section 4.1.2, of dealing with incomplete reporting of lifetimes censored before onset are here mostly absent, and the pedigree data lead to a straightforward survival analysis. The main question is whether mortality rates after onset of EOAD depend on age, or duration since onset, or both.

We divided the survival data into three groups depending on age at onset (n = number of cases of EOAD): 20–39 ($n = 64$), 40–49 ($n = 68$) and 50–59 ($n = 43$): we have an enlarged first group as the number of cases of onset at ages 20–29 was very small. Nelson-Aalen estimates of the integrated hazards are shown in Figure 4.18. We compared duration-dependent survival curves for each group (Peto-Wilcoxon test, see Venables and Ripley (1999)). Table 4.6 shows there is no significant difference in survival between the 20–39 and the 40–49 age-at-onset groups, while there does appear to be some difference between the 50–60 age-at-onset group and the other two.

We decided to use ages at onset 20–49 only, with mortality rates depending on duration. Survival following onset at ages over 50 is not very important for this study; for CI insurance it is irrelevant, and for life insurance not extending beyond age 60 it is relatively insignificant because of the high penetrance of PSEN-1 mutations.

Figure 4.18: Nelson-Aalen estimates of the duration-dependent integrated hazard of death after onset of EOAD, and approximate 95% confidence intervals, for persons with PSEN-1 mutations. Ages at onset 20–39, 40–49, 50–60 and 20–49. The graduated estimate for AAO 20–49 is also shown.

Table 4.6: Peto-Wilcoxon test comparing the survival curves of the three different age-at-onset groups.

Groups Compared (Age at Onset in Years)	P-value
20–39 and 40–49	0.188
40–49 and 50–60	0.0329
20–39 and 50–60	0.000139
20–39, 40–49 and 50–60	0.00175

Smith (1998) presented a model of Huntington's disease (HD) with duration-dependent rates of mortality after onset of HD, and the ABI used this as the basis of a submission to the Genetics and Insurance Committee in the U.K. to be allowed to use DNA-based test results for HD in life insurance underwriting. Although this application succeeded in the first instance, Wilkie (2000) pointed out the anomaly that mortality could be assumed to fall substantially following onset of HD, because the duration-related mortality rates were substantially lower than the normal age-related rates of mortality at certain ages. Here, we avoid this anomaly by assuming that mortality after onset of EOAD is no better than normal age-related population mortality.

Figure 4.19 compares the Nelson-Aalen estimates of the duration-dependent integrated hazard of death after onset of EOAD with the cumulative population mortality rates from the English Life Tables No. 15 (ELT15). We note that the cumulative ELT15 rates for males at ages 20, 30 and 40 years are much lower than the Nelson-Aalen estimates from the combined 20–49 age-at-onset group. This is not so for the 50–60 age-at-onset groups where the cumulative ELT15 rates for males at ages 50, 55 and 60 years exceed those of the Nelson-Aalen estimates at earlier duration.

The distribution function of the following Weibull function of duration d was a good fit (weighted least squares) to the integrated intensity for AAO 20–49:

$$\mu_d^* = 0.012250264\, d^{1.37601}\, \exp\left(-0.00168128 d^{2.37601}\right). \tag{4.46}$$

The fitted function is also shown in Figure 4.18. For reasons given above, in the model we use the intensity $\max[\mu_{x+t}^{ELT15}, \mu_d^*]$.

4.4 Estimating Mutation Frequencies

In a population-based prevalence study of EOAD in the French city of Rouen, with an at-risk population of 94,593, Campion et al. (1999) estimated the prevalence of familial EOAD at 25.4 per 100,000 at risk. Older prevalence studies by Kokmen et al. (1989); Schoenberg et al. (1985); Sulkava et al. (1985) reported prevalences per 100,000 at-risk individuals of 26.9, 45.2 and 18.2 respectively. These figures are

Figure 4.19: Comparing the Nelson-Aalen estimates of the duration-dependent integrated hazard of death after onset of EOAD with the cumulative population mortality rates from the English Life Tables No. 15 (ELT15). We use male cumulative mortality rates for comparison as these are higher than the female cumulative mortality rates.

reasonably consistent with Campion et al. (1999).

Of the 184 affected subjects tested for mutations by Campion et al. (1999), 14.7% carried APP gene mutations while 58.8% had PSEN-1 gene mutations.

Given these figures from Campion et al. (1999), we estimate the mutation frequency for the PSEN-1 gene at 15 per 100,000, which is close to the frequency of 1 in 10,000 used by Cruts et al. (1995) in their linkage analysis.

4.5 Summary

In this chapter, estimates of rates of onset of EOAD associated with PSEN-1 mutations were obtained. They had the following features:

(a) A non-parametric approach was used, based on a Nelson-Aalen estimate. The complicating factor was that the risk set at any given age (healthy persons at risk of contracting EOAD) is a mixture of mutation carriers and non-carriers; the classical Nelson-Aalen estimate gives the integrated intensity of onset in respect of this mixed group, from which the rate of onset among mutation carriers could be found numerically.

(b) Rates of onset for males and females separately were obtained, but were of much poorer quality than those for males and females combined. We use only the latter here.

(c) There is an intrinsic bound to the integrated intensity of onset of a genetic disorder such as EOAD in respect of a mixed group of mutation carriers and non-carriers. This is because non-carriers will never get EOAD, so the lifetime probability of EOAD is less than 1. If μ^*_x is that intensity, $\exp(-\int_0^x \mu^*_t dt) > 0$ at the highest age x, so $\int_0^x \mu^*_t dt$ must be bounded. For a rare dominantly inherited condition like EOAD, the bound is $\log 2$. However, the Nelson-Aalen estimate can exceed that bound, in which case the rate of onset in respect of mutation carriers explodes to infinity. This is made much more likely if there is *ascertainment bias*, meaning that families are selected for study because they have large numbers of cases of EOAD. This is almost certain to be the

case for these estimates, and the $\log 2$ bound was exceeded at about age 50; the rates of onset for mutation carriers were unreliable beyond about age 46.

(d) Some assumptions about the numbers exposed to risk had to be made because of missing data; therefore, two estimates were given, one using the minimum possible exposures and another using the maximum possible exposures. Because ascertainment bias is very likely, we will use the lower estimate, based on maximum possible exposures.

(e) We need to adjust the estimated incidence rates obtained in this chapter to allow for the ascertainment bias discussed in Section 4.1.6. The fitted rates of onset are reduced by 50% and 75% as a sensitivity test for possible ascertainment bias in Section 4.2.

Chapter 5

EARLY-ONSET ALZHEIMER'S DISEASE AND CRITICAL ILLNESS INSURANCE

5.1 Introduction

This chapter and the next form parts of a joint work submitted for publication (Gui and Macdonald, 2002a, 2002b).

5.1.1 Insurance Questions

We can pose quantitative questions from the points of view of an applicant for insurance and of the insurer:

(a) If an insurer is allowed to use genetic information, what would be the increased premium offered to a person with a known mutation, or just with a family history?

(b) If an insurer is not allowed to use genetic information, what might be the costs of adverse selection, if persons possessing knowledge of their own increased risk were more likely to buy insurance?

Both of these can be approached using simple multiple-state models. The first is slightly easier, since it does not involve mutation frequencies but only the rates of

onset and survival of persons *known* to be at risk. The second does need estimates of mutation frequencies, which determine the size of the 'pool' of potential adverse selectors. It is also necessary to include in the model the various underwriting classes that are in use, that may in part be determined by any moratorium on using genetic information.

5.1.2 Genetic Testing for EOAD

Predictive test and diagnostic tests for PSEN-1 mutations are available in the United Kingdom for the PSEN-1 but not for the PSEN-2 and APP genes (European Directory of DNA Diagnostic Laboratories). Population screening for APP or PSEN mutations may not be appropriate though predictive and diagnostic genetic testing for these highly penetrant mutations may be recommended for individuals from families with a clear autosomal dominant pattern of inheritance, particularly those with a family history of early onset symptoms (Emilien et al., 2000; Finckh et al., 2000c). Rogaeva et al. (2001) found a high frequency of PSEN-1 mutations in a referral-based study of 372 AD patients and 42 asymptomatic persons with a strong family history of AD, suggesting that screening in these families should be highly cost effective. Because EOAD is rare and dominantly inherited, genetic testing is unlikely to be recommended to aid diagnosis of the sporadic form of AD. The test may improve the accuracy of diagnosis slightly, but a positive test result does not contribute significantly to the treatment for the patient. Given the widespread use of moratoria on insurers making use of genetic test results, family histories of EOAD will remain important in the future; the advent of DNA-based tests will not lessen their relevance.

5.2 Premium Ratings for Critical Illness Insurance

5.2.1 Critical Illness Insurance

Critical illness (CI) insurance contracts pay a sum assured on contracting any of a specified list of serious conditions. The annual premium is payable continuously until a claim is made, whereupon the sum assured is paid out to the insured and the policy ceases. It is often sold as a rider to a life insurance contract, known as 'accelerated benefits'. It is usual to stipulate that the insured person must survive for at least 28 days after the 'onset' of the condition (if that can be meaningfully identified) so that there is a clear distinction between critical illness and death. Figure 5.20 shows a discrete-state, continuous time, Markov model of EOAD and stand alone CI insurance. We assume that a CI claim is made on onset. It is possible that the claim is delayed, in which case our premium ratings will be on the high side.

5.2.2 Transition Intensities in the Critical Illness Insurance Model

For onset of EOAD associated with PSEN-1 mutations, we use the estimates described in Section 4.5.

There is no industry standard model for CI insurance. We use the model from Gutiérrez and Macdonald (2003), described briefly in Appendix G . This is quite similar to the models used by Dinani et al. (2000); Macdonald et al. (2003b) which so far as we know are the only other published models. Note that all of our results are based on relative rather than absolute CI insurance costs, so they are quite insensitive to the details of the basic CI insurance model.

5.2.3 Differential Equations Associated with the Model

Given the applicant's age and knowledge of whether the applicant is a PSEN-1 mutation carrier, Norberg's equations (Norberg, 1995) enable the calculation of any

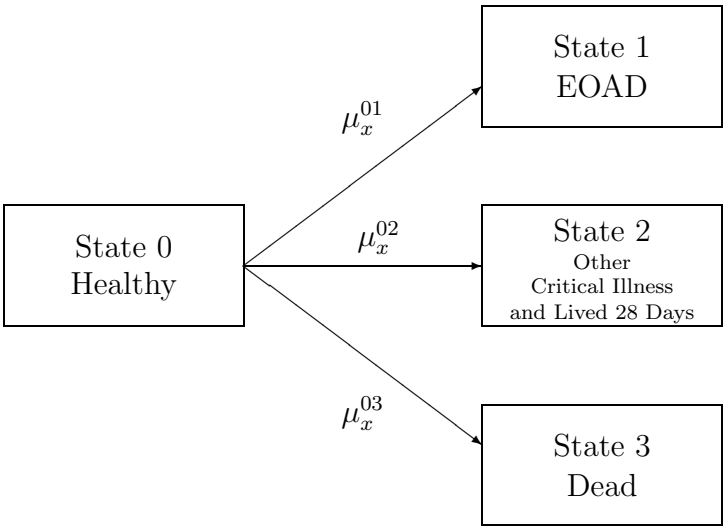

Figure 5.20: A model for EOAD and critical illness insurance.

moments of the present value of:

(a) a benefit payable on transition into any of the states in the model of Figure 5.20; or

(a) a premium payable continuously while in an insured state.

We first need to solve the Kolmogorov's forward equations for ${}_tp_x^{jk}$, the occupancy probabilities that a person in state j at age x will be in state k at age $x+t$:

$$\frac{d}{dt}{}_tp_x^{jk} = \sum_{l\neq k} {}_tp_x^{jl}\mu_{x+t}^{lk} - \sum_{l\neq k} {}_tp_x^{jk}\mu_{x+t}^{kl} \tag{5.47}$$

where μ_x^{jk} is the transition intensity between distinct states j and k in the model of Figure 5.20.

We now add insurance cash-flows to the model in Figure 5.20. Cash-flows received by the insurer are positive by convention. For the first moments, Norberg's equations reduce to Thiele's equations:

$$\frac{d}{dt}{}_tV_x^j = \delta_t\ {}_tV_x^j + \rho_{x+t}^j - \sum_{k\neq j} \mu_{x+t}^{jk}(b_{x+t}^{jk} + {}_tV_x^k - {}_tV_x^j) \tag{5.48}$$

where δ is the force of interest at time t, ρ_x^j is the premium rate payable continuously to the insurer per annum while in state j at age x, b_x^{jk} is the lump sum benefit paid to the policy holder insured on transition from state j to state k at age x, and ${}_tV_x^j$ is the statewise prospective reserve while in state j at age $x+t$.

The reserve at expiry is zero in all states. The expected present values (EPVs) of CI benefits and premiums can be computed by solving Thiele's equations (5.48) backwards. Hence we are able to calculate the level net premium.

5.2.4 Premiums Based on Known PSEN-1 Mutations

Table 5.7 shows level premiums, payable continuously, for level CI cover for female and male PSEN-1 mutation carriers. The premiums are expressed as percentages of the 'standard' premium rate, taken to be that paid by non-mutation carriers. The premiums are shown with estimated EOAD onset intensities of 100%, 50% and 25% of those fitted to the data. We used a Runge-Kutta algorithm with step-size 0.0005 years to solve Thiele's equations (5.48) for the expected present values (EPVs) of benefits and premiums, with a force of interest of $\delta = 0.05$ per annum.

(a) Premiums for cover expiring at age 30 appear to be high, especially for males, but these may be unreliable as they are based on a tiny number of cases, and measured against very low standard CI premiums at these ages.

(b) At practically all ages and terms, and even with the rates of onset reduced to 25% of those observed, the premiums would exceed the limits that currently might be offered in practice (about 300% of standard rates). The highest is over 4,000% of the standard premium. The only possible exception might be females age 20, for a term of 10 years, given the lowest rates of onset.

Table 5.7: Level net premiums for level CI cover with known PSEN-1 mutations, as a percentage of the standard level premiums. Rates of onset of EOAD are 100%, 50% and 25% of those observed.

EOAD Onset Rate at	Entry Age	Females Term (Years) 10 %	20 %	30 %	40 %	Males Term (Years) 10 %	20 %	30 %	40 %
	20	635.23	2,040.43	1,958.24	1,375.30	1,020.61	2,910.53	2,294.84	1,372.66
100%	30	3,251.01	2,896.21	2,040.24		4,263.13	3,175.89	1,935.66	
	40	4,177.72	3,022.60			4,158.54	2,660.51		
	50	3,714.51				2,985.17			
	20	368.66	1,153.03	1,319.29	1,020.22	562.10	1,625.21	1,539.38	1,014.91
50%	30	1,728.84	1,766.02	1,354.03		2,252.02	1,931.88	1,282.30	
	40	2,273.90	1,776.91			2,263.39	1,565.30		
	50	1,994.18				1,610.60			
	20	234.59	649.11	817.03	708.71	331.50	895.33	946.23	703.28
25%	30	928.29	1,024.22	865.97		1,194.34	1,116.02	820.13	
	40	1,226.00	1,032.14			1,220.50	913.02		
	50	1,076.98				878.81			

5.2.5 Premiums Based on Family History of EOAD

Table 5.8 shows level premiums for level CI cover based on a family history of EOAD *known to be associated with PSEN-1 mutations*, where the applicant for insurance has not had a genetic test, or has but the result is not known by the insurer. Here 'family history' means that one of the applicant's parents or siblings is known to have had EOAD, or (less likely in practice) is known to have had a genetic test that shows a PSEN-1 mutation to be present. Because EOAD is very rare, we can assume that any cases that arise in families that carry PSEN-1 mutations have that as their cause. Because PSEN-1 mutations are rare and dominantly inherited, we can assume each child of affected parents carries the mutation with probability 1/2. The EPV of the CI benefit, given family history only, is a weighted average of the EPVs of the benefit in respect of healthy carriers and non-carriers, the weights being the probabilities of surviving in state 0 of the model in Figure 5.20 until the inception of the policy. These probabilities are found by solving the Kolmogorov equations (5.47) from age 0, also using a Runge-Kutta algorithm with step-size 0.0005 years. The EPV of a £1 per annum level premium is found similarly, and hence the rate of premium. The figures in Table 5.8 are percentages of the 'standard' premium rates.

(a) For CI cover expiring at age 30, if rates of onset were 25% of those observed, an extra premium of +50% to +100% might be offered, and if rates of onset were 50% of those observed, about double these ratings might be offered.

(b) For CI cover commencing at age 50, extra premiums of less than +100% could be offered, or less than +50% assuming the lower rate of onset. This is because an at-risk person who is healthy at age 50 has only a small probability of being a mutation carrier.

(c) At all other ages and terms, extra premiums would exceed +200% and in some cases +1,000%.

Table 5.8: Level net premiums for level CI cover for persons with family histories of EOAD known to be associated with PSEN-1 mutations, as a percentage of the standard level premiums. Rates of onset of EOAD are 100%, 50% and 25% of those observed.

EOAD Onset Rate at	Entry Age	Females Term (Years) 10 %	20 %	30 %	40 %	Males Term (Years) 10 %	20 %	30 %	40 %
	20	366.60	1,033.72	935.00	643.69	558.56	1,452.48	1,086.63	643.43
100%	30	1,518.81	1,181.50	769.20		1,974.59	1,290.28	734.97	
	40	1,066.80	604.68			1,062.96	544.88		
	50	197.65				178.56			
	20	234.07	616.09	672.47	513.82	330.61	847.52	775.97	511.94
50%	30	866.04	817.11	594.35		1,112.11	888.74	567.09	
	40	728.62	488.06			725.82	440.54		
	50	178.05				162.54			
	20	167.23	371.76	446.37	385.42	215.64	493.63	508.83	383.12
25%	30	498.28	523.65	431.65		626.21	565.81	412.23	
	40	463.23	363.14			461.53	330.09		
	50	152.94				142.31			

5.3 The Potential Cost of Adverse Selection in Critical Illness Insurance

5.3.1 Genetic Information, Moratoria and Adverse Selection

Adverse selection may arise if persons who know they are at increased risk because they have some genetic information are more likely to buy insurance and need not share that information with the insurer. In the late 1990s, most attention was directed towards DNA-based genetic tests, because it was their novelty that had brought the question of genetics and insurance out into the open, but now 'genetic information' may be interpreted more widely to include:

(a) DNA-based test results;

(b) tests for gene products altered by mutated genes; or

(c) family histories of Mendelian or complex disorders.

Governments may impose moratoria or outright bans on insurers using some or all of these. For example, in the U.K. there is currently an agreed moratorium on the use of DNA-based test results, while in Sweden there is a moratorium covering family history as well. The potential costs of adverse selection will depend on the type of insurance, the nature of the market for that insurance and the form of moratorium imposed, as well as on the details of each particular genetic disorder.

Figure 5.21 shows a Markov model for the life history of a person in the i^{th} of M subpopulations (to be defined shortly). It represents all the relevant events in a CI insurance market; in fact it is a model of the insurance market and not just of a single insurance contract, unlike the model in Figure 5.20.

Everyone in the i^{th} subpopulation starts in state $i0$, not insured and not tested, and follows one of the possible life history paths:

(a) proceeds into state $i1$, becoming insured though remaining untested, then either goes into the CI event state $i4$ with onset of one of the diseases under the CI policy, or dies (state $i5$);

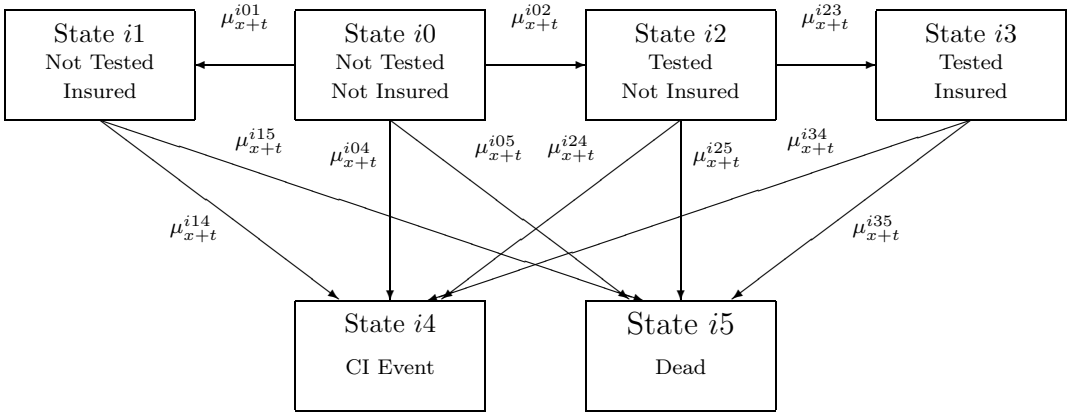

Figure 5.21: A Markov model of genetic testing, insurance purchase and CI insurance events for a person in the i^{th} risk subpopulation.

(b) takes up a genetic test (moves to state $i2$) while still not insured, then

(i) either goes into the CI event state $i4$ with onset of one of the diseases under the CI policy, or dies (state $i5$); or

(ii) moves into state $i3$ (becoming insured) from state $i2$ then, either goes into the CI event state $i4$ with onset of one of the diseases under the CI policy, or dies (state $i5$).

We use the approach of Macdonald (2003b) and Gutiérrez and Macdonald (2003). The M subpopulations are defined by the presence or absence of PSEN-1 mutations, and the presence or absence of a family history of EOAD (we ignore family histories that are due to APP or PSEN-2 mutations, which are relatively less common). This leads to $M = 3$ subpopulations, shown in Figure 5.22:

(a) not at risk, not having a family history of EOAD ($i = 1$);

(b) at risk because of family history but not a mutation carrier ($i = 2$); and

(c) at risk and a mutation carrier ($i = 3$).

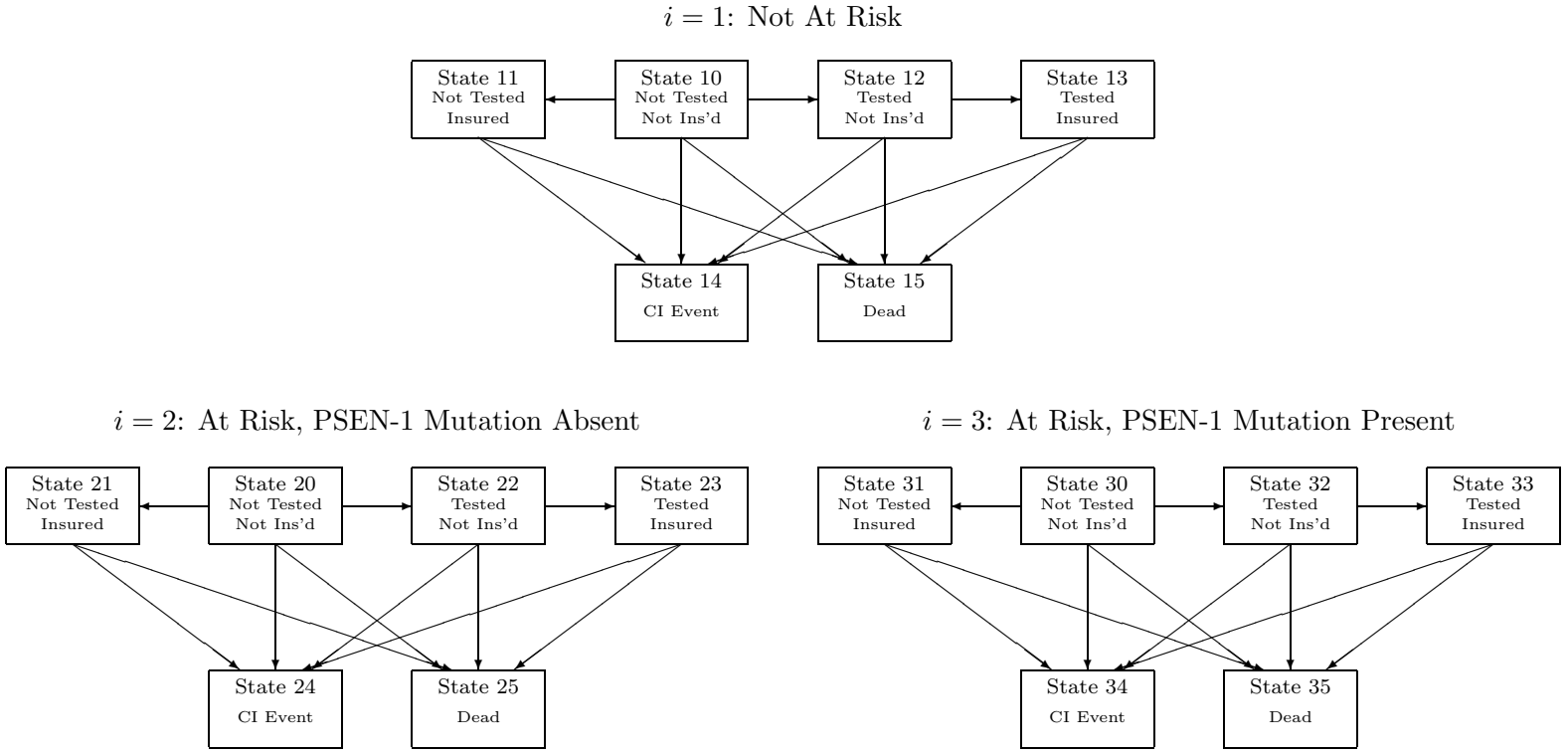

Figure 5.22: A Markov model of a CI insurance market allowing for a family history of EOAD and genetic testing.

We suppose that a proportion p_i are in the i^{th} subpopulation at birth. This model captures all the important features of the problem:

(a) The proportion starting in the 'uninsured, untested' state 30 represents the population frequencies of mutations. The same proportion starts in state 20, not carrying a mutation but not knowing that.

(b) The rate of genetic testing may represent any possibility from a low level of testing restricted to at-risk families, to screening of the population.

(c) The rate of insurance purchase by persons not at risk represents the size of the market.

(d) Adverse selection is represented by:

  (i) the rate of insurance purchase given a family history but before testing;

  (ii) the rate of insurance purchase after receiving an adverse test result; and

  (iii) the amounts of insurance purchased.

(e) Underwriting classes will consist of collections of states, depending on any moratorium, within each of which a premium based on the equivalence principle, assuming no adverse selection, can be charged.

5.3.2 Parameterisation

We suppose that 15 per 100,000 of the population are in each of states 20 and 30 at birth (Section 4.4).

The intensities of occurrence of CI claims and deaths (net of CI claims) are given in Appendix G, and rates of onset of EOAD (in subpopulation $i = 3$ only) were given in Section 4.5. The two remaining intensities in each subpopulation are the rate of genetic testing and the rate(s) of insurance purchase, some of which may represent adverse selection, and some a response to high premium ratings where these may be charged.

(a) *The Rate of Genetic Testing*: Little information is available about the level of DNA-based testing for EOAD. In an observational study of 251 individuals at 50% risk for EOAD or frontotemporal dementia by Steinbart et al. (2001), 8.4% of at risk persons requested genetic testing. These individuals were mainly concerned about the early symptoms of the disease, family and financial planning, and anxiety associated with carrying the risk.

Huntington's disease (HD) is comparable to EOAD in that it is rare, dominantly inherited, highly penetrant and untreatable. Genetic testing for HD families has now been available in a clinical (rather than research) setting for some time, and some experience has been gained. The proportion of at-risk persons who choose to be tested is quite low, ranging from 6% (Panegyres et al., 2000) to 10–20% (Meiser and Dunn, 2000). Again, the reasons for the low rate of requests are likely to be issues like employment, insurability and the psychological implications of knowing a test result.

We use an annual intensity of 0.01 to represent a very moderate rate for genetic testing, which implies that almost 10% of at-risk individuals will have the test within ten years. Take-up of for genetic testing is likely to be lower than expected for reasons outlined above and in Section 5.1.2.

If this intensity of 0.01 is an over-estimate then increases in premiums payable for CI insurance under investigation in this chapter will be on the high side. As this might not be the case, we need to perform sensitivity testing later (Section 5.3.8).

(b) *'Normal' Rates of Insurance Purchase*: We consider two different market sizes: a large market with an annual rate of insurance purchase $\mu_{x+t}^{101} = 0.05$, and a small market with rate $\mu_{x+t}^{101} = 0.01$.

In the at-risk subpopulations, insurance may be purchased at a lower rate if higher premiums may be charged, whether because of family history or a disclosed genetic test result. We suppose that in the larger market, persons charged an extra premium either buy no insurance, or buy insurance at half the normal rate (0.025 per annum), or buy insurance at the normal rate. The

former is probably more realistic; in some jurisdictions persons with a family history may be declined, while in other jurisdictions they must be offered a premium but Table 5.8 makes it clear that it would be extremely high. In the smaller market, we suppose that persons charged an extra premium buy no insurance.

(c) *Rates of Insurance Purchase With Adverse Selection*: It is impossible to say what rates of insurance purchase might be given some adverse genetic information. No research has yet been done that shows how elasticity of demand might vary. What we can do is suggest rates of purchase that are higher than normal, up to some extreme level that would give an upper bound to the costs of adverse selection. We therefore suppose:

(i) that an extreme level of adverse selection in both markets is a rate of purchase of 0.25 per annum; this would result in most people buying insurance within a very few years of receiving adverse information; and

(ii) for sensitivity testing, that a more moderate level of adverse selection is that 'adverse selectors' buy insurance at twice the 'normal' rate (0.10 per annum in the 'large' market and 0.02 per annum in the 'small' market).

5.3.3 Computation

We followed the methods presented in Macdonald (2003b) to calculate the EPVs of benefits, premiums and insurance losses for the different combinations of market size and insurance buying behaviour. These quantities will define the costs of changing underwriting classes and of adverse selection under the various moratoria considered. A force of interest $\delta = 0.05$ was used.

We compute the occupancy probability, ${}_tp_x^{ijk}$, the probability that a life in state ij (of the i^{th} sub-population) at age x is in state ik at age $x+t$, by solving the Kolmogorov's forward equations:

$$\frac{d}{dt}{}_tp_x^{ijk} = \sum_{l \neq k} {}_tp_x^{ijl}\mu_{x+t}^{lk} - \sum_{l \neq k} {}_tp_x^{ijk}\mu_{x+t}^{kl} \tag{5.49}$$

with boundary conditions ${}_0p_0^{ijk} = p_i$ if $j = k = 0$, zero otherwise.

A rate of premium must be calculated within each underwriting class. Suppose there are W underwriting classes denoted $\Phi_1, \ldots \Phi_W$, each being a collection of insured states (excluding 'CI Event' and 'Dead', see Section 5.3.4). The rate of premium ρ_x^w payable per unit sum assured at age x in the underwriting class Φ_w is then defined as the weighted average of the intensities from the states in Φ_w to the CI claim state(s) *in the absence of adverse selection*:

$$\rho_x^w = \frac{\sum\limits_{ij \in \Phi_w} p_i \ {}_xp_0^{i0j} \mu_x^{ij4}}{\sum\limits_{ij \in \Phi_w} p_i \ {}_xp_0^{i0j}}. \tag{5.50}$$

This is the 'current cost' method of charging, in which the premium rate paid between ages $x + t$ and $x + t + dt$ is just the expected cost of claims during dt. It is a function of the current age alone (in a Markov model) so while it satisfies the equivalence principle it avoids the problem that level premiums would depend on the age at which insurance was purchased.

With these premium rates, policy values are then computed using Thiele's equations, solving backwards using the fact that the reserve at expiry is zero in all states. If state ij belongs to underwriting class Φ_w then:

$$\frac{d}{dt}{}_tV_x^{ij} = \delta \ {}_tV_x^{ij} + \rho_{x+t}^w - \sum_{k \neq j} \mu_{x+t}^{ijk} (b_{x+t}^{ijk} + {}_tV_x^{ik} - {}_tV_x^{ij}) \tag{5.51}$$

where b_{x+t}^{ijk} is the benefit paid on transition from state ij to state ik. We used a Runge-Kutta algorithm with step-size 0.0005 years to solve Kolmogorov's and Thiele's equations.

We calculate the EPV of the loss in this market (discounted benefits minus premiums) with and without adverse selection; normally the latter EPV should be nil. We also calculate the EPV of all the premiums payable in the market with adverse selection present. Then:

$$\frac{\text{EPV[Loss with adverse selection]} \ - \ \text{EPV[Loss without adverse selection]}}{\text{EPV[Premiums with adverse selection]}}$$

Table 5.9: Possible underwriting classes with three sub-populations: $i = 1$ not at risk of EOAD; $i = 2$ at risk of EOAD but not PSEN-1 mutation carriers; $i = 3$ at risk of EOAD and PSEN-1 mutation carriers. (T) denotes persons who have had a genetic test and (U) denotes persons who have not.

		Factors Allowed in Underwriting?			Composition of Underwriting Classes		
No.	Genetic Testing Exists?	Family History	Negative Test Results	Positive Test Results	OR Class	Rated for Family History	Rated for Genetic Test
1	No	Yes	n/a	n/a	$i = 1$	$i = 2, 3$	
2	Yes	Yes	No	No	$i = 1$	$i = 2, 3$	
3	Yes	Yes	Yes	No	$i = 1$ and $i = 2$ (T)	$i = 3$ and $i = 2$ (U)	
4	Yes	Yes	Yes	Yes	$i = 1$ and $i = 2$ (T)	$i = 2$ (U) and $i = 3$ (U)	$i = 3$ (T)
5	Yes	No	No	No	$i = 1, 2, 3$		

is the proportion by which all premiums would have to increase to absorb the cost of the adverse selection.

5.3.4 Moratoria and Underwriting Classes

We study the effect three forms of moratoria on the use of genetic information:

(a) a moratorium on all genetic test results;

(b) a moratorium on adverse genetic test results only; and

(c) a moratorium on all genetic test results and family history.

Some moratoria in theory apply to all genetic test results (for example that in the U.K.) but in practice insurers are likely to grant standard rates to persons who have been shown, by a test, to be non-carriers; this is why (a) and (b) above are both considered. Table 5.9 shows the composition of the underwriting classes under different moratoria.

5.3.5 Moratoria on Genetic Test Results

Table 5.10 shows the percentage increases in all premium rates arising from both moderate and severe adverse selection following a moratorium on the use of genetic

Table 5.10: Percentage increases in premium rates for CI cover, arising from moderate and severe adverse selections following a moratorium on the use of genetic test results, with family history underwriting allowed, for a market operating between ages 20 and 60.

Adverse Selection	Market Size	Rate of Purchase by Persons Rated-up	Moratorium on using: All test results Female %	All test results Male %	Adverse results Female %	Adverse results Male %
Moderate	Large	Same as 'normal'	0.003	0.003	0.003	0.003
		Half of 'normal'	0.008	0.007	0.007	0.007
		Uninsured	0.016	0.015	0.015	0.014
	Small	Uninsured	0.016	0.014	0.015	0.014
Severe	Large	Same as 'normal'	0.007	0.006	0.007	0.006
		Half of 'normal'	0.012	0.011	0.012	0.011
		Uninsured	0.021	0.020	0.021	0.019
	Small	Uninsured	0.066	0.060	0.064	0.059

Table 5.11: Percentage increases in premium rates for CI cover, arising from severe adverse selection following a moratorium on the use of genetic test results, with family history underwriting allowed, for a market operating between ages 20 and 60. EOAD rates of onset 50% and 25% of those observed.

EOAD Onset Rate at	Market Size	Rate of Purchase by Persons Rated-up	Moratorium on using: All test results Female %	All test results Male %	Adverse results Female %	Adverse results Male %
50%	Large	Same as 'normal'	0.005	0.005	0.005	0.005
		Half of 'normal'	0.010	0.009	0.010	0.009
		Uninsured	0.019	0.018	0.019	0.017
	Small	Uninsured	0.059	0.055	0.057	0.053
25%	Large	Same as 'normal'	0.004	0.003	0.003	0.003
		Half of 'normal'	0.007	0.007	0.007	0.006
		Uninsured	0.014	0.013	0.014	0.013
	Small	Uninsured	0.044	0.041	0.042	0.039

test results, with family history underwriting allowed, in a CI insurance market operating between ages 20 and 60. The increases are all very small, even with severe adverse selection.

Because these percentage increases are extremely small, appearing as 0% in all cases if rounded to integers, it is sensible to show at least some significant figures. It will eventually be useful to aggregate the costs in respect of different genetic disorders to obtain a global estimate of the effect of adverse selection, and then knowing whether 0% means 0.49% or 0.049% will be useful. For this reason we show three decimal places, but we do not mean thereby to imply unwarranted accuracy.

Premium increases are *lower* if the moratorium applies only to adverse test results. This is because the underwriting class based on family history will then contain a higher proportion of mutation carriers, and the premium charged within that class will increase.

Table 5.11 shows the premium increases if the rates of onset of EOAD are 50% or 25% of those observed (see Section 4.5). For brevity, we show severe adverse selection only. The effect of moderate adverse selection with the observed rates of onset is about the same as severe adverse selection with the lowest rates of onset.

Although small in absolute terms, these increases result from considering just one gene, with mutation frequency 15 per 100,000, that does not even account for all of EOAD. It would be unwise to conclude that adverse selection in total would be negligible, until comparable figures are available for more of the major single-gene disorders.

5.3.6 A Moratorium on Genetic Test Results and Family History

Table 5.12 shows the percentage increases in standard premium rates following a moratorium on the use of genetic test results and family history, for a CI insurance market operating between ages 20 and 60. The increases split into two parts:

(a) Everyone will have access to insurance on the same terms, including those who would previously have been rated up. If these people just buy insurance at the

Table 5.12: Percentage increases in standard premium rates for CI cover, arising from new underwriting classes, moderate and severe adverse selections following a moratorium on the use of genetic test results and family history, for a market operating between ages 20 and 60. Rates of onset of EOAD 100%, 50% and 25% of those observed.

EOAD Onset Rate at	Market Size	New Underwriting Classes		Moderate Adverse Selection		Severe Adverse Selection	
		Female	Male	Female	Male	Female	Male
		%	%	%	%	%	%
100%	Large	0.118	0.110	0.050	0.047	0.084	0.080
	Small	0.103	0.094	0.095	0.088	0.549	0.508
50%	Large	0.102	0.095	0.038	0.035	0.060	0.056
	Small	0.095	0.085	0.084	0.077	0.429	0.395
25%	Large	0.077	0.071	0.025	0.024	0.039	0.037
	Small	0.075	0.067	0.064	0.059	0.301	0.277

'normal' rate, and do not buy above-average amounts of cover, the standard premium rate will increase but this cannot be called adverse selection. It is simply because new, more inclusive, underwriting classes have been imposed. The behaviour of those who were previously rated up is not relevant since they were not charged the standard premium rate before. The market size has only a small effect.

(b) In addition to these increases, adverse selection might occur; in Table 5.12 we show the effect of moderate and severe levels of adverse selection. Now, the 'adverse selectors' includes those with a family history who have not had a genetic test, as well as those who have had an adverse test result. The previous behaviour of those who were rated up before is not relevant here either. The market size now has a very large effect if adverse selection is severe.

We see that just redefining the underwriting class has a larger effect than adverse selection with a moratorium on test results only, and that adverse selection then has a much smaller effect in the larger market, and a similar effect in the smaller market. Bearing in mind the rarity of PSEN-1 mutations, this shows that a small

CI insurance market may be vulnerable to adverse selection.

5.3.7 Adverse Selection Extending to Higher Sums Assured

Tables 5.10 to 5.12 do not show the effect of 'adverse selectors' opting for larger sums assured. Some jurisdictions have recognised that any tendency, on the part of those with adverse genetic information, to select abnormally high sums assured, is a form of adverse selection that goes beyond any notion of fairness in access to insurance, and have imposed ceilings on any moratorium, above which genetic test results may be taken into consideration. In the U.K., for example, from 2001 these ceilings are £500,000 for life insurance and £300,000 for CI insurance.

To investigate the impact of an increase in sum assured of the at risks, we doubled and quadrupled the sum assured purchased by 'adverse selectors'. As expected, the results were to double and quadruple the premium increases shown in Tables 5.10 to 5.12, so we omit the details.

5.3.8 The Rate of Genetic Testing

We chose a rate of genetic testing of 0.01 per annum, consistent with a low demand for testing, confined to a clinical setting. We doubled this to 0.02 per annum. The effect, given a moratorium on the use of genetic test results and family history were negligible, as expected because the genetic risk has no effect on access to insurance. The premium increases under the moratoria on use of genetic test results alone are shown in Table 5.13. The premium increases are roughly twice those shown before, and still very small.

5.4 Summary

In this chapter, we apply the rates of onset of EOAD associated with PSEN-1 gene mutations estimated in Chapter 4. We use a Markov model for the CI insurance market to investigate:

(a) premium ratings given either mutation or a family history; and

Table 5.13: Percentage increases in CI premium rates arising from severe adverse selection following a moratorium on the use of genetic test results, with family history underwriting allowed, for a market operating between ages 20 and 60. Rate of genetic testing 0.02 per annum.

		Moratorium on using:			
Market	Rate of Purchase by	All test results		Adverse results	
Size	Persons Rated-up	Female	Male	Female	Male
		%	%	%	%
	Same as 'normal'	0.013	0.012	0.012	0.011
Large	Half of 'normal'	0.022	0.021	0.021	0.020
	Uninsured	0.039	0.037	0.037	0.035
Small	Uninsured	0.120	0.110	0.113	0.104

(b) the effects of moratoria on the use of genetic test results and family history.

5.4.1 Premium Ratings

CI insurance premium increases implied by known PSEN-1 mutations or a family history of PSEN-1 mutations were extremely high, even with the reduced rates of onset. Only in a few cases would the premium fall within the limits currently offered.

Older people in at-risk families can be offered very much better terms than if they were known PSEN-1 mutation carriers. For exactly the same reason, that their very survival implies much reduced risk, it is perhaps unlikely that they would be advised to be tested on clinical grounds, so no conflict between medical and insurance interests should arise. However, this is likely to be a rather small segment of the CI insurance market.

In fact, the premiums based on a family history of EOAD, but not known to be associated with mutations in any particular gene, should probably be lower than those in Table 5.8, because:

(a) PSEN-1 mutations are thought to cause an aggressive form of EOAD with earlier onset and worse survival (Russo et al., 2000; Bird et al., 1996) , though both the onset rates and survival rates after onset associated with mutations in other genes are not available to confirm this; and

(b) all forms of EOAD are rare, and not all show clear dominant inheritance, so the assumption that 50% of offspring of affected parents will carry causative mutations is an upper bound.

5.4.2 Adverse Selection

The cost of adverse selection, in terms of premium increases, appears to be negligible except in the case of small markets, extreme behaviour on the part of 'adverse selectors' and high rates of onset of EOAD. Hence, it is difficult to draw firm conclusions about the costs of adverse selection, should one of various kinds of moratorium be imposed.

Chapter 6

EARLY-ONSET ALZHEIMER'S DISEASE AND LIFE INSURANCE

6.1 A Model of EOAD and Life Insurance

6.1.1 The Model

In Section 4.3, we found that probabilities of survival after onset of EOAD depend on duration since onset as well as age. Therefore a Markov model is inappropriate: Figure 6.23 shows a semi-Markov model for a person in the i^{th} of several subpopulations.

(a) There are two states representing onset of EOAD while insured, $i4$ and $i5$. This is because the sum assured could depend on knowledge of a genetic test result, either because of adverse selection among mutation carriers, or the offer of ordinary rates to non-carriers who have been tested.

(b) Transitions from the states $i4$ and $i5$ may depend on both age and duration. We need to define appropriate probabilities for transitions into these states and for surviving after entering them. Define the probability:

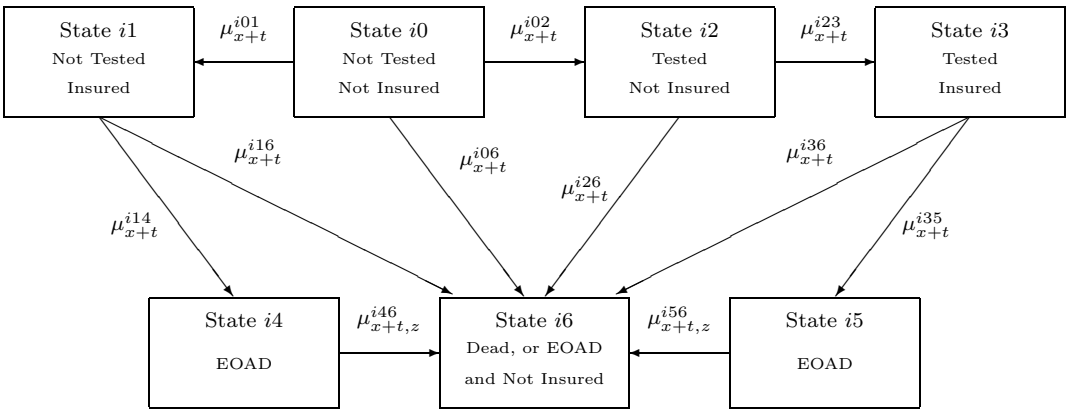

Figure 6.23: A semi-Markov model of genetic testing, insurance purchase and life insurance events for a person in the i^{th} subpopulation. z is duration since onset of EOAD.

$$ {}_{z,t}\Pi^{ijk}_x = \mathrm{P}[\text{In state } ik, \text{ duration} \leq z \text{ at age } x+t \mid \text{In state } ij \text{ at age } x] \tag{6.52} $$

and let ${}_{z,t}p^{ijk}_x$ denote its (partial) derivative w.r.t. z, so that ${}_{z,t}p^{ijk}_x.dz$ can be interpreted as the probability that a person is in state ik at age $x+t$ with duration from z to $z+dz$, given that he or she is in state ij at age x; for $j \neq 4, 5$, $k = 4, 5$.

We define the probabilities for surviving after entering these states; for $k = 4, 5$:

$$ {}_tp^{ikk}_{x,z} = \mathrm{P}[\text{In state } ik \text{ at age } x+t \mid \text{In state } ik, \text{ duration } z \text{ at age } x]. \tag{6.53} $$

(c) Onset of EOAD while uninsured removes the person from the insurance market, which we represent by transition into the absorbing state, which is now labelled 'Dead, or EOAD and Not Insured'. We could define a separate absorbing state for this event but that is unnecessary.

Using the equivalence principle, the rate of premium payable at age $x+t$ for a unit sum assured, in a given underwriting class, should be the weighted average intensity into 'dead' states from the insured states in that underwriting class, in

the absence of adverse selection. Let Φ_w and Φ_w^E be the insured states in the w^{th} underwriting class, containing non-EOAD and EOAD states respectively. Then the rate of premium is:

$$\rho_{x+t}^w = \frac{\sum\limits_{ij\in\Phi_w} p_i \ {}_tp_x^{i0j}\mu_{x+t}^{ij6} + \sum\limits_{ij\in\Phi_w^E} p_i \int\limits_0^t {}_{z,t}p_x^{i0j}\mu_{x+t+z,z}^{ij6}dz}{\sum\limits_{ij\in\Phi_w} p_i \ {}_tp_x^{i0j} + \sum\limits_{ij\in\Phi_w^E} p_i \int\limits_0^t {}_{z,t}p_x^{i0j}dz}. \tag{6.54}$$

We can compute the integrals in Equation (6.54) using (for example):

$${}_{z,t}p_x^{i04} = {}_{t-z}p_x^{i01}\mu_{x+t-z}^{i14} \ {}_zp_{x+t-z,0}^{i44} = {}_{t-z}p_x^{i01}\mu_{x+t-z}^{i14}\exp\left(-\int\limits_0^z \mu_{x+t-z+r,r}^{i46}dr\right) \tag{6.55}$$

for state $i4$, and similarly for state $i5$.

Note that Thiele's equations no longer apply because our model is not Markov. But for the purpose of computing the reserves, we can exploit the particular form of the model in Figure 6.23, and bring it back within a Markov framework. Instead of setting up the reserve ${}_{t,0}V_x^{i4}$ or ${}_{t,0}V_x^{i5}$ on onset of EOAD at age $x+t$ (in the obvious notation), and then continuing to pay premiums, and later paying the sum assured on death, we pay sums assured ${}_{t,0}V_x^{i4}$ or ${}_{t,0}V_x^{i5}$ on entering states $i4$ or $i5$, respectively, and the normal sum assured on death while in states $i1$ or $i3$. In other words, in Equation (5.51) put $b_{x+t}^{i14} = {}_{t,0}V_x^{i4}$ and $b_{x+t}^{i35} = {}_{t,0}V_x^{i5}$, and $b_{x+t}^{i46} = b_{x+t}^{i56} = 0$. These sums assured depend on age alone, and the duration dependent intensities are needed only to compute ${}_{t,0}V_x^{i4}$ and ${}_{t,0}V_x^{i5}$. Therefore we can just solve Thiele's equations as before. Of course, this trick would not work for more complex models, or for second and higher moments.

For a policy with unit sum assured, entry age x and term n years, and if state ij belongs to underwriting class w, we have:

$${}_{t,0}V_x^{ij} = \int\limits_0^{n-t} e^{-\delta z} \ {}_zp_{x+t,0}^{ijj} \ (\mu_{x+t+z,z}^{ij6} - \rho_{x+t+z}^w) \ dz \qquad j = 4, 5. \tag{6.56}$$

and we can easily write down similar expressions for computing the EPVs of level benefits and premiums.

6.1.2 Parameterisation

The parameterisation is the same as in Section 5.3.2, with one addition: mortality rates in non-EOAD states are those of the English Life Tables No. 15, and mortality rates after onset of EOAD are as described in Section 4.3.

6.2 Premium Ratings for Life Insurance

6.2.1 Life Insurance Premiums Based on Known PSEN-1 Mutations

Table 6.14 shows level premiums for level life insurance cover for female and male PSEN-1 mutation carriers, based on estimated EOAD onset intensities of 100%, 50% and 25% of those fitted to the observed data. The premiums are payable continuously and expressed as percentages of the 'standard' premium rate.

(a) Because of their lower mortality in general, premium increases are markedly higher for females, especially for cover expiring at later ages, and the higher rates of onset of EOAD.

(b) The increases are lower than those for CI insurance, except for cover expiring at age 30.

(c) In many cases, notably with the lower rates of onset of EOAD, the increased premiums are mostly less than 500% of standard rates which is about the limit for an offer of cover in practice. Therefore unless the highest penetrance estimates turn out to be well-founded, terms could be offered to most people with a known PSEN-1 mutation. Again, the fact that PSEN-1 mutations are believed to be associated with aggressive EOAD suggests that this conclusion should hold for familial EOAD in general.

Table 6.14: Level net premiums for level life cover with known PSEN-1 mutations, as a percentage of the standard level premiums.

EOAD Onset Rate at	Entry Age	Females Term (Years) 10 %	20 %	30 %	40 %	Males Term (Years) 10 %	20 %	30 %	40 %
	20	177.56	835.96	1,617.25	1,400.08	130.17	443.26	905.35	817.54
100%	30	1,109.99	2,099.51	1,735.59		668.22	1,314.64	1,078.53	
	40	1,469.02	1,679.81			971.14	1,057.05		
	50	898.53				556.86			
	20	138.87	484.54	1,004.96	1,014.61	115.12	279.30	579.71	602.17
50%	30	626.79	1,270.33	1,213.76		396.30	810.13	763.14	
	40	891.78	1,171.67			603.19	746.59		
	50	614.17				392.65			
	20	119.46	296.68	599.65	673.58	107.57	191.69	364.64	413.59
25%	30	369.15	738.72	781.26		251.37	487.28	504.06	
	40	528.31	745.76			371.98	488.39		
	50	397.28				268.61			

Table 6.15: Level net premiums for level life cover for persons with family histories of known PSEN-1 mutations, as a percentage of the standard level premiums.

EOAD Onset Rate at	Entry Age	Females Term (Years) 10	20	30	40	Males Term (Years) 10	20	30	40
		%	%	%	%	%	%	%	%
	20	138.77	466.03	836.79	709.51	115.08	270.73	491.25	436.91
100%	30	592.90	1,031.90	812.54		377.33	666.48	527.38	
	40	577.56	581.61			404.12	393.07		
	50	154.77				131.51			
	20	119.43	291.75	545.17	539.04	107.56	189.41	336.04	341.32
50%	30	358.03	658.68	607.96		245.14	439.13	402.98	
	40	380.73	447.86			278.49	310.53		
	50	136.50				120.85			
	20	109.73	198.20	347.67	380.10	103.78	145.78	231.20	253.24
25%	30	232.09	409.21	420.92		174.29	287.52	290.55	
	40	253.34	319.56			197.40	232.31		
	50	121.62				112.29			

6.2.2 Life Insurance Premiums Based on Family History of EOAD

Table 6.15 shows level premiums for level life insurance cover based on a family history of EOAD known to be associated with PSEN-1 mutations, expressed as percentages of the 'standard' premium rate.

(a) For life cover expiring at age 30, extra premiums may not be needed, especially at the lower rates of onset.

(b) For life cover commencing at age 50, extra premiums of 50% or less could be offered.

(b) For almost all ages and policy terms, the increased premiums are less than 500% of the standard, so terms could be offered within current practice.

6.3 The Potential Costs of Adverse Selection in Life Insurance

6.3.1 Moratoria and Underwriting Classes

The model of Figure 6.23 is extended to a model of three subpopulations just as in Figure 5.22, and we consider exactly the same moratoria and underwriting classes as in Section 5.3.4. We use the same rates of insurance purchase and genetic testing as for CI insurance, though here it is the larger market that is most relevant.

6.3.2 Moratoria on Genetic Test Results

Table 6.16 shows the percentage increases in standard life insurance premium rates arising from moderate and severe adverse selection following a moratorium on the use of genetic test results with family history underwriting allowed, for a market operating between ages 20 and 60. All are less than 0.1%, and may be regarded as negligible if PSEN-1 is taken alone. Table 6.17 shows the premium increases as a

Table 6.16: Percentage increases in life insurance premium rates arising from moderate and severe adverse selections, following a moratorium on the use of genetic test results, with family history underwriting allowed, for a market operating between ages 20 and 60.

			Moratorium on using:			
Adverse	Market	Rate of Purchase by	All test results		Adverse results	
Selection	Size	Persons Rated-up	Female	Male	Female	Male
			%	%	%	%
		Same as 'normal'	0.004	0.002	0.004	0.002
Moderate	Large	Half of 'normal'	0.008	0.005	0.008	0.005
		Uninsured	0.017	0.010	0.016	0.010
	Small	Uninsured	0.016	0.010	0.015	0.009
		Same as 'normal'	0.008	0.005	0.008	0.005
Severe	Large	Half of 'normal'	0.014	0.008	0.013	0.008
		Uninsured	0.024	0.014	0.023	0.014
	Small	Uninsured	0.073	0.044	0.070	0.042

result of severe adverse selection with rates of onset of EOAD of 50% and 25% of those observed.

6.3.3 Moratorium on All Genetic Test Results and Family History

Table 6.18 shows the percentage increases in standard life insurance premium rates arising from new underwriting classes, and moderate and severe adverse selection in addition, following a moratorium on the use of genetic test results and family history. The results and conclusions are similar to those in respect of CI insurance: the only noticeable increases result from severe adverse selection in a small market with the highest rate of onset.

6.3.4 Adverse Selection Extending to Higher Sums Assured

If an 'adverse selector' opts for a higher than average sum assured, the increase in premium is proportionate to the level of sum assured chosen, relative to the average. This is similar to the case for CU insurance.

Table 6.17: Percentage increases in life insurance premium rates arising from severe adverse selection following a moratorium on the use of genetic test results, with family history underwriting allowed, for a market operating between ages 20 and 60. EOAD rates of onset 50% and 25% of those observed.

EOAD Onset Rate at	Market Size	Rate of Purchase by Persons Rated-up	Moratorium on using: All test results Female %	All test results Male %	Adverse results Female %	Adverse results Male %
50%	Large	Same as 'normal'	0.006	0.004	0.006	0.003
		Half of 'normal'	0.010	0.006	0.010	0.006
		Uninsured	0.019	0.011	0.018	0.010
	Small	Uninsured	0.057	0.034	0.054	0.032
25%	Large	Same as 'normal'	0.004	0.002	0.004	0.002
		Half of 'normal'	0.007	0.004	0.006	0.004
		Uninsured	0.012	0.007	0.011	0.007
	Small	Uninsured	0.037	0.022	0.034	0.020

Table 6.18: Percentage increases in standard life insurance premium rates arising from new underwriting classes and severe adverse selection following a moratorium on the use of genetic test results and family history, for a market operating between ages 20 and 60.

EOAD Onset Rate at	Market Size	New Underwriting Classes Female %	New Underwriting Classes Male %	Moderate Adverse Selection Female %	Moderate Adverse Selection Male %	Severe Adverse Selection Female %	Severe Adverse Selection Male %
100%	Large	0.147	0.084	0.061	0.036	0.103	0.062
	Small	0.126	0.072	0.112	0.067	0.657	0.396
50%	Large	0.115	0.065	0.043	0.026	0.070	0.042
	Small	0.103	0.058	0.089	0.053	0.477	0.286
25%	Large	0.077	0.043	0.027	0.016	0.043	0.025
	Small	0.070	0.039	0.060	0.036	0.307	0.183

6.3.5 Increasing the Rate of Genetic Testing

Increasing the rate of genetic testing to 0.02 per annum had exactly the same effects as in Section 5.3.7.

6.4 Summary

As in Chapter 5, we apply the rates of onset and survival rates after onset of EOAD associated with PSEN-1 gene mutations estimated in Chapter 4. We use a Markov model for the life insurance market to investigate:

(a) premium ratings given either mutation or a family history; and

(b) the effects of moratoria on the use of genetic test results and family history.

6.4.1 Premium Ratings

Life insurance premium increases were only outside the limits currently offered if a PSEN-1 mutation was confirmed by a genetic test, and given the highest rates of onset. With a few exceptions, terms could be offered otherwise, in particular if only a family history were known. As with CI insurance, older people in at-risk families can be offered very much better terms than if they were known PSEN-1 mutation carriers.

6.4.2 Adverse Selection

The cost of adverse selection is comparable to that in CI insurance (Section 5.3). In terms of premium increases, the adverse selection cost again appears to be negligible except in the case of small markets, severe adverse selection and high rates of onset of EOAD. For the life insurance market, our models of the larger markets may be more appropriate.

It is difficult to draw firm conclusions about the costs of adverse selection for both the CI and life insurance markets as investigated in these chapters (Chapters 5 and 6), should one of various kinds of moratorium be imposed. However we have only considered here one very rare disorder, whereas a moratorium would apply to all

genetic disorders. Except in those extreme cases where this work by itself suggests that adverse selection could be a problem, we should regard the premium increases arising from adverse selection as one part of a program that should be extended to cover all the major late-onset single-gene disorders.

Chapter 7

ESTIMATE OF THE INCIDENCE RATES OF EARLY-ONSET ALZHEIMER'S DISEASE ASSOCIATED WITH THE PSEN-2 and APP GENES

7.1 Introduction

In this and the next two chapters, we investigate conditions that may be of importance in insurance (two of which are on the ABI's list, refer to Section 1.3.2). Due to the lack of data or penetrance estimates in the literature, these cannot yet be developed into actuarial models. However, we are able to conclude that multiple endocrine neoplasia and hereditary haemochromatosis (Sections 8.5 and 9.6) are not likely to have significant implications for insurance.

In this chapter, the modified Nelson-Aalen method discussed in Chapter 3 is applied to published pedigrees on the PSEN-2 and APP gene mutations to estimate the rates of onset of EOAD due to the respective mutations. Pedigree data with ages at onset and survival duration after onset of EOAD associated with mutations in the PSEN-2 and APP genes are gathered from published papers reporting (usually

novel) mutations in the two genes. See Appendices B and C. Only pedigrees with complete sibship information can be used.

The estimates of incidence rates in respect of PSEN-2 and APP gene mutations in this paper are novel, but unlike the case with PSEN-1, we do not find them to be useable because of insufficient data.

7.2 Estimates of Incidence Rates

Refer back to Chapter 2 and Chapter 4 on the treatment of data. Figure 7.24 shows the approximate maximum and minimum exposure times in the $p = 1/2$ risk group, arising from PSEN-2 and APP gene mutations. There are not enough data to consider males and females separately.

Figure 7.24: Estimated exposure times for all persons in the $p = 1/2$ risk group. Each line represents the time spent in the risk group by a single individual. The estimated exposure times due to PSEN-2 gene mutation are on the left (60 lives), and the estimated exposure times due to APP gene mutation are on the right (34 lives). Exposures ending with onset of EOAD are indicated by a triangle.

Biweight kernel smoothing (secton 4.1.3) is used to smooth the modified Nelson-Aalen estimate. The optimal bandwidth for the smoothing for each of the PSEN-2 and the APP gene mutation data (2.3 and 4.6 years respectively) are shown in Figure 7.25.

Figure 7.25: Estimated risk function, G(b), for use in determining the optimal bandwidth for the PSEN-2 and APP mutation data.

7.2.1 Bootstrap Confidence Intervals

For approximate confidence limits, we generate 500 random samples of onset based on the observed exposures and onsets at each age (the 'Weird Bootstrap', see section 4.1.4). For each of these samples, the intensity is calculated as before, and at each age the 25^{th} and 475^{th} samples give an approximate 95% confidence interval for $\hat{\mu}_x^{02}$.

7.3 Results

Figures 7.26 and 7.27 show the resulting estimates of $\mu_{02}(x)$, for onset of EOAD with PSEN-2 and APP mutations respectively. These estimates have several features:

- Although estimates are obtained up to about ages 60 (PSEN-2) and 55 (APP), when $\hat{\Lambda}(x)$ exceeds $\log 2$ (see Section 3.4.3 for details), their behaviours change at about ages 57 (PSEN-2) and 52 (APP).

- The confidence limits are limited to shorter age ranges than the estimates, because in each case, among the 500 simulated experiences there were some in which $\hat{\Lambda}(x)$ exceeded $\log 2$ at a lower age than in the actual sample.

Figure 7.26: Estimated incidence rates of EOAD with PSEN-2 mutations, with approximate 95% confidence limits.

Figure 7.27: Estimated incidence rates of EOAD with APP mutations, with approximate 95% confidence limits.

Figure 7.28: Probabilities of surviving free of EOAD among persons with PSEN-2 mutations, with approximate 95% confidence limits.

Compared with the estimated incidence rates of EOAD associated with PSEN-1 gene mutations (Section 4.1.5), the estimated incidence rates associated with mutations in the PSEN-2 and APP genes are not as smooth, due to the smaller sample sizes used. Also for the latter, the ages at which $\hat{\Lambda}(x)$ exceeds $\log 2$ are higher at about 57 for PSEN-2 and 52 for APP (compared with about 50 for PSEN-1). These could signify less ascertainment bias in the PSEN-2 and APP data (Section 3.4.3), than in the PSEN-1 data. There is a need for further investigation as available data are not sufficient for a decision to be made.

Probabilities of survival free of EOAD ($\exp(-\int_0^x \mu_{02}(t)dt)$) are shown in figures 7.28 and 7.29, with bootstrapped 95% confidence limits. These survival probabilities are very low (< 0.4) just after age 55 as a consequence of the high penetrance of PSEN-2 and APP mutations.

Though the incidence rates of EOAD are very irregular after smoothing, the survival curves are more regular, as is to be expected since integration itself imposes a degree of smoothing. Therefore it might be possible to fit a reasonably regular curve to the survival probabilities and proceed with modelling the insurance cost

Figure 7.29: Probabilities of surviving free of EOAD among persons with APP mutations, with approximate 95% confidence limits.

due to the two genes, if not for the uncertain reliability of the estimates due to scarce data.

7.3.1 Comparing the Rates Due to Mutations in the PSEN-2 and APP Genes

For PSEN-2, the rate of onset of EOAD begins at around age 38, and reaches about 0.2 by age 50. While for APP, the rate of onset of EOAD starts at around age 30, and reaches about 0.1 by age 50. These features are consistent with the high penetrance but slightly later onset of EOAD associated with mutations in the PSEN-2 and APP genes when compared to EOAD associated with PSEN-1 gene mutations (Section 2.2). For PSEN-1, onset of EOAD starts at around age 25, and the rate of onset reaches about 0.1–0.2 by age 45.

However, the results suggest that PSEN-2 is more severe than APP. This may not be consistent with the suggestion by Campion et al. (1999) that PSEN2 was the less severe of the two. The age ranges for onset of EOAD due to PSEN-2 from Campion et al. (1999) extend well into the 80s (when it is impossible to ascribe

AD to an EOAD mutation) while nonpenetrance of APP mutations by age 60 is infrequent. Iwatsubo (1998) has also shown that the number of senile plaques and the percentage area of the senile plaques covered by Aβ_{42} or Aβ_{43} in EOAD patients with APP gene mutations are significantly higher than in EOAD patients with PSEN-2 gene mutations.

7.4 Summary

In this chapter, we have estimated the rates of onset of EOAD due to PSEN-2 and APP gene mutations, based on published pedigrees. Missing data, mainly those of unaffected siblings of sufferers, have been a major problem. These estimates for the incidence rates of EOAD are not applied to insurance models as the data available from the published pedigrees with mutations in the PSEN-2 and APP genes are too scarce.

The question of the uncertainty surrounding the epidemiology of PSEN-2 and APP raises an important question about how such apparent risks should be handled by insurers. The information is inadequate to construct a model as was done for PSEN-1, but what there is points to considerably increased insurance risk. This is different from the cases with multiple endocrine neoplasia type II (Chapter 8) and hereditary haemochromatosis (Chapter 9) where there is also a lack of epidemiological information but the etiology, natural history and clinical management of both disorders suggest an absence of increased insurance risk.

We note the exceeding rarity of PSEN-2 mutations in the U.K. and the exclusion of PSEN-2 when the A.B.I. made submissions to GAIC (in December 2000) for EOAD, in respect of PSEN-1 and APP.

Should the fact that no kind of statistical model can be established mean that the insurer is obliged to treat PSEN2 risk as 'ordinary rates'? This could be consistent with existing legislation on sex and disability discrimination, that requires some degree of actuarial or statistical justification for discriminatory pricing, but it would lead to increasingly impractical underwriting as advances in knowledge split up

genetic disorders into heterogeneous subgroups (as the discovery of the APP, PSEN-1 and PSEN-2 genes did for EOAD). Finding a balance will be difficult but input from actuarial modelling will be important.

This chapter has highlighted the need for further research into the epidemiology of EOAD due to PSEN-2 and APP to provide reliable estimates of onset rates and survival rates after onset, so that actuarial modelling can be done. The application process to GAIC needs to be strengthened with more credible actuarial research (Wilkie, 2000).

Chapter 8

MULTIPLE ENDOCRINE NEOPLASIA TYPE 2

8.1 Introduction

The genetics and insurance debate in the U.K. originally concentrated on single-gene disorders, since these have the most serious implications, and within that class of disorders eight (later seven) disorders were listed as being of significance by the ABI. Several of these have now been the subject of actuarial models, including familial breast and ovarian cancer (Lemaire et al., 2000; Subramanian et al., 2000; Macdonald et al., 2003a,b), Huntington's disease (Gutiérrez and Macdonald, 2002a,b), Adult Polycystic Kidney Disease (Gutiérrez and Macdonald, 2003) and, in this thesis, EOAD. In all cases, the conclusions were that high extra premiums were indicated for CI insurance (and sometimes for life insurance) in respect of mutation carriers, moderated considerably if family history was the only known risk factor, but that adverse selection was unlikely to be a problem because of the rarity of these diseases.

Another of the disorders listed as potentially significant is Multiple Endocrine Neoplasia (MEN). In this chapter we present the first investigation of the insurance significance of MEN, with results that are completely at odds with any of the actuarial investigations of other single-gene disorders. This will lead us to the conclusion that the clinical significance and insurance significance, even of a highly penetrant single-gene disorder, can be completely different. This is an important message in

the context of the genetics and insurance debate, since it is usually assumed (for example, by the ABI originally) that significance for insurance follows automatically from clinical significance.

Referred to by Thakker (1998) as a syndrome of the twentieth century, MEN syndrome is characterised by the occurrence of tumours in two or more endocrine glands, within a patient. The endocrine gland is a ductless group of secretory cells that secretes one or more hormones into the bloodstream, helping to integrate and control bodily metabolic activities. MEN was previously known as multiple endocrine adenopathy and also as the pluriglandular syndrome.

MEN has several subtypes, of which the major forms are MEN type 1 (MEN1, also known as Werner's syndrome) and MEN type 2 (MEN2, Sipple's syndrome). MEN2 is the type that was listed by the ABI as being of significance for insurance.

MEN2 comes in three forms: multiple endocrine neoplasia type 2A (MEN2A), multiple endocrine neoplasia type 2B (MEN2B) and familial medullary thyroid carcinoma (FMTC).

MEN2A is an inherited disease characterised by medullary thyroid carcinoma (MTC), phaeochromocytoma — small vascular tumour of the adrenal gland which can cause increased blood pressure and heart rate, palpitations and headaches, and parathyroid adenoma — a benign tumour of the parathyroid gland which may undergo malignant change. MEN2A accounts for 90% of inherited MTC.

The much rarer and earlier onset MEN2B is characterised by MTC, phaeochromocytoma, and widespread tumours affecting the mucous membrane of the gastrointestinal tract. Patients have a characteristic facial appearance and marfanoid habitus — abnormal elongation of the long bones resulting in excessive tallness, abnormally long and slender toes and fingers.

FMTC is not associated with any endocrinopathy, and MTC occurs without the other abnormalities. FMTC represents the least aggressive form of MTC.

Table 8.19 (Thakker, 1998) lists the different tumours within specific endocrine glands characterised by each form of MEN. MTC occurs in about 95% of affected individuals, and phaeochromocytoma in about 50%.

Table 8.19: Subtypes of multiple endocrine neoplasia syndromes, with percentages of patients with the clinical symptoms. Source: Thakker (1998).

Type	Subtype	Syndromes (% patients)
MEN1		Werner's syndrome
		— pituitary adenomas
		— pancreatic islet cell tumour
		— adrenal cortical adenomas
		— hyperparathyroidism
		— associated tumours
MEN2	MEN2A	Sipple's syndrome
		— medullary thyroid carcinoma (MTC)
		— phaeochromocytoma (50%)
		— hyperparathyroidism (10–30%)
	MEN2B	— MTC
		— phaeochromocytoma (50%)
		— multiple mucosal intestinal ganglioneuromas (100%)
		— marfanoid habitus
		— other associated abnormalities like characteristic facies
	FMTC	— MTC

MEN2 syndromes are inherited as autosomal dominant disorders. MEN2 is uncommon and has been identified to date in 500–1,000 kindreds worldwide (Brandi et al., 2001). It has a high degree of penetrance and variable expression. The syndromes also occur sporadically. Therefore, clinical screening and genetic testing of patients is essential to determine whether the syndromes are familial or sporadic. This has been important to the patients and their families. Unless diagnosed with MEN2, one will not be aware of the precautions to be taken so that future generations in the family can avoid the disease's sometimes deadly ramifications.

Germline mutations in the RET (REarranged during Transfection) proto-oncogene on chromosome 10 have been identified in patients with MEN2 (Learoyd et al., 2000; Thakker, 1998). When a mutation on the RET proto-oncogene is found in an individual, it is advisable for relatives to undergo genetic testing and be monitored more closely. In cases where MEN2 is discovered early, the tumour present can be removed surgically and this is often curative. However, the symptoms often go undiagnosed due to their mild nature, and complications can set in as the disease progresses. Early diagnoses will mean earlier treatment before the disease becomes

deadly. If genetic testing detects the at-risks carrying the RET mutations, and necessary monitoring and treatment follow before irreversible damages occur, mortality will be normalised.

Wallin et al. (2001) mentions that mutation analysis of the RET proto-oncogene is crucial for decision-making regarding each patient. Carriers of MEN2 mutations should be offered prophylactic thyroidectomy with the potential to eliminate the risk for potentially lethal MTC. The report advises that patients should be treated at centres with adequate multidisciplinary expertise and competence as the operations are usually performed on healthy children, with confounding medical and ethical issues. As far as insurance is concerned, this means that presymptomatic genetic testing should normalise the mortality risk before the ages of economic activity are even reached.

8.1.1 Medullary Thyroid Carcinoma

Table 8.20: Characteristics of medullary thyroid carcinoma. Source: Lewinski et al. (2000).

	Sporadic	In FMTC	In MEN2A	In MEN2B
% of MTC	75%	7%	15%	3%
Mean age (yr)	44–50	41–43	21–38	12–23
Sex (M:F)	1:1.3	1:1	1:1	1:1
Proliferation	varies	slow	slow	invasive

Medullary tumors of the thyroid are the third most common of all thyroid cancers, after papillary and follicular thyroid cancers. Medullary thyroid cancer (MTC), also known as C-cell hyperplasia (CCH), accounts for approximately 4–5% of all thyroid cancers (Moley, 1995; Randolph, 2000). These malignancies arise from the parafollicular C cells of the thyroid gland. These C-cells secrete a hormone called calcitonin which acts to lower the concentration of calcium in the blood. An overproduction of calcitonin marks the onset of MTC.

Approximately 75% of MTC is sporadic, occurring as a non-inherited lesion (Randolph, 2000). The remaining 25% of the cases, with an autosomal dominant transmission, age-related penetrance and variable expressivity, occurs in one of the three

inherited forms: MEN2A, FMTC, and MEN2B. See Table 8.20.

The main morbidity from MEN2 is MTC, the aggressiveness of which depends upon the MEN2 variants, being most severe in MEN2B and least so in FMTC. Diagnosis of MTC is established by physical examination, elevated serum calcitonin levels and family history. As thyroid tissues are easily accessible to needles diagnosis is usually by fine-needle aspiration where a very small needle can be inserted and cells removed for microscopic examination.

Though MTC is significantly less common than the other thyroid cancers, it has the worse prognosis. MTC is highly malignant and is not curable unless diagnosed at an early stage. Medullary cancers tend to spread to large numbers of lymph nodes in the very early stage. It requires total thyroidectomy, an operation to completely remove the thyroid gland. If lymph nodes are involved, an additional and more aggressive central neck dissection is required to remove the lymph nodes of the front and sides of the neck. These remain the most desired treatments for patients with MTC due to a high incidence of multicentricity and the more aggressive course of this tumor. The level of calcitonin is measured after an operation to determine if the cancer is still present and recurrence can be detected by regular monitoring of the hormone.

Randolph (2000) quoted a 35% lifetime risk of developing disease for at-risk offspring of FMTC patients. The rate of progression is variable, and survival of 10 years or more with metastatic disease is not common.

The mean age at diagnosis is about 37 years (Koch et al., 2001). MTC has a much lower cure rate than papillary and follicular thyroid cancers. For all types of MTC, the 5-year survival rate is between 78% and 91%, and the 10-year rate between 61% and 75%. Survival probabilities are highest for FMTC and lowest in MEN2B (Randolph, 2000).

The clinical course of MTC varies according to the tumour characteristics with an overall 10-year survival rate of about 65% (Heshmati and Hofbauer, 1997). Age at onset, stage of disease and completeness of initial surgery affect the prognosis of patients with MTC significantly. The Endocrine Web Inc. has quoted an overall 10 year survival rate of 90% when all the disease is confined to the thyroid gland,

70% with spread to cervical lymph nodes, and 20% when spread to distant sites is present.

MEN2 patients diagnosed by biochemical or genetic screening have tumours at an earlier developmental stage, and have a higher chance of surgical cure. In a survey by Goretzki et al. (1998), only 5% of MEN2 patients diagnosed clinically was cured, compared with 59% and 100% cure rates for patients diagnosed biochemically and by genetic tests, respectively. See Table 8.21. We note that patients are regarded as surgically cured of MTC if their postoperative calcitonin levels are normal (Orlandi et al., 2001).

Table 8.21: Diagnosis and cure rates of MEN2. Source: Goretzki et al. (1998).

	Number of	Age (years)		Postoperative
Diagnostic test	patients	Mean	Median	calcitonin normal
Genetic	11	13	12	11 (100%)
Biochemical	32	24	25	19 (59%)
Index	20	45	40	1 (5%)

From an insurance point of view, this suggests that MTC is sufficiently severe that an asymptomatic person in an affected family would be regarded as high risk. This assumes that, in the absence of a genetic test, prophylactic surgery on all at-risk persons would not be carried out, but would be deferred until symptoms are detected by biochemical tests, or symptoms have become clinically overt at the later stages of the disease. Therefore, the development of a presymptomatic genetic test will reduce the the morbidity and mortality of the siblings and first cousins of the probands, some of whom (though asymptomatic) might have started developing tumours. They will be rated according to the current underwriting practice for MEN2 (Section 8.4). However, persons at-risk in the subsequent generations will be able to have their risks normalised with presymtomatic genetic screening at very young ages. Non-carriers will be cleared of their risks for MEN2 while carriers will have their risks effectively removed following preventive prophylactic surgery. Asymptomatic carriers diagnosed genetically will have their developing or already exisiting malignant disease completely cured (Goretzki et al., 1998).

8.1.2 Phaeochromocytoma

Phaeochromocytomas are small vascular catecholamine-secreting tumours located mostly in the adrenal medulla. Catecholamines, including adrenaline and noradrenaline, form a physiologically important group of substances with various essential roles in the nervous system. Phaeochromocytoma has an incidence rate of approximately 1–2 per 100,000 adults (Samaan et al., 1988; Sheps et al., 1990; van Heerden et al., 1982; Beard et al., 1983). With the peak incidence between the third and fourth decade (Modlin et al., 1979). From an autopsy study of 54 phaeochromocytoma patients at the Mayo Clinic in the period 1928–1977 however, the peak incidence was reported between the sixth and seventh decades (St. John Sutton et al., 1981). This discrepancy may be explained by the increased detection of the disease in its earlier stages.

By its uncontrolled and irregular secretion of the hormones adrenaline and noradrenalin, the tumour causes hypertension, and is associated with a wide variety of symptoms related to catecholamine secretion like increased heart rate, palpitations, sweating and headache. Uncontrolled release of catecholamine can give rise to lethal complications. Diagnostic evaluation is important for patients that show suggestive clinical symptoms. Surgical removal of the tumor is curative in more than 90% of all cases (Sheps et al., 1990; van Heerden et al., 1982; Gifford et al., 1994). The adrenal medulla can be removed as the gland is not essential for the general wellbeing of an individual. However as a potential fatal hypertensive crisis may be precipitated by anaesthesia or surgery, measures like administering of drugs to control the blood pressure need to be taken.

About 85% of phaeochromocytomas are sporadic while the remaining cases are familial and occur in association with simple familial phaeochromocytomas, MEN2A, MEN2B and other familial syndromes.

Phaeochromocytoma develops in about 50% of MEN2A patients and appears about 10 years after MTC diagnosis, and in 40–50% of MEN2B patients (Ball, 1996; Lewinski et al., 2000). The lifetime penetrance rates vary widey, from 10% to 90% among kindreds (Ball, 1996). As phaeochromocytomas in MEN type 2 carriers are rarely malignant, the main concern of undiagnosed phaeochromocytomas remains

the uncontrolled release of catecholamine, which in turn can lead to catastrophic consequences. The over secretion of adrenaline and noradrenaline if gone unnoticed can also lead to fatal hypertensive episodes. Due to improved management, phaeochromocytoma in both MEN2A and MEN2B has not been a major cause of death (Brandi et al., 2001). Phaeochromocytoma now accounts for less than 0.1% of hypertension in the general population (Ball, 1996).

Historically, serious complications arising from undetected cases of phaeochromocytoma were common. But genetic screening with periodic biochemical testing, modern imaging and surgical techniques have effectively minimised the morbidity and mortality stemming from phaeochromocytoma in MEN2. Phaeochromocytoma discovered by genetic screening is unlikely to have significant implications for insurance because symptoms will be accompanied by the more severe MTC in MEN2A or MEN2B. Insurance claims, if made, will be for the associated MTC (Section 8.1.1). Also, we note that persons at-risk may not develop phaeochromocytoma due to its very variable penetrance.

8.1.3 Hyperparathyroidism

Hyperparathyroidism (HPT) is the excess secretion of parathyroid hormone and it occurs in approximately 0.02–0.1% of the population (Gard, 1998). The symptom usually presents between ages of 30 and 60 years. HPT also occurs in 20–30% of MEN2A patients (Brandi et al., 2001) in which tumours arise within several endocrine glands simultaneously.

The predominant symptoms of HPT are those caused by hypercalcaemia — presence of abnormally high concentration of calcium in the blood: tiredness, lethargy and general unwellness, occasionally polyuria — excessive production of urine, dilute and of a pale colour with dehydration. If untreated, these will lead to increased muscular weaknesses and cardiac arrhythmias. There may be mental confusion culmulating in coma and death, renal stones and bone rarefraction. The usual treatment for HPT is by surgical removal of the parathyroid glands with follow-up drug treatment (Ball, 1996). Parathyroidectomy is performed if there is biochemical evidence of HPT expression or parathyroid tumours are encountered during thyroid

Table 8.22: RET proto-oncogene mutations. Source: Human Gene Mutation Database.

Mutation Type	Number	Phenotype(s)
Nucleotide substitution (Missense/ nonsense)	99	MEN2A/2B, FMTC, HSCR
Nucleotide substitution (Splicing)	14	HSCR
Nucleotide substitution (Regulatory)	1	HSCR
Small deletions	7	HSCR
Small insertions	5	MEN2A, FMTC, HSCR
Small insertions/deletions	2	MEN2A/2B
Gross deletions	1	HSCR
Complex rearrangements	1	HSCR
TOTAL	130	

surgery (Brandi et al., 2001). Delbridge et al. (1998) reports a 99% cure rate for surgery though disease recurrences still present a significant surgical challenge.

As with phaeochromocytoma, genetic screening for HPT in MEN2A is unlikely to have significant implications for insurance on its own, due to its low penetrance, mild nature and the availablility of effective treatment. Again, insurance claims, if made, will be for the accompanying MTC which is much more severe.

8.2 The RET proto-oncogene

The RET proto-oncogene encodes a cell-surface glycoprotein related to the family of receptor tyrosine kinases, which are cell-surface molecules that interpret signals for cell growth and differentiation (Brandi et al., 2001). Containing 21 exons, the gene is located on chromosome 10q11.2, covering about 60kb of genomic region.

Mutations in the RET proto-oncogene result in the unregulated activation of oncogenic tyrosine kinases and confer a gain of function at the cellular level. Unlike susceptibility genes implicated in other familial cancers where both alleles need to be affected for expression of the disease, mutations in the RET proto-oncogene are dominant. Germline RET proto-oncogene mutations are responsible for two strikingly different disorders, the MEN2 syndromes and Hirschsprung disease (HSCR). Table 8.22 lists the current known number of mutations of the RET proto-oncogene classified under the type of mutations, provided by the Human Gene Mutation Database

(HGMD). MEN2 syndromes are associated with germline mutations in exons 10, 11, and 16 of the RET proto-oncogene.

8.2.1 RET proto-oncogene mutations

Approximately 97% of MEN2A patients, 95% of MEN2B patients and 86% of FMTC patients have germline mutations in the RET codons listed in Table 8.23.

Table 8.23: Summary of RET proto-oncogene mutations. Source: Randolph (2000).

Subtype	Cases with mutations	Exon	Codons
MEN2A	97%	10	609, 611, 618, 620
		11	630, 634
		13	768, 790
MEN2B	95%	15	883
		16	918, 922
FMTC	86%	10	609, 611, 618, 620
		11	630, 634
		13	768, 790, 791
		14	804
		15	891

Mutations causing MEN2A and FMTC are mainly confined to codons for cysteine residues in exons 10 and 11 of the gene. Individuals in MEN2A families carrying the defective gene have a very high chance of developing MTC; the penetrance being age-related (Lips et al., 1994). Rare germline mutations occurring in exons 13 and 14 have also led to FMTC.

The missense mutation, a 'T' to 'C' transversion in codon 918 resulting in the conversion of methionine to threonine, is associated with 95% of MEN2B cases (Kahn et al., 1996; Randolph, 2000; Siegelman et al., 1997; Toogood et al., 1995). The mutations in codons 883 and 922 (Table 8.23) account for only a handful of MEN2B cases.

8.2.2 Prevalence and age-related penetrance

Prevalence of MEN2 has been estimated to be one in 20,000–30,000 (Learoyd et al., 2000; Wiesner and Snow-Bailey, 2003). The incidence of MTC is estimated at 20–25

new individual cases per year among the 55 million residents in the United Kingdom (Ponder, 1997).

Penetrance of MEN2 syndromes is age-related. Approximately 70% of MEN2A mutation carriers present with MTC by age 70 years (Randolph, 2000).

Using standard screening tests to detect earliest manifestation of the syndrome, Easton et al. (1989) reported high penetrance for RET mutations predisposing to MEN2A, and the estimated penetrance by age 31 to be 93%. However when based on clinical history, the report estimated that 41% of the carriers were not presenting with the disease by age 70.

MEN2A and FMTC are often associated with family history whereas approximately 50% of MEN2B cases are *de novo*.

Over their lifetime, more than 95% of individuals with inherited RET mutations that are associated with MEN2 will develop MTC if the thyroid gland is not removed before the disease is diagnosed by clinical symptoms (Ball, 1996). The average age of onset differs among the three inherited syndromes. It is in the childhood years for MEN2B, in the third decade of life for MEN2A, and fourth decade for FMTC (Randolph, 2000). See Table 8.20.

MEN2B has 100% penetrance and a variable expression. The first clinical expression in all MEN2 cases is a growing cervical mass on the site of the thyroid place and marfanoid habitus. The inherited forms also differ in aggressiveness; the tumours are least aggressive in FMTC, and are most aggressive in MEN2B (Brandi et al., 2001).

8.2.3 Genotype-phenotype correlation

Different RET mutations are highly correlated with different clinical features of the MEN2 syndrome. Besides the interfamilial variation due to different germline mutations, there are variations between individuals within the same family which may be due to chance, environmental factors or modifying gene effects.

In a study to establish the relationship between specific mutations and the presence of certain disease features in MEN2, the International RET Mutation Consortium (Eng et al., 1996) carried out a correlative survey study of 477 MEN2 families

from 18 tertiary referral centres worldwide. Statistically significant association was found between the presence of mutations in codon 634 and the presence of phaeochromocytoma and HPT. Mutations at codons 768 and 804 were seen only with FMTC, and codon 918 mutation was MEN2B specific. Patients with Hirschsprung disease presenting with the rare mutations occurring in both MEN2 and Hirschsprung disease families are advised to be monitored for possible development of MEN2 tumours. The consortium suggested that genotype-phenotype correlations existed and further understanding of these correlations could prove useful in clinical management with respect to screening, surveillance, and prophylaxis. Insight could also be provided into the genetic effects of particular mutations.

Table 8.24: Stratified levels for MTC risks according to the mutated codon on the RET proto-oncogene. Level 3 is the most severe. Adapted from Brandi et al. (2001).

Mutated codons	Syndrome(s)	Level	Recommended action(s)
883, 918, 922	MEN2B	3	Thyroidectomy within first 6 months of life
611, 618, 620, 634	MEN2A, MEN2B, FMTC	2	Thyroidectomy before age 5 years
609, 768, 790, 791, 804, 891	MEN2A, FMTC	1	Thyroidectomy between age 5 and 10 years. Periodic biochemical testing for MTC expression if Thyroidectomy not performed

The mutated RET codon and the features within the family are important in planning thyroid management. A consensus statement has been reached during the international MEN97 Workshop where the risk for MTC is being stratified according to the mutated RET codon (Brandi et al., 2001). Table 8.24 lists the three stratified levels of MTC risks, level 3 being the level with the highest risk.

The correlation between genotype and phenotype in MEN2 syndrome highlights the ability of genetic testing to reveal great heterogeneity in one syndrome. Underwriting may become more complex if syndromes previously thought homogeneous but variable become heterogeneous with much reduced sample sizes. More underwriting classes, each with a smaller pool size, may be harder to administer without clear distinction among classes. Actuarial justifications may be required to justify the more detailed underwriting.

8.3 Genetic and biochemical screening

Delbridge and Robinson (1998) suggest that molecular genetic screening for endocrine disease is cost-effective and the required therapy acceptable and well-tolerated. Genetic screening for germline RET mutations in members of MEN2 families is cost-effective and now widely performed (Delbridge et al., 1998; Brandi et al., 2001). A worldwide survey conducted by the International Association of Endocrine Surgeons of its members showed that molecular genetic screening for endocrine disease is available in 67% of institutions.

Screening based on DNA analysis requires a single blood test which can provide diagnostic information before development of foci of MTC. Once a mutation of the RET proto-oncogene is identified in an individual of the family, screening of at-risk members should be carried out so that beneficial total thyroidectomy can be performed on family members carrying the mutation.

Of those who present with clinical signs and symptoms, almost half die of the disease and others may suffer significant morbidity. By contrast, early diagnosis by screening of family members allows for effective treatment with thyroidectomy. Testing of first-degree relatives of patients with MTC should be started by the age of 3 to 5 years. In families with the MEN2B syndrome, screening should be started during the first year after birth and include a search for the characteristic phenotype. See Table 8.24.

Early intervention and screening is vital in reducing morbidity rates of MEN2. A rapid, inexpensive, nonradioactive screening technique was presented by Siegelman et al. (1997). It can detect germline mutations in the RET proto-oncogene with a sensitivity of about 90%. Once the presence of the mutation is confirmed, the method could be used to screen additional family members at relatively low cost.

8.4 Insurance Implications

Rating of MEN cases depends on successful surgery to remove the tumours and effective follow-up to detect the presence of developing malignancies (Brackenridge and Elder, 1998). Carriers of RET proto-oncogene mutations and those at risk of

carrying mutations are only considered for insurance if they are subjected to yearly biochemical tests for microscopic MTC, or in the case of at-risk persons, if they are cleared from the at-risk category by genetic screening.

In the absence of any moratorium, at-risk individuals are unlikely to purchase insurance, whether life or critical illness policies, at a greater than normal rate. Based on their family history, they would have been advised to undergo screening to determine whether they are carriers of the disease genotypes. Asymptomatic carriers tested positive for the RET proto-oncogene mutations will have a greater propensity to opt for thyroidectomy. There should be few MEN2 carriers opting out of thyroidectomy as MTC, once developed, is deadly.

We assume that the availability of genetic tests for RET mutations in a clinical setting, together with the very high success rate of surgery following genetic testing at an early enough age (Table 8.21) will mean that once a family has been identified as carrying a RET mutation causing MEN2, all at-risk persons will be screened, and as a result their risk will be reduced to the minimum possible.

One slightly circular reason for making this assumption is that, were we to assume otherwise and hence load premiums for the risk that people opt not to be tested, we would create the very reason why they might opt not to be tested. This is exactly the concern that insurance considerations may deter people from having tests that are entirely beneficial, and it is, we believe, incumbent on the industry to avoid creating the circumstances where it can happen, when it is genuinely avoidable. When effective interventions exist, any clear signal from the insurance industry (that a test either will or will not be regarded as relevant) might become self-fulfilling.

Therefore, the only remaining risk that might trouble insurers is siblings or first cousins of a person who is the first family member diagnosed with MEN2, because they may have passed the ages at which either biochemical or genetic screening can normalise the risk. This problem ought to be small and diminishing, because of the rarity of MEN2, and is covered by the existing practice outlined in Brackenridge and Elder (1998).

The other MEN2 symptoms, HPT and phaeochromocytoma, also do not have any implications for insurance. Morbidity and mortality due to phaeochromocytoma

have improved dramatically following improved surgical techniques and management of the disease (Brandi et al., 2001). HPT is rare among MEN2 patients and in most cases, symptoms are not present (Ball, 1996; Brandi et al., 2001). Parathyroidectomy is a simple procedure with an extemely high cure rate (Ball, 1996; Delbridge et al., 1998).

8.5 Summary

MEN2 provides a unique model for early prevention and cure of cancer, and for differentiated roles of mutation-based diagnosis of carriers (Brandi et al., 2001). The mutated codon of the RET proto-oncogene correlates with the MEN2 variant and the aggressiveness of MTC.

Detailed family history of a MEN2 family is extremely important, allowing proper screening and follow up to be carried out. Determination of MEN2 carriers by genetic screening allows a highly effective clinical intervention. Early detection and intervention can alter the course of MTC, improving the prognosis of the patients. There is a direct correlation between tumour stage at diagnosis and the success of postoperative cure (Goretzki et al., 1998). Treatment of early MTC by thyroidectomy is well tolerated by most infants, and there is evidence for long-term cure in most children operated upon (Brandi et al., 2001).

In EOAD, genetic tests reveal groups with higher risks. Increased premium rates for carriers and adverse selecting can be of concern to the insurer because there are no effective intervention or treatment strategies for AD. In contrast, genetic tests and intervention normalise or reduce the risk for MEN2. With no genetic tests, prophylactic surgery on asymptomatic persons at-risk is unlikely to be carried out, hence members of at-risk families always carry with them their Mendelian risk and would be declined or rated (as in Brackenridge and Elder (1998)). With genetic testing, those who are non-carriers are clear but those who are carriers can have their risk reduced by a simple and effective surgery.

Other than the current generation of the proband, the at-risk individuals in the subsequent generations will be cleared of the risk if they opt for the genetic tests and

undergo the necessary prophylactic surgery to cure or prevent the disease. It will be undesirable if the experience of insurance declinature or higher ratings received by at-risk persons discourage future genetic screening for a disease which is preventable or curable when diagnosed at an early stage, or can have its prognosis improved through prophylactic surgery and follow up management following genetic diagnosis.

This chapter on MEN2 suggests that classification of genetic disorders into single-gene/multifactorial may be too coarse for insurance purposes. A more detailed stratification may be necessary as we learn more of the etiology and epidemiology of these genetic disorders.

Chapter 9

HEREDITARY HAEMOCHROMATOSIS

9.1 Introduction

Hereditary haemochromatosis (HHC) is an autosomal recessive disorder of iron metabolism. This contrasts with the autosomal dominant inheritance patterns of EOAD and MEN2 studied so far. HHC is the commonest genetic disorder in white populations, affecting one in 200–300 people of Northern European or Anglo-Saxon descent (Merryweather-Clarke et al., 1997). David Porteous, Professor of Medical Genetics at the University of Edinburgh and a member of the GIRC steering committee, has recommended the study of HHC, its actuarial implications for insurance and the cost-effectiveness of population screening for this very common hereditary disease which looks to have a wide social and economical role to play.

HHC was first described in 1865 as a clinical triad consisting of:

- glycosuria — presence of excessive amount of glucose in the urine;
- cirrhosis — a condition in which interlacing strands of fibrous tissue are generated, together with the formation of regenerating cells, causing widespread disruption to the normal structure and functions of the liver; and
- hyperpigmentation of the skin — abnormal coloration of the skin caused by deposition of bodily pigment in excessive quantity.

The disorder is characterised by progressively high iron absorption from the gut and deposition of excess iron in major organs of the body like the liver, pancreas, heart, joints, and pituitary gland. Without treatment, chronic increase in iron overload can cause cirrhosis, primary liver cancer, diabetes and cardiomyopathy, ultimately leading to death.

Phlebotomy, repeat venesection, is simple and effective if the treatment is instituted before organ damage has occurred. However, due to the non-specific nature of clinical manifestations, HHC is often diagnosed after life threatening complications have set in (Bradley et al., 1998).

9.1.1 Clinical Features

Patients with haemochromatosis regularly absorb two to three times as much dietary iron as normal persons. Excess iron is deposited in the liver, heart, pituitary gland, pancreas, and parathyroid gland. Most do not have symptoms until adulthood, though the transferrin saturation (TS) is usually increased by adolescence. Transferrin is a protein in the blood plasma which combines with ferric ions and transports iron in the body. When the TS level exceeds 50% in premenopausal women and 60% in men and postmenopausal women, haemochromatosis should be suspected (Andrews, 1999). Ferritin is an iron-containing protein found especially in the liver and spleen that functions in the storage of iron. In untreated HHC patients, the serum ferritin (SF) concentration will increase progressively over time. However, it cannot be used alone to diagnose the disease as it is not specific for HHC (Kowdley et al., 2000).

Early symptoms of the disease may include fatigue, pain in one or more joints, palpitations, abdominal pain, erectile dysfunction, increased skin pigmentation and general weakness. Because of the non-specific nature of these symptoms, HHC is often not diagnosed at this stage.

Tender enlargement of the liver develops as the disease progresses and this later leads to liver fibrosis and cirrhosis. There is increased incidence of carcinoma of the liver cells. The disease can ultimately lead to hyperpigmentation of the skin, arthritis, chronic abdominal pain, and severe fatigue.

Iron deposition in the heart causes cardiomyopathy. Conditions associated with diseases of the endocrine glands like diabetes mellitus, hypopituitarism — deficient production of growth hormone by the pituitary gland, hypogonadism — functional incompetence of the ovaries or testes, and hypoparathyroidism — deficiency of the parathyroid hormone in the body, may develop. Patients are also more susceptible to certain bacterial infections. As most of these advanced complications are common primary disorders, HHC may still be undiagnosed unless iron overload is specifically looked for.

Symptoms of HHC usually appear between the fourth and sixth decades of life. It is this late onset that makes it potentially significant for insurance. Onset in women is normally later, likely due to the loss of iron with menstruation, pregnancy and lactation. Men are more likely to develop clinical symptoms of the disease. It is noted too that the symptoms and disease complications increase with age (Hanson et al., 2001).

9.1.2 Insurance and Health Cost Implications

Iron overload diseases are very common conditions and HHC is the most frequent form of genetically determined iron overload and one of the most common hereditary metabolic diseases in Caucasians.

All of the genetic disorders that have, to date, been the subject of actuarial models have been dominantly inherited. There are a number of reasons for this, including the fact that someone who is heterozygous for a dominantly inherited disorder still has one working copy of the gene, which can sometimes sustain health for long enough that late onset results, and late onset is important for insurance. Inheritance of a recessive disorder implies complete loss of function, which usually is incompatible with late onset.

HHC is recessively inherited but has very variable expression, and modest penetrance (see Section 9.2.3). Therefore, homozygosity is not incompatible with late disorder, so it is potentially significant for insurance. However, these same features mean that it is unlikely to impose the same burden as the severe dominantly inherited disorders. These are reasons why it should be included in the genetics and

insurance debate.

In the following sections, we review the mutations in the haemochromatosis gene (HFE) responsible for HHC, the diagnostic and therapeutic management of the disease.

Our concluding section investigates the possible insurance implications of HHC, the effect of early detection of the disease, and possibility of any adverse selecting by persons at risk.

9.2 The Haemochromatosis Gene

The HFE gene was mapped in 1996 on the short arm of chromosome 6, by extensive positional cloning by many groups over a period of 20 years. The HFE gene is located at 6p21.3 and covers approximately 10 kilobases.

The HFE protein is a transmembrane protein involved in regulating iron homeostasis. The normal HFE protein product binds to the transferrin receptor and reduces its affinity for iron-loaded transferrin by 5 to 10 times.

9.2.1 HFE gene mutations

The majority of patients with HHC are descended from a common Celtic ancestor who lived 60–70 generations ago (Andrews, 1999), carrying a missense mutation (C282Y) on the HFE gene.

C282Y (substitution of a tyrosine for a conserved cysteine in codon 282) and H63D (substitution of an aspartic acid for a histidine in codon 63), two missense mutations of the 37 allelic variants of the HFE gene described to date (Pointon et al., 2000), are significantly correlated with HHC. Homozygosity for the C282Y mutation accounts for 60–100% of HHC patients (Pointon et al., 2000), and was found in the majority of studies on clinically diagnosed probands. Beutler et al. (1996) reports that 82.3% of haemochromatosis patients are homozygous for the C282Y mutation with 6.8% heterozygous in the same mutation. These figures are consistent with those in Table 9.25 which presents the percentage of HHC probands with the various genotypes, from a review by Hanson et al. (2001). The global

Table 9.25: HFE genotypes as percentage composition (with 95% confidence intervals) of HHC probands in a review by Hanson et al. (2001) (2,229 probands in Europe and 2,929 globally). '++' denotes mutation in both copies of the gene, '+−' denotes mutation in one copy, and '−−' denotes normal gene copies.

Percentage of Probands (%)		Mutation	
Europe	Global	C282Y	H63D
75.4 (73.6,77.2)	77.5 (75.9,79.0)	++	−−
5.8 (4.9,6.9)	5.3 (4.5,6.2)	+−	+−
3.9 (3.9,4.8)	3.6 (2.9,4.3)	+−	−−
1.6 (1.1,2.2)	1.5 (1.1,2.1)	−−	++
5.9 (4.9,6.9)	5.2 (4.4,6.1)	−−	+−
7.4 (6.3,8.5)	6.9 (6.0,7.9)	−−	−−

figures are compiled from studies in North America and Australia.

The role of HFE in the process of normal iron metabolism has yet to be clearly defined, though mechanisms by which C282Y and H63D may disrupt the normal functioning of HFE have been suggested. The C282Y mutation results in a greater loss of protein function than does H63D. The C282Y mutation alters the HFE protein structure and beta2-microglobulin association, disrupting its transport to and presentation on the cell surface. Beta2-microglobulin is a lightweight protein usually present at low level in plasma which is homologous in structure to part of an antibody and forms part of the body's immune system. The role of the H63D mutation in HHC is still unclear.

From twenty haemochromatosis probands who lacked C282Y homozygosity, C282Y/H63D compound heterozygosity, or H63D homozygosity, Barton et al. (1999) discovered two novel mutations of the HFE gene, I105T and G93R, and identified a S65C mutation. They show that uncommon HFE exon and intron mutations may be discovered among haemochromatosis patients who do not carry the 'typical' HFE genotypes. Table 9.26 lists the 20 coding mutations which have so far been identified in the HFE gene, as adapted from Pointon et al. (2000). Some of these mutations were identified in individuals with iron overload conditions whereas others have no proven disease association. Pointon et al. (2000) also lists 17 diallelic intronic polymorphisms which are not thought to be implicated with HHC.

Table 9.26: HFE gene mutations showing nucleotide change, location within the gene, adapted from Pointon et al. (2000).

Mutation Type	Mutation	Location	Comments
Missense	V53M (157G→ A)	Exon 2	Identified in South African and bushman populations
	V59M (175G→ A)	Exon 2	Identified in 1 out of 102 control Caucasians in South Africa
	H63D (187C→ G)	Exon 2	Mutation implications in some cases of HHC
	S65C (193A→ T)	Exon 2	First described in a normal realtive of a C282Y homozygous patient
	G93R (277G→ C)	Exon 2	In HHC affected sibs who were compound heterozygotes for C282Y and G93R
	I105T (314T→ C)	Exon 2	In a family in which a compound heterozygote for I105T and H63D has HHC
	Q127H (317A→ C)	Exon 3	Identified in a compound heterozygote in severely affected varigate porphyria patient
	V272L (814G→ T)	Exon 4	Identified in one individual
	E277K (829G→ A)	Exon 4	Identified in 1 Asian male with normal iron indices
	C282Y (845G→ A)	Exon 4	Mutation causing most cases of HHC
	R330M (1198G→ T)	Exon 5	Identified in one C282Y and H63D-negative HHC referal
Synonymous	H28H (84C→ T)	Exon 2	Found in one obligate C282Y carrier
	H63H (189T→ C)	Exon 2	Silent mutation
	V212V (636G→ C)	Exon 4	Silent mutation
Frameshift	P160△ C	Exon 3	Single cytisine deletion; found in a heterozygous HHC patient with no other HFE mutation
	V68△ T	Exon 2	Single base deletion leading to premature termination of codon 19 amino acids downstream; identified in a C282Y heterozygous patient
Splice site	IVS3+1G→ T	Intron 3	Guanine-to-thymine transversion; found in a single Caucasian family, causing HHC in conjunction with C282Y heterozygosity
Non-coding region	-7T→ C	5' UTR	thymine-to-cytosine transition 7 nucleotides upstream of the translation initiation codon; found in a patient with dysmetabolic iron syndrome
	124G→ C	3' UTR	Guanine-to-thymine transversion at nucleotide 124 of exon 7 (nucleotide 2,186)
	poly A+5 (C→ T)	3' UTR	Cytosine-to-thymine transition at nucleotide 2,484

9.2.2 Phenotypic expressions

Mutations in the HFE gene are more widespread than their phenotypic expression, and epidemiological studies suggest the heterozygous state may be implicated in the expression of other diseases of the liver. Adams (1999) explains that the discrepancy between the genotyping and clinical disease is due to the failure to detect haemochromatosis in many patients with nonspecific symptoms like diabetes, impotence, arthritis, fatigue and minor liver dysfunction. Besides underdiagnosis of haemochromatosis in patients with the disease, haemochromatosis is also overdiagnosed in those without the disease (Adams, 1999). Many patients with end-stage liver disease can have a high level of TS or SF with minor iron overload and may have been wrongly classified as having haemochromatosis by liver biopsy.

It appears that mainly patients homozygous for the C282Y mutations develop severe iron overload, while heterozygotes for C282Y, H63D and homozygotes for H63D seem much less likely to develop iron overload.

9.2.3 Prevalence and penetrance

Table 9.27: HFE genotype frequencies in white subjects, predominantly of northern European heritage, as given in Bradley et al. (1998).

		Bradley *et al.*		Published controls†		Combined	
C282Y	H63D	No.	Frequency per 10,000	No.	Frequency per 10,000	No.	Frequency per 10,000
++	−−	7	70	3	32	10	51
+−	−+	22	220	25	266	47	242
+−	−−	97	969	79	839	176	906
−−	++	17	170	19	202	36	185
−−	+−	246	2,457	212	2,253	458	2,358
−−	−−	612	6,114	603	6,408	1,215	6,256
All genotypes		1,001		941		1,942	

† Jouanolle et al. (1996) (n=95); Roberts et al. (1997) (n=101); Merryweather-Clarke et al. (1997) (n=413);

C282Y is most frequent in northern European populations and absent from African, Asian and Australasian populations. Mutation in the HFE gene remains a rare cause of iron overload among indigenous persons of the Asia-Pacific region. Merryweather-Clarke et al. (1997) found allele frequencies of 3.8% for C282Y and 13.6% for H63D in the European population. These figures compare well with those of Bradley et al. (1998) which gives allele frequencies of 6.6% and 15.1% for C282Y and H63D respectively. Worldwide allele frequencies are lower, 1.9% for C282Y and 8.1% for H63D (Merryweather-Clarke et al., 1997). Genotype frequencies and C282Y and H63D allele frequencies are not statistically different between males and females (Bradley et al., 1998). Table 9.27 displays the HFE genotype frequencies in white subjects, predominantly of northern European heritage, as given in Bradley et al. (1998).

Bradley et al. (1998) reports a HHC prevalence of 60 per 10,000. The prevalence ranges from 50 to 90 per 10,000 in published literature (Hanson et al., 2001).

Consistent with the theory of a proposition of a north European origin for the mutation, the distribution of the C282Y mutation coincides with that of populations with cases of haemochromatosis. Bradley et al. (1998) reports that homozygosity for the C282Y mutation occurs in 51 per 10,000 white Northern European subjects, corresponding well with the HHC prevalence of about 60 per 10,000. Globally, the frequency of the C282Y/C282Y genotype is 0.4% (Hanson et al., 2001). C282Y heterozygosity ranges from 9.2% in Europeans to nil in Asian, Indian subcontinent, African/Middle Eastern, and Australasian populations.

The H63D polymorphism is more widely distributed with unclear association with haemochromatosis. The H63D carrier frequency is 22% in European populations. Table 9.28 shows the European and global HFE genotype frequencies in the general population, as given in Hanson et al. (2001).

Table 9.28: HFE genotype frequencies (per 1,000) in the general population, as given in Hanson et al. (2001); with 95% confidence intervals.

C282Y	H62D	European (6,203)	Global (11,668)
++	−−	4 (3,6)	4 (3,5)
+−	−+	18 (14,21)	16 (14,19)
+−	−−	92 (85,100)	78 (74,83)
−−	++	20 (16,24)	19 (16,21)
−−	+−	216 (206,226)	194 (187,202)
−−	−−	651 (639,663)	689 (680,697)

Accurate data on the penetrance of the different HFE genotypes are not available. Extrapolating from clinical observations in screening studies, Hanson et al. (2001) estimates that 40–70% of persons with the C282Y homozygous genotype will develop clinical evidence of iron overload. A smaller proportion will die from complications of iron overload. Compound heterozygotes for both the C282Y and H63D mutations have a significant risk of developing HHC.

Early population screening studies to establish HHC prevalence were based on the biochemical expression of HHC rather than on clinical expression of the disorder. This may explain the apparent high penetrance of the homozygotes for the C282Y mutation in the HFE gene. Willis et al. (2000) reports that deaths attributed to HHC are rare in Britain, despite the fact that 1 in 250 of the 700,000 who die in

Britain annually is homozygous for the C282Y gene.

In one of the largest DNA-based genetic epidemiological studies ever conducted, Beutler et al. (2002) screened 41,038 individuals attending a health appraisal clinic in the U.S. for the C282Y and H63D mutations. Laboratory data and data on signs and symptoms of haemochromatosis as elicited by questionnaire were analysed. The authors concluded that the most common symptoms of haemochromatosis were no more prevalent among the 152 identified C282Y homozygotes than among the controls. The age distribution of homozygotes and compound heterozygotes did not differ significantly from that of the controls. Only one of the 152 homozygotes had signs and symptoms that would suggest a diagnosis of haemochromatosis. Beutler et al. (2002) estimates that fewer than 1% of homozygotes develop frank clinical haemochromatosis, which is a much lower penetrance than generally thought (see Section 9.2.3). The authors pointed out that previous high percentage estimates of homozygotes developing clinical haemochromatosis may be due to the fact that those estimates were based upon the occurrence of symptoms such as arthritis and diabetes that are also common in the normal population. This result from this study is substantiated by a large Scandinavian study by Åsberg et al. (2001), where only 4 persons were found to have liver fibrosis out of more than 65,000 subjects screened by determining their blood iron levels.

9.3 Management of HHC

9.3.1 Treatment

Therapeutic phlebotomy (venesection) is the surgical removal of blood and is a safe, effective and inexpensive treatment for haemochromatosis. The treatment consists of weekly removal of 450—500 mL of blood (containing 200—250 mg of iron) until the SF level is approximately 20—50 μg/L and TS $< 30\%$ (Adams, 1999; Adams et al., 2000). This venesection therapy has not changed substantially since 1950. Ideally, therapy is begun before clinical symptoms appear. Patients can have a normal life expectancy and quality of life if treatment starts before end-stage organ damage has occurred. If phlebotomy is instituted later, it can still improve symptoms, relieve

liver enlargement and tenderness, and protect joints from arthritis (Andrews, 1999).

However, it has not been a practice to recommend venesection therapy on immediate detection of homozygosity for the C282Y mutation without positive demonstration of iron overload (Adams and Chakrabarti, 1998). In a young adult who is homozygous for the C282Y mutation with normal iron studies, Adams and Chakrabarti (1998) recommends careful assessment for pathological blood loss and a repeat assessment with biochemical iron studies in 5 years. Venesection therapy is only started if the serum ferritin level increases to above the normal range (>200μg/L for non-pregnant, premenopausal women and >300μg/L for men and postmenopausal women).

Maintenance venesection is then performed three to four times per year for men and one to two times per year for women. This is done on a lifelong basis to maintain the iron stores in the normal range, as determined by the serum ferritin level and transferrin saturation. Continuing monitoring is essential as the rate of iron reaccumulation is highly variable, and many patients will continue to have an elevated transferrin saturation value despite iron depletion (Adams, 1999).

In addition to performing phlebotomy, it is important to advise patients to modify their diets, to avoid iron supplementation and to restrict intake of vitamin C which facilitates absorption of iron. Consumption of red meat and alcohol must be limited, and raw shellfish avoided as cases with fatal infection have been reported with haemochromatosis patients (Barton et al., 1998).

9.3.2 Survival Rates

The prognosis of untreated HHC is affected by the duration and amount of excess iron storage present in the liver at diagnosis. Before 1935, death occurred within 1–5 years of presentation. Medical advances both in the areas of early diagnosis and treatment have significantly improved the survival rates, with median survival after onset of up to 15 years after clinical presentation if treated early with phlebotomy (Brackenridge and Elder, 1998). The survival rates are poor for untreated HHC patients, 18% and 6% for 5 years and 10 years after diagnosis respectively (Adams et al., 2000).

Overall life expectancy is worse in HHC patients, and death can occur from cirrhosis, hepatoma, cardiac dysfunction and diabetes. Presence and level of liver cirrhosis is the primary factor affecting survival. Symptomatic HHC patients have lower survival than the normal population in general. Advanced ages (greater than 60 years) and alcohol abuse are other factors which may worsen the prognosis of cirrhotic HHC patients (Fargion et al., 1992).

However if phlebotomy is initiated before the development of cirrhosis, survival does not differ significantly from that of the normal population (Niederau et al., 1996). Certain non-fatal complications like arthritis may still persist despite early initiation of treatment. Those with evidence of liver injury may have the progression of hepatic fibrosis stopped by phlebotomy, but the risk of hepatoma remains.

9.4 Testing and population screening for HHC

The discovery of the HFE gene and its associated mutations have made screening for HHC a new possibility. Genetic testing for the C282Y and H63D mutations can help to reduce the cost of HHC case detection and lighten the dependence on liver biopsy with its associated morbidity and mortality (Bassett et al., 1997).

Though the most sensitive means of testing for iron overload is the TS test, the predictive power of a TS test is poor. This is primarily due to low prevalence of HHC, compounded by the variability and uncertainty about laboratory proficiency (McDonnell et al., 1999). Hence a combination of iron status and DNA testing may offer the best specificity and sensitivity to detect risk from iron overload.

The availability of a genetic test for haemochromatosis has given rise to controversy about the benefits of screening for the disease. There are fears that persons found to be homozygous for the C282Y mutation may face discrimination when purchasing health and life insurance. Also, the test is not always predictive. Adams and Chakrabarti (1998) have described both iron-loaded patients without the C282Y mutation in the HFE gene, and homozygous patients for the C282Y mutation without iron overload.

9.4.1 Liver Biopsy

Liver biopsy has been the standard diagnostic test for haemochromatosis before the availability of genetic tests. It has been useful in evaluating the magnitude and distribution of iron overload within the liver. Liver biopsy still remains important for patients with additional risk factors for liver disease such as alcoholism and viral hepatitis. Patients with unexplained elevations in serum ferritin level but with a negative genetic test will also require liver biopsy.

Niederau et al. (1996) and other studies have demonstrated that cirrhosis is a major risk factor determining the long-term outcome in haemochromatosis as hepatocellular carcinoma and liver failure remain the most frequent causes of death. Liver biopsy then plays an important role as a prognostic test in haemochromatosis.

If a heterozygote for the C282Y mutation has iron levels elevated into the range anticipated for a homozygote (ferritin $>$ 1000 ng/mL), a biopsy should be performed to determine whether venesection therapy is necessary. These atypical cases could be due to mutations that are yet to be discovered.

9.4.2 Genetic Testing

Genetic testing for HHC is a simple polymerase chain reaction-based test on DNA obtained from a blood sample. It provides a powerful non-invasive method to detect the C282Y and H63D missense mutations. The genetic test is available in UK and the cost is approximately £10 (Worwood, 2001) for both mutations.

Detection of HFE gene mutations can supplement iron studies to confirm the diagnosis in symptomatic patients and more importantly, to identify individuals at risk for developing haemochromatosis. Genotyping is also more accurate than iron studies as results of genetic testing are independent of diet, alcoholism or other conditions which might affect the TS or SF levels.

9.5 Implications for Insurance

By measuring the serum transferrin saturation or hepatic iron content level, the diagnosis of HHC can be made in the presymptomatic state. All complications from

the iron disorder can be avoided once the iron stores are lowered by phlebotomy. A HHC patient who does not show evidence of liver disease and who is undergoing regular treatment is a standard risk when purchasing life insurance (Brackenridge and Elder, 1998). Table 9.29 shows the ratings applicable to a person with HHC with various conditions of the disease. Though heterozygotes in the C282Y mutation are given normal ratings, we note from Section 9.2.1 that heterozygotes in the C282Y and H63D mutations have a significant risk of developing HHC, and there are a significant proportion of HHC expressions not linked to the C282Y and H63D mutations.

Table 9.29: Ratings for life insurance as given in Brackenridge and Elder (1998)

Condition(s)	Rating (%)
Non-cirrhotic, non-diabetic, treated & followed	0
Early liver fibrosis or mild diabetic without complications or proteinuria	+100
Established cirrhosis, hepatoma	decline
Cardiomyopathy	decline
Diabetes other than above, not otherwise declinable	rate as diabetes
Incomplete details, followed	+100 or more
Diagnosis definite, not followed	decline
Heterozygotes	+0

Anti-selection with HHC might not have a heavy impact on critical illness insurance. Though potentially fatal if left untreated, the disease is easily treatable once detected. Asymptomatic persons homozygous in the C282Y mutation will be advised to undergo blood studies regularly and once the serum ferritin level increases to above the normal range, venesection therapy can then be initiated.

Therapeutic phlebotomy is an inexpensive, safe and effective treatment for haemochromatosis. If the treatment is started before the initiation of end-stage organ damage, the patient will still enjoy a normal life expectancy and suffer no loss of quality of life. Hence the implication of genetic testing for HHC for life insurance products may not be significant.

9.5.1 Implications of Population Screening

If population screening for HHC is found to be cost-effective and implemented in a population, what will be the insurance implications? This would contrast with the other single-gene disorders considered where screening is not contemplated.

With population screening, individuals with a family history of HHC will be screened. Non-mutation carriers will be cleared and return to the normal underwriting pool. Those carrying HFE gene mutations will be monitored closely and effective treatment can be started once the early symptoms of the disease develop. Claims for CI are not made on diagnosis of the disease but when irreversible damages are inflicted on the vital organs in the later stages of the disease. Hence, there will be few if any insurance implications.

If screening is found not to be cost-effective and is not implemented as a result, those persons at risk with a family history of HHC who have not been tested will remain in the high-risk group. But the number will be minimal as regular monitoring of TS or SF levels will enable early symptoms of iron overloading to be detected and effective treatment to be instituted before major damage can occur to the organs. Therefore even without screening for HHC, there will be very few at-risks who will claim under their policies with major illnesses arising from severe iron overload as a consequence of HHC onset.

9.6 Summary

The epidemiology and clinical characteristics of HHC are reviewed in this chapter. The premium ratings for CI and life insurance of symptomatic HHC patients will remain normal for those without clinical evidence of cirrhosis, if there is treatment and constant monitoring of iron level. Patients with severe cirrhosis conditions may not be accepted for insurance due to their increased mortality rates. Detection of probands by genetic testing will enable early treatment to be implemented and genetic counselling to be offered to family members. Hence, premium ratings for individuals with family history of HHC should be normal as the at-risks do not pose extra risks.

There appear to be few reasons to suspect that knowledge of genetic test results will bring persons at risk of the disorder due to genetic predisposition to select against insurance companies. There will be a greater tendency to undergo regular check-up for potential iron overloading and to institute treatment if needed.

Further work would be to estimate the intensities of onset of this iron disorder at various ages, if detailed onset data become available. Together with survival data, these intensities will enable the current ratings applicable to insurance applicants with HHC to be justified.

As a disease, HHC satisfies the prerequisites set by the World Health Organisation for screening (Bassett et al., 1997). HHC presents important clinical problems with a clearly understood natural history, tests which are acceptable to the general public are available to detect the disease in its latent stage, and treatment and management strategies are well defined.

However, results from Beutler et al. (2002) suggest a much lower penetrance of C282Y mutation, with fewer than 1% of homozygotes developing frank clinical haemochromatosis. This implies that screening for HHC, whether by genetic testing or by measuring transferrin saturation, will be more costly per clinical case treated than previously estimated. Further research on the penetrance of the disease genotypes needs to be carried out, and views on the cost-effectiveness of population screening for HHC need to be thoroughly reviewed.

Chapter 10

CONCLUSIONS

Use of the results of genetic testing of inherited disease for insurance has been the source of heated discussion between the public at large and the insurance industry. In the eyes of the public, the industry is not often portrayed in a good light and not many decisions by insurers are greeted without suspicion. This thesis forms part of the growing actuarial research on genetics and insurance necessary to provide quantitative information in this debate.

In this thesis, we have attempted to model single-gene disorders in order to study the actuarial implications for insurance. Three different cases emerged from our study:

- where sufficient data exist, a model can be constructed that suggests a pricing basis. Then there is a clear basis on which to proceed, through the GAIC procedure, if there is to be an application for the genetic information associated with the disease to be used for insurance underwriting. This is the case with EOAD associated with PSEN-1 gene mutations;

- where sufficient data or information exist to effectively rule out insurance relevance even if a model cannot be constucted. This is the case with MEN2 and HHC; and

- where the evidence suggests high risk but sufficient data do not exist that a model can be constructed that suggests a pricing basis. Then the procedures laid down in the U.K. are not clear about how that risk should be managed.

The 'precautionary principle' may provide a useful framework for discussing this. This is the case with EOAD associated with APP and PSEN-2 gene mutations.

10.1 Novel Estimates of Rates of Onset of EOAD

Genetic tests have created new risk groups in families that carry dominant single-gene disorders. We have extended Newcombe's (1981) life table method of estimating rates of onset to allow for these, in a Nelson-Aalen framework. Such methods will be needed to analyse pedigrees in which genetic testing is incomplete, which is likely to be the case in the absence of effective treatments.

A non-parametric approach is preferred for insurance purposes, rather than the parametric approach often used by genetic epidemiologists. Life and other insurances can be purchased by persons of any age, to cover any term. Therefore premiums and other financial quantities depend quite strongly on the detailed shape of the penetrance or survival function. Given the vast amount of data on the mortality of insured and national populations that has been collected over the years, certain well-known parametric functions (for example the Gompertz, Makeham or Heligman-Pollard functions) may often be used for graduation with some confidence that they represent the data well. However when estimating penetrance or survival in the absence of this *a priori* knowledge, and often with more limited data, there is not necessarily any reason to choose a particular parametric function. Epidemiologists may often be most interested in a few key parameters such as lifetime penetrance, or mean and median ages of onset, but we are strongly interested in the shape of the penetrance function. Non-parametric methods may therefore be particularly useful, even if they ultimately serve to guide later parametric estimation or curve-fitting.

We have estimated rates of onset of EOAD based on published pedigrees of PSEN-1 mutations. While we were hampered by missing data, chiefly in respect of unaffected siblings of sufferers, we were able to obtain upper and lower estimates based on approximate minimum and maximum exposure times respectively. These showed enough consistency to be useful, especially since they were sufficiently high

(roughly 0.1–0.2 by age 45) as to demonstrate penetrance exceeding 50%. If more complete pedigrees were available, it would be possible to extend the estimates to all relevant ages.

These estimates are used in a multi-state Markov model to estimate premium rates and the cost of adverse selection in the critical illness insurance market, in the presence of genetic information in respect of individual applicants. The cost of adverse selection is studied under various moratoria on the use of genetic information and family history. Similarly, estimates of rates of survival after onset of EOAD, associated with PSEN-1 gene mutations, were obtained and applied to a semi-Markov model for life insurance.

Similar estimates for the rates of onset were obtained for EOAD associated with mutations in the APP and PSEN-2 genes. But due to insufficient data, we were not able to apply these estimates to insurance models.

10.2 Novel Negative Conclusions on MEN2 and HHC

While MEN2 is a highly penetrant single-gene disorder, HHC is a very common genetic disorder especially among white populations. They both have the potential to become significant points of contact between persons in affected families and insurance issues, raising the same concerns as are encountered in respect of other single-gene disorders.

Although our studies on MEN2 and HHC have not led to actuarial models, we are still able to arrive at the novel conclusion of the irrelevance of the two disorders for insurance. To date, very few strong conclusions based on research have been published to counter the impression that all single-gene disorders are equally serious for insurers, so there is a risk that the very real concerns that arise in respect of Huntington's disease, EOAD, breast cancer and so on may be transferred erroneously to conditions such as MEN2 and HHC. Were this to discourage screening in the case of HHC, which is practically 100% beneficial, this would be a most serious outcome. Genuine criticism could be directed at the insurance industry if it allowed this to

happen.

It is therefore vital that an assessment is made of the insurance implications, based on sound epidemiological evidence as for any other disorders, and that this is published, even though the result may appear to be 'null' from the point of view of actuarial modelling. The fact that it is inconclusive in that respect does not mean that it is unimportant for the public policy debate; quite the contrary if it serves to introduce some balance to the perception of single-gene disorders and insurance.

10.3 Epidemiology and Models

A significant problem of genetic epidemiology is ascertainment bias; rates of onset may be based on families selected because of the severity of the condition, and may be significantly overstated. We allowed for this by using rates of onset that were 100%, 50% and 25% of those fitted to the data. In some cases these differences affected the conclusions.

We have identified the following data that should be included in pedigrees, in respect of each complete sibship, to allow the time spent in various risk groups to be found:

(a) the ages at which any genetic tests were taken;

(b) the parents' ages at the birth of each child; and

(c) the age at censoring or death of all unaffected siblings.

At present, genetic testing is so recent that (a) above is not yet important, but it will be necessary in future.

This study shows that it is possible, with the help of good published pedigree data, to model the likely impact on insurance of information relating to a specific genetic disorder, from the perspectives of both the individual and the insurer.

10.4 Premium Ratings

Our conclusions regarding premium ratings are different for CI and life insurance.

(a) CI insurance premium increases implied by known PSEN-1 mutations or a family history of PSEN-1 mutations were extremely high, even with the reduced rates of onset. Only in a few cases would the premium fall within the limits currently offered.

(b) Life insurance premium increases, on the other hand, were only outside the limits currently offered if a PSEN-1 mutation was confirmed by a genetic test, and given the highest rates of onset. With a few exceptions, terms could be offered otherwise, in particular if only a family history were known.

10.5 Adverse Selection

It is difficult to draw firm conclusions about the costs of adverse selection, should one of various kinds of moratorium be imposed. The reason is that the cost, in terms of premium increases, appears to be negligible except in the case of small markets, extreme behaviour on the part of 'adverse selectors' and high rates of onset of EOAD. In this respect our conclusions were the same for CI and life insurance, except that our models of the smaller and larger markets may be more appropriate for CI and life insurance, respectively. However we have only considered here one very rare disorder, whereas a moratorium would apply to all genetic disorders. Except in those extreme cases where this work by itself suggests that adverse selection could be a problem, we should regard the premium increases arising from adverse selection as one part of a program that should be extended to cover all the major late-onset single-gene disorders.

10.6 Implications for Policy

Interest in the United Kingdom centres on the reformed Genetics and Insurance Committee (GAIC). Until 2001, GAIC had a rather narrow remit to consider applications from insurers to be allowed to use genetic test results in certain circumstances. Considerations such as the possible effect of adverse selection if test results were ignored, and the appropriate levels of premium rates if they were used, fell

outside its remit. Following a report of the Human Genetics Commission in 2001, GAIC is to be reconstituted with a much broader remit, possibly covering exactly the kind of questions addressed here. Since PSEN-1 is one of the genes identified as being significant for insurers by the ABI, it is possible that research such as this will be needed to inform the policy-making process, in the U.K., through GAIC.

10.7 Further Research

The pedigree information available is often less than desirable, as reflected in this work. It is hoped that a central database for each genetic disease containing useful pedigree information can be made available in the public domain for the benefits of medical, actuarial and other beneficial researches.

Currently, besides a few of the monogenic disorders like Huntington's disease and EOAD due to PSEN-1 gene mutations studied in this thesis, our knowledge about the patterns of genetic test results does not translate into good estimates of the incidence and severity of disease or of the time of death. Further research is needed to yield useful information.

Other single-gene and multifactorial disorders may be studied likewise if sufficient pedigree information on onset ages and disease durations is available.

The issue of ascertainment bias in estimating the rates of onset from pedigree data was raised in Chapter 3 and Chapter 4. Ascertainment bias is likely to arise because the families studied are often those with unusually severe histories of the disorder or those with a larger number of members affected. Research is at present being carried out at GIRC to investigate how the rates of onset can be affected by the penetrance of the disorder, the censoring and ascertainment bias that might be present in the sample.

This research has modelled the usual critical illness product in the insurance market where the sum assured is paid on the onset of one of the insured disorders. The model may be extended to accelerated critical illness insurance policies where the sums assured are paid on the earlier of the insured critical illness event and death. This methodology could also be extended to disorders (such as HD) where

the age at onset is earlier than the age where critical illness claims can be made.

There is evidence to suggest variations in the ages at onset and duration of the disease among families with history of the disease, even among those families affected by the same gene mutations. We have not tried to model differences in ages at onset among different families, but that is a worthwhile subject for future research.

We have employed a non-parametric method in the form of a modified Nelson-Aalen method to estimate the incidence rates of a single-gene disorder. Likelihood-based methods to estimate the penetrance function may also be considered in the future, and results from the two approaches compared.

From our work on MEN2 and HHC, it is clear that it would be useful to obtain a finer classification of the significance for insurance of single-gene genetic disorders, which must include clinical outcomes following medical intervention. The A.B.I.'s original list was based solely on genetic factors such as penetrance. Considering broader medical factors could affect the conclusion of actuarial studies even for some of the established high-risk mutations (for example, breast cancer and APKD).

HHC perhaps points to some of the problems that may have to be solved as the focus of actuarial models shifts from single-gene disorders to multifactorial disorders. Although HHC is primarily a single-gene disorder, it displays the genetic heterogeneity and variable penetrance and expressivity that we might expect to find among multifactorial disorders.

Advances in molecular genetics over the past few years have been more than remarkable. Soon many of the genetic loci associated with human disease will be identified and our knowledge of the disease mechanisms and clinical course of common disorders will be enhanced greatly. With parallel advancement in the field of genetic epidemiology, more actuarial research can be undertaken on common serious disorders that have significant implications in insurance. As actuaries, we have every intention to meet the challenge of genetic advance in this new century!

Appendix A

Presenilin-1 gene mutations

The following table summarises the family studies in which PSEN-1 mutations have been found.

(a) The mutations are specified in the standard notation in the genetics literature: for example Ala79Val means that at the 79^{th} position in the amino acid chain, the amino acid Alanine has been replaced by Valine. Note that this refers to the product of transcription; the amino acid chain may be subject to further processing resulting in a shorter functional protein. The mutations are ordered by position.

(b) The pedigree IDs identify the particular family referred to in the study, with some information about ethnicity (when available). The following abbreviations have been used: Amer = American, Amer-C = American-Caucasian, Arg = Argentinian, Ashk-J = Ashkenazi-Jewish, Aus = Australian, Bel = Belgian, Brit = British, C = Caucasian, Col = Colombian, Dan = Danish, Eng = English, Fin = Finnish, Fr = French, Fr-Can = French-Canadian, G = German, It = Italian, J = Japanese, Mex = Mexican, Mex-A = Mexican-American, Pol = Polish, Rom-J = Romanian-Jewish, Russ-J = Russian-Jewish, Scot = Scottish, Scot-I = Scottish-Irish, Sp = Spanish, Swe = Swedish.

(c) The 'Used' column specifies whether the pedigree has been used for the estimates made in this paper.

(d) The key to the pedigree summary is as follows:

c: Number of cases of EOAD in the family

g: Number of generations affected

a: Ages at onset of affected individuals

m: Mean age at onset of affected individuals (n = No. included in mean)

r: Range of ages at onset (minimum – maximum) of affected individuals

No.	Mutation	Pedigree ID	Used	Pedigree Summary	Reference
1	Ala**79**Val	1005, C	No	c:8, g:3, m:53	Cruts et al. (1998)
		1087, C	No	c:3, g:3, m:55	Cruts et al. (1998)
		1061, C	No	c:2, g:2, m:58	Cruts et al. (1998)
			No	m:64	St.George-Hyslop (1998)
		G	Yes	c:2, g:2, a:55, 58	Finckh et al. (2000b)
2	Val**82**Leu	SAl 508, Fr	No	c:3, g:3, m:55, r:53–58	Campion et al. (1995a, 1999)
3	del**ΔI83/M84**	Scot	Yes	c:5, g:3, median:36	Steiner et al. (2001)
4	Val**94**Met	Col	No	a:53 (sporadic?)	Jacquier et al. (2000)
5	Val**96**Phe	OS-3. J	Yes	c:4, g:2, m: 52.5±5.07, r:49–60	Kamino et al. (1996)
6	Phe**105**Leu	G	Yes	c:3, g:3, a:50, 52, < 60	Finckh et al. (2000b)
7	Leu**113**Pro	SAL 513, Fr	Yes	c:6, g:4, m:42.4±5.0, r:38–50	Raux et al. (2000a)
8	del **Intron4**	FD177, Eng	No	c:6, g:3	Tysoe et al. (1998), DeJonghe et al. (1999)
		142, Eng	No	c:1 (no family history)	Tysoe et al. (1998), De Jonghe et al. (1999)
		F105/160, Brit	No	c:17, g:6, m:37±3, r:36-40	De Jonghe et al. (1999)
		Tor122, Brit	No	c:10, g:3, m:37	De Jonghe et al. (1999)
		79/95, Brit	No	c:4, g:3, m:37	De Jonghe et al. (1999)
		593, Brit	No	c:1 (no family history)	De Jonghe et al. (1999)
9	Tyr**115**His	ALZ 025, Fr	No	c:2, g:2, a:35, 37	Campion et al. (1995a)
		ALZ 076, Fr	No	c:3, g:3, r:36–47	Campion et al. (1999)
10	Tyr**115**Cys	1066, C	No	c:10, g:4, m:45	Cruts et al. (1998), Hardy (1997)
11	Tyr**116**Asn	Dan	Yes	c:4, g:3, m:38, r:35–41	Romero et al. (1999)
12	Pro**117**Leu	Pol	Yes	c:8, g:3, m: 30.3±4.2, r:24–33	Wisniewski et al. (1998)
13	Glu**120**Asp	Rom-J	Yes	c:4, g:3, r:43–48	Reznik-Wolf et al. (1996a, 1996b), St.George-Hyslop (1998)
		ALZ 057, Fr	No	c:4, g:3, r:42–53	Campion et al. (1999)
		V, Brit	Yes	c:10, g:4, m:46.4±4.2, r:41-53	Poorkaj et al. (1998), Bird et al. (1996)
14	Glu**120**Lys	F121, Brit	No	c:6, g:3, r:32–39	Huttonet al. (1996), Hardy(1997)
15	Glu**123**Lys	ABCD-2, J	No	c:4, g:3, a:56, 62 (2 unknown)	Yasuda et al. (1999)
16	Asn**135**Asp	Mex-A	Yes	c:9, g:5, r:34–38	Crook et al. (1998)
17	Met**139**Ile	1674, C	No	details not reported	Boteva et al. (1996)

No.	Mutation	Pedigree ID	Used	Pedigree Summary	Reference
18	Met**139**Lys	ALZ 034, Fr	No	c:1, g:1, a:37 (isolated case)	Dumanchin et al. (1998)
19	Met**139**Thr	CAE 010, Fr	No	c:2, g:2, a:48, 50	Campion et al. (1995a, 1999)
		Sp	No	c:2, g:1, a:47, 48	Queralt et al. (2001)
20	Met**139**Val	F148, Brit	Yes	c:7, g:3, m:44.3, r:42–48	Clark et al. (1995), Hutton et al. (1996), Fox et al. (1997), Palmer et al. (1999)
		F206, Brit	Yes	c:9, g:4, m:37.7, r:36–40	Clark et al. (1995), Hutton et al. (1996), Fox et al. (1997), Palmer et al. (1999)
		G	No	c:6, g:3, r:42–44	Hüll et al. (1998)
		G	Yes	c:3, g:3, a:32 (2 unknown)	Finckh et al. (2000b)
		G	No	c:1, g:1, a:40 (isolated case)	Sandbrink et al. (1996)
21	Ile**143**Phe	A, Brit	No	c:3, g:2, a:55, 53, 57	Rossor et al. (1996), Palmer et al. (1999)
22	Ile**143**Thr	AD/A, Bel	Yes	c:43, g:6, m:35.1±4.8, r:26–45	Cruts et al. (1995), Martin et al. (1991)
23	Met**146**Ile-a	Dan	Yes	c:7, g:3, m:44.4, r:38–57	Jørgensen et al. (1996), Cervenakova et al. (1996)
24	Met**146**Ile-b	E-M, Swe	Yes	c:6, g:4, m:42.7±6.3, r:35–49	Gustafson et al. (1998)
25	Met**146**Leu	FAD4(Okla1), It	No	c:8, g:3, m:45	Sherrington et al. (1995), Clark et al. (1995)
		Tor1.1, It	No	No details published	Sherrington et al. (1995)
		FAD4? It	No	c:3, m:45	Sorbi et al. (1995)
		It	No	c:3, m:36	Sorbi et al. (1995)
		It	No	m:35	Sorbi et al. (1995)
		It	No	3 from 3 families	Terreni et al. (2000)
		AR1, Arg	Yes	c:10, g:3, m:42±2.5 (gen II–III, n:6, r:40–46), m:35±2 (gen IV, n:4, r:33–38)	Morelli et al. (1998)
		ALZ 204, Fr	No	c:6, g:3, r:38–47	Campion et al. (1999)
26	Met**146**Val	Fin1	No	c:3, g:3; m:36	Clark et al.(1995)
		Man92/20	No	c:2, g:2, m:40	Clark et al.(1995)
		NY5201	No	c:7, g:2, m:37	Clark et al.(1995)
			No	c:1 (no other details)	Cervenakova et al. (1996)
27	Thr**147**Ile	ALZ 047, Fr	No	c:4, g:3, r:37–46	Campion et al. (1999)
28	Leu**153**Val	Fr	No	c:5, g:3, r:34–38	Raux et al. (2000b)
29	His**163**Arg	LH 603, Fr-Can	No	c:25, m:47.9±6.2, r:37–68	Bird et al. (1996), Sherrington et al. (1995), Boteva et al. (1996), Poorkaj et al. (1998)
		Tor 42, C	No	c:2, m:45	Sherrington et al. (1995)
		SAL 001, Fr	No	c:4, g:3, r:42–47	Campion et al. (1995a, 1999)
		TK-2, J	Yes	m:47.4±4.04, r:43–50	Kamino et al. (1996)
		H-1, J	No	c:14, m:39	Kamimura et al. (1998)

No.	Mutation	Pedigree ID	Used	Pedigree Summary	Reference
		J	No	c:1, a:38	Kamimura et al. (1998)
		J	No	c:1, a:51	Kamimura et al. (1998)
		Miy, J	No	c:2, m:45	Kamimura et al. (1998)
		HR1, G	Yes	c13, g:4, m:46.9±4.8, r:40–55	Bird et al. (1996), Poorkaj et al. (1998)
		J	No	c:14, g:5	Tanahashi et al. (1995)
		AD-Kae, J	No	c:1, a:41(sporadic)	Tanahashi et al. (1996)
		J	No	c:3, g:2, a: all late 40s	Poduslo et al. (1996)
		Fr	No	c:2 (no other details)	Cervenakova et al. (1996)
30	His**163**Ile	J	No	m:47	Kamino et al. (1996)
31	His**163**Tyr	Swed 2	No	c:8, g:3, m:47	Clark et al. (1995)
		Swed	Yes	c:22, g:4, m:54	Axelman et al. (1998)
32	Trp**165**Cys	ALZ 064, Fr	No	c:3, g:3, r:37–47	Campion et al. (1999)
33	Trp**165**Gly	J	Yes	c:5, g:3, m:35.8, r:34–38	Higuchi et al. (2000)
34	Leu**166**Arg	Sp	Yes	c:6, g:3, r:32–44	Ezquerra et al. (2000)
35	Ser**169**Leu	PERTH-4, Aus	Yes	c:3, g:2, a:31, 36, 39	Taddei et al. (1998)
36	Ser**169**Pro	Sp	Yes	c:4, g:2, a:33, 34, 35, 35	Ezquerra et al. (1999)
37	Leu**171**Pro	Ped 1, Mex	No	c:3, g:4, m:40	Ramirez-Dueñas et al. (1998)
		Ped 2-4, Mex	No	3 families, m:36, 37, 39	Ramirez-Dueñas et al. (1998)
38	Leu**173**Trp	ROU 118, Fr	No	c:2, g:2, a:24, 29	Campion et al. (1999)
39	Phe**177**Ser		No	details not published	Fraser et al. (2000)
40	Ser**178**Pro		No	details not published	Fraser et al. (2000)
41	Glu**184**Asp	ABCD-1, J	Yes	c:4, g:3, m:38.1±5.1	Yasuda et al. (1997)
42	Gly**206**Ser		No	details not published	Fraser et al. (2000)
43	Gly**209**Arg	J	Yes	c:3, g:2, m:49.6±3.1, a:46, 48, 53	Sugiyama et al. (1999)
44	Gly**209**Val	L, G	Yes	c:19, g:4, m:41.3±4.5, r:30–48	Bird et al. (1996), Cruts & Van Broeckhoven (1998), Poorkaj et al. (1998)
45	Ile**213**Thr	OS-2, J	Yes	c:4, g:2, m:45.0±4.24, r:42–48	Kamino et al. (1996)
46	Leu**219**Phe	It	No	details not published	Terreni et al. (2000)
47	Leu**219**Pro	MELB-1, Aus	Yes	c:10, g:5, a:47, 53, 54 (7 unknown)	Smith et al. (1999)
48	Gln**222**Ala		No	details not published	Fraser et al. (2000)
49	Ala**231**Thr	ALZ 043, Fr	No	c:4, g:3, m:52, r:45–57	Campion et al. (1995a, 1999)
50	Ala**231**Val	1072, C	No	c:6, g:3, m:58	Cruts et al. (1998), Hardy (1997)
51	Met**233**Leu	Sp	No	c:1, a:46 (isolated case)	Aldudo et al. (1999)
52	Met**233**Thr	PERTH-1, Aus	Yes	c:4, g:2, m:35	Kwok et al. (1997)
		ALZ 079, Fr	No	c:5, g:3, r:38–45	Campion et al. (1999)
53	Leu**235**Pro	SAL 510, Fr	Yes	c:4, g:2, m:32.5	Campion et al. (1996a)
				c:5, g:3, r:29–39 (update)	Campion et al. (1999)
54	Ala**246**Glu	FAD 1, C	No	c:9, g:3, m:55	Sherrington et al. (1995)
55	Leu**250**Sel	F184, Brit	Yes	c:7, g:3, median:52, r:49–56	Hutton et al. (1996), Hardy(1997), Harvey et al. (1998)

No.	Mutation	Pedigree ID	Used	Pedigree Summary	Reference
56	Ala**260**Val	AM/JPN 1, J	No	c:9, g:3, m:40.3±5.5, r:27–46	Rogaev et al. (1995), Ikeda et al. (1996), Poorkaj et al. (1998)
57	Val**261**Phe		No	c:4, g:2, a:38 (3 unknown)	Farlow et al. (2000)
58	Leu**262**Phe	Swe	No	c:3, g:1, a:47, 48, 56	Forsell et al. (1997)
59	Cys**263**Arg	MGH12, C	No	c:5, m:50	Wasco et al. (1995)
			No	m:47	St.George-Hyslop (1998)
60	Pro**264**Leu	KG, Brit	Yes	c:5, g:2, m:43.2±1.6, r:41–45	Bird et al. (1996), Poorkaj et al. (1998)
		MGH6, C	No	c:2, g:1, a:45, 50	Wasco et al. (1995)
		SAL 511, Fr	No	c:6, g:3, r:45–56	Campion et al. (1995a, 1999)
		SAL 506, Fr	No	c:4, g:3, r:46–52	Campion et al. (1999)
		SAL 1633, Fr	No	c:4, g:3, r:51–55	Campion et al. (1999)
		EOFAD-6	No	m:39	Kwok et al. (1997)
61	Pro**267**Ser	F196, Brit	No	c:5, g:3, m:35, r:32–38	Clark et al. (1995), Hutton et al. (1996), Palmer et al. (1999)
62	Arg**269**Gly	Amer-C	No	c:3, g:2, a:47, 52, 54	Perez-Tur et al. (1996), Hardy (1997)
63	Arg**269**His	Amer-C	No	c:2, g:2, a:46, 61	Gómez-Isla et al. (1997)
		MAT-1, J	No	c:2, m:50	Kamimura et al. (1998), Hardy (1997)
64	Glu**273**Ala	Ok-1, J	No	c:2, m:63	Kamimura et al. (1998)
65	Arg**278**Thr	P-2, C	No	c:1, g:1, a:37 (isolated case)	Kwok et al. (1997)
66	Glu**280**Ala	C1, Col	No	c:11, g:3, m:49.9±6.9, r:41–55	Clark et al. (1995), Lendon et al. (1997)
		C2, Col	No	c:67, g:6, m:47.4±4.8, r:39–55	Clark et al. (1995), Lendon et al. (1997)
		C3, Col	No	c:10, g:4, m:52.0±4.9, r:41–59	Clark et al. (1995), Lendon et al. (1997)
		C4, Col	No	c:10 m:52.2±5.3, r:46–60	Lendon et al. (1997)
		C5, Col	No	c:9 m:47.4±11.9, r:36–62	Lendon et al. (1997)
		C8, Col	No	c:6 m:52.2±2.7, r:47–55	Lendon et al. (1997)
		C12, Col	No	c:1, a:42	Lendon et al. (1997)
		FAD-Ok, J	No	c:2, m:57	Tanahashi et al. (1996)
		F771	No	m:45	Clark et al. (1995)
		Col	No	c:2 (from separate families?)	Jacquier et al. (2000)
		COL	No	c:1, a:47	Kwok et al. (1997)
67	Glu**280**Gly	F168, Brit	No	c:5, g:3, m:41, r:39–42	Clark et al. (1995), Hutton et al. (1996)
		F183, Brit	No	c:2, g:3, m:43, r:42–45	Clark et al. (1995), Hutton et al. (1996)
		F196, Brit	No	c:1, g:1 (no age data)	Palmer et al. (1999)
68	Leu**282**Arg	Sp	Yes	m:43±5	Aldudo et al. (1998)
69	Ala**285**Val	SD-6, J	Yes	c:3, g:3, m:51	Ikeda et al. (1996)

No.	Mutation	Pedigree ID	Used	Pedigree Summary	Reference
		TOH-1, J	Yes	c:2, g:3, a:55, 45	Aoki et al. (1997)
		J	No	related to SD-6 or TOH-1 ?	Rogaev et al. (1995)
70	Leu**286**Val	FAD2	No	c:9, g:3, m:50	Sherrington et al. (1995)
		Ashk-J	No	c:4, g:2, a:42,47,48,50s	Chapman et al. (1995)
71	Ser**289**Cys		No	no age data	Cruts et al. (1996)
72	**291**–**319** Del	AusAD-1 (EOFAD-3), Aus	Yes	c:13, g:3, m:45.8±6.1, r:36–54	Kwok et al. (1997, 2000b), Smith et al. (2001)
		AusAD-2, Aus	No	c:4	Kwok et al. (2000b)
		AusAD-3, Aus	No	No details published	Kwok et al. (2000b)
		Finn2, Fin	Yes	c:22, g:4, m:50.9±5.2, r:40–61	Crook et al. (1998) Prihar et al. (1999), Verkkoniemi et al. (2000)
		Fin	Yes	c:4, g:2, a:43, 45, 42, 40	Hiltunen et al. (2000)
		F74, Brit	Yes	c:7, g:4, r:39–50	Perez-Tur et al. (1995), Hutton et al. (1996)
	(+Ser**290**Cys)	TK-1, J	No	c:15, g:4, m:47.5±3.3	Sato et al. (1997), Hardy (1997)
73	Glu**317**Gly		No	no age data	Hardy(1997)
74	Glu**318**Gly	ALZ 059, Fr	No	c:3, g:3, r:42–50	Campion et al. (1999)
		G	No	c:1, g:1, a:47 (isolated case)	Sandbrink et al. (1996)
		Swe	Yes	c:4, g:2, r:60–68	Forsell et al. (1997)
		PERTH-5, Aus	Yes	c:3, g:2	Taddei et al. (1998)
		1069	No	c:2, g:2, m:57	Cruts et al. (1998)
75	Gly**378**Glu	Fr	Yes	c:6, g:3, m:35, r:34–38	Besançon et al. (1997)
76	Gly**384**Ala	AD/B, Bel	No	c:25, g:5, m:34.7±3.0, r:30–39	Cruts et al. (1995), Martin et al. (1991)
		FAD-Yg, J	No	c:4, m:35	Tanahashi et al. (1996)
		Yg1, J	No	c:10, m:36	Kamimura et al. (1998)
77	Ser**390**Ile	ALZ 107, Fr	No	c:4, g:3, r:39–40	Campion et al. (1999)
78	Leu**392**Pro	It	Yes	c:4, g:3, m:38.3±4.0	Tedde et al. (2000)
79	Leu**392**Val	FAD R01, Fr	No	c:38, g:5, r:39–52	Campion et al. (1995b, 1999)
		It	No	results unpublished	Rogaev et al. (1995)
80	Asn**405**Ser	HI-1, J	No	c:1, g:1, a:48 (isolated case)	Yasuda et al. (2000)
81	Ala**409**Thr	Sp	No	c:1, a:58	Aldudo et al. (1999)
82	Cys**410**Tyr	FAD3(SNW), Russ-J	No	c:20, g:4?, m:51.7±2.7, r:48–56	Sherrington et al. (1995), Clark et al. (1995), Poorkaj et al. (1998)
		NIH2	No	No details published	Sherrington et al. (1995)
		ROU 011, Fr	No	c:14, g:4, r:40–60	Campion et al. (1995a, 1999)
			No	c:1 (no other details)	Cervenakova et al. (1996)
83	Leu**418**Phe		No	details not published	Fraser et al. (2000)
84	Leu**424**Arg		No	no details available	Kowalska et al. (1999)
85	Ala**426**Pro	HRX-III(XIII), Scot-I	Yes	c:6, g:2, m:46.0±3.5, r:41–51	Bird et al. (1996), Hardy (1997), Poorkaj et al. (1998)
86	Ala**431**Glu		No	details not published	Fraser et al. (2000)

No.	Mutation	Pedigree ID	Used	Pedigree Summary	Reference
87	Ala**434**Cys		No	details not published	Fraser et al. (2000)
88	Pro**436**Gln	SYD-1	Yes	c:2, g:2	Taddei (1998)
89	Pro**436**Ser	F223, Brit	Yes	c:2, g:2, a:44, 50	Palmer et al. (1999), Hardy (1997)
90	Ile**439**Val		No	details not published	Fraser et al. (2000)

Appendix B

Presenilin-2 gene mutations

The following table summarises the family studies in which PSEN-2 mutations have been found.

(a) The mutations are specified in the standard notation in the genetics literature (see Appendix A).

(b) The pedigree IDs identify the particular family referred to in the study, with some information about ethnicity (when available). The following abbreviations have been used: C = Caucasian, G = German, It = Italian, Sp = Spanish, VG = Volga-German.

(c) The 'Used' column specifies whether the pedigree has been used for the estimates made in this study.

(d) The key to the pedigree summary is as in Appendix A.

Table B.30: Mutations in the PSEN-2 gene

No.	Mutation	Pedigree ID	Used	Pedigree Summary	Reference
1	Arg**62**His	1121, C	No	c:1, a:62 (sporadic)	Cruts et al. (1998)
2	Thr**122**Pro	G	Yes	c:3, g:3, m:46	Finckh et al. (2000b)
3	Asn**141**Ile	BE, VG	No	c:3, g:1, m:59.0±2.2, r:57–62	Levy-Lahad et al. (1995a)
		E, VG	Yes	c:6, g:3, m:56.7±4.1, r:51–69	Bird et al. (1988), Levy-Lahad et al. (1995a)
		H, VG	No	c:8, g:3, m:59.5±3.9 (n=6), r:56–68	Bird et al. (1988), Levy-Lahad et al. (1995a)
		R, VG	Yes	c:21, g:4, m:50.2±7.3 (n=17), r:40–67	Bird et al. (1988), Levy-Lahad et al. (1995a, 1995b)
		HB, VG	No	c:26, g:5, m:60.8±7.1 (n=22), r:54–75	Levy-Lahad et al. (1995a), Nochlin et al. (1998)
		HD, VG	No	c:19, g:5, m:59.6±10.3 (n=17), r:46–82	Levy-Lahad et al. (1995a)
		KS, VG	Yes	c:14, g:4, m:64.8±5.4 (n=13), r:55–71	Bird et al. (1988), Levy-Lahad et al. (1995a)
		W, VG	Yes	c:5, g:3, m:52.8±4.5, r:47–58	Bird et al. (1988), Levy-Lahad et al. (1995a)
		WFL, VG	No	c:6, g:2, m:63.8±7.6, r:55–76	Levy-Lahad et al. (1995a)
4	Val**148**Ile	Sp	No	c:1, a:71 (late-onset)	Lao et al. (1998)
5	Met**239**Ile	It	Yes	c:4, g:2, r:44–58	Finckh et al. (2000a, 2000b)
6	Met**239**Val	Flo10, It	No	c:9, g:4, m:64.9±17.8, r:45–88 (late onset)	Sherrington et al. (1996), Rogaev et al. (1995)
		It	Yes	c:4, g:2, m:50.7±7.0 (n=3), r:44–58	Finckh et al. (2000c) Hardy (1997)

Appendix C

Amyloid precursor protein gene mutations

The following table summarises the family studies in which APP mutations have been found.

(a) The mutations are specified in the standard notation in the genetics literature (see Appendix A).

(b) The pedigree IDs identify the particular family referred to in the study, with some information about ethnicity (when available). The following abbreviations have been used: Amer = American, Amer-C = American-Caucasian, Aus = Australian, Aust= Austrian, C = Caucasian, Du = Dutch, Eng = English, Fr = French, G = German, It = Italian, J = Japanese, Sp = Spanish, Swe = Swedish, Th = Thai, Wel = Welsh.

(c) The 'Used' column specifies whether the pedigree has been used for the estimates made in this study.

(d) The key to the pedigree summary is as in Appendix A.

Table C.31: Mutations in the APP gene

No.	Mutation	Pedigree ID	Used	Pedigree Summary	Reference
1	Gln**665**Asp	Amer-C	Yes	Late onset	Peacock et al. (1994)
2	Lys**670/671**	F139, Swe	No	c:7, g:3	Mullan et al. (1992)
	Met→Asn→Leu	F144, Swe	No	c:10, g:4	Mullan et al. (1992)
				(2 families above: m:55, r:45–61)	
3	Ala**673**Thr	C	No	c:1,no disease	Peacock et al. (1993)
4	Ala**692**Gly	1302, Du	No	c:11, m:45.7±7.3, r:35–61	Hendriks et al. (1992)
5	Glu**693**Gly	SB, Swe	Yes	c:5, g:3, m:62.0±7.3	Kamino et al. (1992), Nilsberth et al. (2000)
6	Glu**693**Gln	HCHWA-D	No	Hereditary cerebral haemorrhage, c:11, r:40–60	Levy et al. (1990), Fidani et al. (1992)
7	Ala**713**Val		No	Schizophrenia, no segregation	Jones et al. (1992)
8	Ala**713**Thr	Fr	No	c:1, g:2, a:59 (isolated case)	Carter et al. (1992)
9	Thr**714**Ile	AD156, Aust	Yes	c:3, g:2, a:34	De Jonghe et al. (2000), Kumar-Singh et al. (2000)
10	Val**715**Met	ALZ 074, It	No	c:4, g:3, r:41–60	Ancolio et al. (1999), Campion et al. (1999)
11	Ile**716**Val	Amer-C	Yes	c:4, g:3, m:53	Eckman et al. (1997)
12	Val**717**Gly	F19	No	c:11, g:3, m:59±4	Chartier-Harlin et al. (1991), Fidani et al.(1992)
13	Val**717**Ile	F23, Eng	No	c:9, g:4, m:57±5, r:53–61	Goate et al. (1991), Mullan et al. (1993), Hardy et al. (1991), Fidani et al. (1992)
		372, Amer	No	m:50	Goate et al. (1991), Hardy et al. (1991)
		F172	No	c:10, r:44–64	Fidani et al. (1992)
		G	Yes	c:4, g:2, m:51.8±5.7	Finckh et al. (2000b)
		G	No	c:1, g:1, a:53 (isolated case)	Finckh et al. (2000b)
		Th	No	c:1, g:1, a:54 (isolated case)	Finckh et al. (2000b)
		FAD R03, Fr	No	c:6, g:3, r:50–60, m:54±5.1	Campion et al. (1996b, 1999)
		FAD R04, Fr	No	c:5, g:3, r:53–55, m:54±1.4	Campion et al. (1996b, 1999)
		FAD SAL1, Fr	No	c:9, m:47±7.8	Campion et al. (1996b)
		JUB 001	No	c:9, g:4, r:38–51	Campion et al. (1999)
		ALZ 066	No	c:4, g:3, r:53–60	Campion et al. (1999)
		Aus (Wel origin)	Yes	c:4, g:2, m:48.5, r:46–51	Brooks et al. (1995)
		FAD1/2/3, J	No	No age details published	Naruse et al. (1991)
		J	Yes	c:3, g:3	Matsumura et al. (1996)
		Flo12, It	Yes	c:6, g:3, r:54–65	Sorbi et al. (1993)
		Flo13, It	No	c:6, g:3, r:46–52	Sorbi et al. (1993)
		Flo33, It	No	c:14, g:3, m:44.7±6.3	Sorbi et al. (1993)
14	Val**717**Leu	Amer	Yes	c:5, g:4	Murrell et al. (2000)

No.	Mutation	Pedigree ID	Used	Pedigree Summary	Reference
15	Val**717**Phe	INDIANA, Amer	No	c:5, g:3, m:42.7±2.1 (n=3), r:41–45	Murrell et al. (1991), Fidani et al. (1992)
16	Leu**723**Pro	Aus	No	c:4, g:3, m:56	Kwok et al. (2000a)

Appendix D

Pedigree database of presenilin-1 gene mutations

The following table summarises the family studies in which the PSEN-1 mutations have been found. It is hoped that this database will serve as an useful starting point for analysis into the onset, duration and other studies of the early onset Alzheimer's disease due to mutations in the PSEN-1 gene.

(a) The mutations are specified in a notation which is slightly different from the usual one used in the genetics literature: for example 079AV means that at the 79^{th} position in the amino acid chain, the amino acid Alanine has been replaced by Valine. Note that this refers to the product of transcription; the amino acid chain may be subject to further processing resulting in a shorter functional protein. The mutations are ordered by position.

(b) The ID is coded in the form 'mutation.family_generation.parent_individual'. As an example 282LR.A2.0102 denotes an individual (numbered 02) whose parent is numbered 01 in the earlier generation, in the second generation of family A (coded A2) of the mutation 282LR which is the missense replacement of Arginine for Leucine in the codon 282 of the PSEN-1 gene; while 282LR.a2.0102 denotes the spouse of 282LR.A2.0102.

(c) Sex: 0 — unknown, 1 — male, 2 — female.

(d) AAO — age at onset.

ID	Sex	AAO	Age censored (at death)	Comments	Reference
079AV.A1.0001	1		(?)	Family 1005, Caucasian	Cruts et al. (1998)
079AV.a1.0001	2		(?)		
079AV.A2.0101	2	73	(?)		
079AV.a2.0101	1		(?)		
079AV.A2.0102	1	71	(?)		
079AV.a2.0102	2		(?)		
079AV.A2.0103	1	78	(?)		
079AV.a2.0103	2		(?)		
079AV.A2.0104	2	60	(?)		
079AV.a2.0104	1		(?)		
079AV.A3.0101	2		82	CVA (cardiovascular accident)	
079AV.A3.0102	1				
079AV.A3.0203	1		75	CVA	
079AV.A3.0204	1	62	(?)		
079AV.a3.0204	2				
079AV.A3.0305	2	50	(?)		
079AV.a3.0305	1		(?)		
079AV.A3.0406	1				
079AV.A3.0407	2	55	(?)		
079AV.A3.0408	2	60	(?)		
079AV.a3.0408	1				
079AV.A3.0409	2				
079AV.A4.0401	0				
079AV.A4.0402	0				
079AV.A4.0503	0				
079AV.A4.0504	0				
079AV.A4.0505	0				
079AV.A4.0506	0				
079AV.A4.0507	0				
079AV.A4.0508	0				
079AV.A4.0509	0				
079AV.A4.0810	0				
079AV.A4.0811	0				
079AV.B1.0001	2		(?)	Family 1087, Caucasian	Cruts et al. (1998)
079AV.b1.0001	1		(?)		
079AV.B2.0101	0				
079AV.B2.0102	0				
079AV.B2.0103	0				
079AV.B2.0104	0				
079AV.B2.0105	0				
079AV.B2.0106	0				
079AV.B2.0107	2	50	(?)		
079AV.b2.0107	1		(?)		
079AV.B3.0701	1		(?)		
079AV.B3.0702	1				
079AV.B3.0703	2		(?)		
079AV.B3.0704	1	58	(?)	proband, autopsy confirmation of AD	
079AV.B3.0705	1		(?)		
079AV.C1.0001	2		(39)	Family 1061, Caucasian	Cruts et al. (1998)
079AV.c1.0001	1		(52)		
079AV.C2.0101	1	59	(?)		
079AV.C2.0102	2			CVA	
079AV.C2.0103	2		(?)		

ID	Sex	AAO	Age censored (at death)	Comments	Reference
079AV.C2.0104	2	53	(?)	proband, autopsy confirmation of AD	
079AV.D1.0001	2	∼55	(65)	German	Finckh et al. (2000b)
079AV.d1.0001	1		(?)		
079AV.D2.0101	1		80		
079AV.D2.0102	2	∼58	78	proband, +/-	
096VF.A1.0001	1	?	(?)	Family OS-3, Japanese	Kamino et al. (1996)
096VF.a1.0001	2		(?)		
096VF.a1b.0001	2			second spouse of 096VF.A1.0001	
096VF.A2.0101	1	51		+/-	
096VF.a2.0101	2		55	-/-	
096VF.A2.0102	1	49		+/-	
096VF.a2.0102	2		57	-/-	
096VF.A2.0103	1	50		+/-, Child with 096VF.a1b.0001	
096VF.a2.0103	2		47	-/-	
096VF.A2.0104	1		47	-/-, Child with 096VF.a1b.0001	
096VF.a2.0104	2		44	-/-	
096VF.A3.0101	0		25	-/-	
096VF.A3.0202	0		27	+/-	
096VF.A3.0203	0		25	+/-	
096VF.A3.0304	0		22	-/-	
096VF.A3.0305	0		19	+/-	
096VF.A3.0406	0		20	-/-	
096VF.A3.0407	0		17	-/-	
105FL.A1.0001	2	<60	(?)	German	Finckh et al. (2000b)
105FL.a1.0001	1		(?)		
105FL.A2.0101	2	∼50	(58)		
105FL.a2.0101	1		(?)		
105FL.A3.0101	2	∼52	(63)	proband, +/-, auptosy confirmation	
113LP.A1.0001	2	?	(?)	Family SAL 513, French	Raux et al.(2000)
113LP.a1.0001	1		(?)		
113LP.A2.0101	1		(?)		
113LP.A2.0102	2	38	(44)		
113LP.A2.0103	2	45	(56)		
113LP.a2.0103	1		(?)		
113LP.A3.0301	2		67	-/-	
113LP.A3.0302	2	50	65	+/-	
113LP.A3.0303	2	39	(50)		
113LP.a3.0303	1		(?)		
113LP.A4.0301	2	40	43	+/-	
IN04D.A1.0001	1	?	(early 40's)	Family FD177, English	Tysoe et al.(1998), De Jonghe et al.(1999)
IN04D.a1.0001	2				
IN04D.A2.0101	0	?	(early 40's)		
IN04D.A2.0102	0				
IN04D.A2.0103	0				
IN04D.A2.0104	0	?	(early 40's)		
IN04D.a2.0104	0				
IN04D.A2.0105	0				
IN04D.A2.0106	0	?	(early 40's)		
IN04D.A2.0107	0	?	(?)		
IN04D.A2.0108	0				
IN04D.A2.0109	0				
IN04D.A3.0401	0	?	(45)	proband	
IN04D.A3.0402	0				
IN04D.B1.0001	1		(?)	Family TOR122, British	De Jonghe et al.(1999)

ID	Sex	AAO	Age censored (at death)	Comments	Reference
IN04D.b1.0001	2		(?)	IN04D.B1.0001's and IN04D.b1.0001's health before death not clear	
IN04D.B2.0101	1	?	(?)		
IN04D.b2.0101	2				
IN04D.B2.0102	2	?	(?)		
IN04D.b2.0102	1				
IN04D.B3.0101	2	?	(?)		
IN04D.b3.0101	1				
IN04D.B3.0102	2	?	(?)		
IN04D.B3.0103	1	?	(?)		
IN04D.B3.0104	1	?	(?)		
IN04D.B3.0105	1	?	(?)		
IN04D.B4.0101	2	?			
IN04D.B4.0102	2	35		proband	
IN04D.C1.0001	2	?	(?)	Family 79/95, British	De Jonghe et al.(1999)
IN04D.c1.0001	1		(?)		
IN04D.C2.0101	2	?	(?)		
IN04D.c2.0101	1				
IN04D.C2.0102	2	?	(?)		
IN04D.C3.0101	2	35	(41)	proband	
IN04D.D1.0001	1	?	(?)	Family FD105/160, British	De Jonghe et al.(1999)
IN04D.d1.0001	2		(?)		
IN04D.D2.0101	2	?	(?)		
IN04D.d2.0101	1		(?)		
IN04D.D2.0102	2	?	(?)		
IN04D.d2.0102	1		(?)		
IN04D.D3.0101	1	?	(?)		
IN04D.d3.0101	2		(?)		
IN04D.D3.0202	1	?	(?)		
IN04D.d3.0202	2		(?)		
IN04D.D4.0101	2				
IN04D.D4.0102	2	?	(?)		
IN04D.D4.0103	1	?	(?)		
IN04D.D4.0103	2		(?)		
IN04D.D4.0104	1	?	(?)		
IN04D.D4.0104	2				
IN04D.D4.0105	2	?	(?)	autopsy confirmation of AD	
IN04D.D4.0105	1		(?)		
IN04D.D4.0106	2				
IN04D.D4.0107	2	?	(?)	autopsy confirmation of AD	
IN04D.D4.0107	1				
IN04D.D5.0301	0	?	(?)		
IN04D.d5.0301	0				
IN04D.D5.0302	0	?	(?)		
IN04D.D5.0403	0	?	(?)		
IN04D.d5.0403	0				
IN04D.D5.0504	0	?	(?)		
IN04D.D5.0504	0				
IN04D.D5.0505	0				
IN04D.D5.0706	0	?	(?)		
IN04D.D5.0707	0	?	(?)		
IN04D.D6.0101	0				
IN04D.D6.0102	0				
IN04D.D6.0303	0				

ID	Sex	AAO	Age censored (at death)	Comments	Reference
IN04D.D6.0304	0				
IN04D.D6.0305	0				
IN04D.D6.0406	0	38			
115YC.A1.0001	1	?	(64)	Family 1066, Caucasian	Cruts et al. (1998)
115YC.a1.0001	2				
115YC.A2.0101	2	39	(?)		
115YC.a2.0101	1		(?)		
115YC.A2.0102	2		(?)		
115YC.a2.0102	1		(?)		
115YC.A2.0103	2	45	(?)		
115YC.a2.0103	1		(?)		
115YC.A2.0104	1		(?)		
115YC.a2.0104	2				
115YC.A2.0105	2	39	(?)		
115YC.a2.0105	1				
115YC.A3.0101	2	38	(?)		
115YC.a3.0101	1				
115YC.A3.0102	0				
115YC.A3.0103	0				
115YC.A3.0104	0				
115YC.A3.0105	0				
115YC.A3.0206	0				
115YC.A3.0207	0				
115YC.A3.0208	0				
115YC.A3.0209	0				
115YC.A3.0210	0				
115YC.A3.0211	0				
115YC.A3.0212	0				
115YC.A3.0213	0				
115YC.A3.0314	1	40	(?)	autopsy confirmation of AD	
115YC.A3.0315	1				
115YC.A3.0316	1	49	(?)	autopsy confirmation of AD	
115YC.a3.0316	2				
115YC.A3.0317	1				
115YC.A3.0318	2	39	(?)	autopsy confirmation of AD	
115YC.a3.0318	1				
115YC.A3.0419	1				
115YC.A3.0520	2	49	(?)		
115YC.a3.0520	1				
115YC.A3.0521	0				
115YC.A3.0522	0				
115YC.A3.0523	0				
115YC.A3.0524	0				
115YC.A4.0101	2				
115YC.A4.0102	1	45			
115YC.A4.0103	1				
115YC.A4.1404	0				
115YC.A4.1405	0				
115YC.A4.1406	0				
115YC.A4.1607	0				
115YC.A4.1608	0				
115YC.A4.1609	0				
115YC.A4.1610	0				
115YC.A4.1811	0				
115YC.A4.1812	0				

ID	Sex	AAO	Age censored (at death)	Comments	Reference
115YC.A4.1813	0				
115YC.A4.1814	0				
115YC.A4.1815	0				
115YC.A4.2016	2				
116TN.A1.0001	0	41	(45)	Danish	Romero et al. (1999)
116TN.a1.0001	0		(?)		
116TN.A2.0101	0	35	(43)	+/-	
116TN.a2.0101	0				
116TN.A3.0101	0	38	(43)		
116TN.A3.0102	0	38	41	+/-	
117PL.A1.0001	1	32	(37)	Polish	Wisniewski et al. (1998)
117PL.a1.0001	2				
117PL.A2.0101	1	24	(28)		
117PL.a2.0101	2			-/-	
117PL.A2.0102	2	32	(35)	autopsy confirmation of AD	
117PL.a2.0102	1			-/-	
117PL.A2.0103	2	33	(37)	autopsy confirmation of AD	
117PL.a2.0103	1			-/-	
117PL.A3.0101	1		13		
117PL.A3.0102	1		17		
117PL.A3.0203	1		2	-/-	
117PL.A3.0204	2		11	+/-	
117PL.A3.0205	2		11	twin with 117PL.A3.0204, +/-	
117PL.A3.0206	2		15	+/-	
117PL.A3.0307	1		8	+/-	
117PL.A3.0308	2		14	-/-	
117PL.A3.0309	2		15	-/-	
117PL.A3.0310	2		12	-/-	
120ED.A1.0001	0	?		Family V, British	Poorkaj et al.(1998)
120ED.A2.0101	0		73	censored age or age at death	
120ED.A2.0102	0	50			
120ED.A2.0103	0	45			
120ED.A2.0104	0		76	censored age or age at death	
120ED.A2.0105	0		47	censored age or age at death	
120ED.A2.0106	0	45			
120ED.A2.0107	0		50	censored age or age at death	
120ED.A3.0201	0	53		+/-	
120ED.A3.0202	0	50			
120ED.A3.0203	0	50		+/-	
120ED.A3.0304	0	41			
120ED.A3.0605	0				
120ED.A3.0606	0				
120ED.A4.0101	0				
120ED.A4.0102	0				
120ED.A4.0203	0	43		+/-	
120ED.A4.0204	0				
120ED.A4.0205	0				
120ED.A4.0206	0				
120ED.A4.0407	0	41		+/-	
120EN.A1.0001	1	?	(55)	Romanian-Jewish	Reznik-Wolf et al (1996)
120EN.a1.0001	2		(?)		
120EN.A2.0101	1	48	56	proband	
120EN.a2.0101	2	43	49	+/-	
120EN.A2.0102	2	46	48	+/-	
120EN.A2.0103	1				

ID	Sex	AAO	Age censored (at death)	Comments	Reference
120EN.A3.0101	1				
123EK.A1.0001	1	?	(65)	Family ABCD-2, Japanese	Yasuda et al. (1999)
123EK.a1.0001	2		(72)		
123EK.A2.0101	2		(33)		
123EK.a2.0101	1		(80)	Had a second spouse, with unaffected son (52) and daughter(50)	
123EK.A2.0102	1	?	(56)		
123EK.A2.0103	1		(18)		
123EK.A2.0104	1		(22)		
123EK.A2.0105	2		(8)		
123EK.A2.0106	2		78		
123EK.A3.0101	1	62	65	+/-	
123EK.A3.0102	1	56	57	proband, +/-	
135ND.A1.0001	2		(?)	Family Mex-A	Crook et al. (1997)
135ND.a1.0001	1		(?)		
135ND.A2.0101	2	?	(?)		
135ND.a2.0101	1		(?)		
135ND.A2.0102	1	?	(?)		
135ND.A2.0103	0		(?)		
135ND.A3.0101	0				
135ND.A3.0102	2	?			
135ND.a3.0102	1		(?)		
135ND.A3.0103	2	34	(49)		
135ND.a3.0103	1		(68)		
135ND.A4.0201	2				
135ND.A4.0202	2				
135ND.A4.0203	1	?	(?)		
135ND.A4.0304	0				
135ND.A4.0305	1	37	(54)		
135ND.A4.0306	2	34	(45)		
135ND.a4.0306	1		(68)		
135ND.A5.0601	1	36	41	+/-	
135ND.A5.0602	2		40	-/-	
135ND.A5.0603	2	36	39	proband, +/-	
135ND.A5.0604	2		37		
135ND.A5.0605	1		35		
135ND.A5.0606	2		34		
135ND.A5.0607	1		33		
135ND.A5.0608	2		32		
139MT.A1.0001	2		(30)	Spanish	Queralt et al.(2001)
139MT.a1.0001	1		(65)		
139MT.A2.0101	2	47	65		
139MT.A2.0102	2	48	60		
139MV.A1.0001	1		(46)	German, reports of previous histopathological analyses of affected relatives	Finckh et al. (2000b)
139MV.a1.0001	2		(?)		
139MV.A2.0101	1		(41)	reports of previous histopathological analyses of affected relatives	
139MV.a2.0101	2		78		
139MV.A3.0101	2	32	45	proband, +/-	
139MV.B1.0001	1		(?)	Family F148, British	Fox et al.(1997)
139MV.b1.0001	2		(?)		
139MV.B2.0101	2	?	(?)		
139MV.B2.0102	1	44	(47)		
139MV.b2.0102	2		(?)		

ID	Sex	AAO	Age censored (at death)	Comments	Reference
139MV.B3.0201	0	43	(53)		
139MV.B3.0202	0				
139MV.B3.0203	0	42	(49)		
139MV.B3.0204	0	48	59		
139MV.B3.0205	0	43	55		
139MV.B3.0206	0	45	55		
139MV.C1.0001	2	?	(?)	Family F206, British	Fox et al.(1997)
139MV.c1.0001	1		(?)		
139MV.C2.0101	2	?	(?)		
139MV.c2.0101	1		(?)		
139MV.C2.0102	1		(?)		
139MV.C2.0103	2	36	(43)		
139MV.c2.0103	1		(?)		
139MV.c2b.0101	1		(?)	second spouse of 139MV.C2.0101	
139MV.C3.0101	0	40	(49)		
139MV.c3.0101	0				
139MV.C3.01b02	0	39	(46)	child of 139MV.c2.0101 & second spouse	
139MV.C3.01b03	0			child of 139MV.c2.0101 & second spouse	
139MV.C3.01b04	0			child of 139MV.c2.0101 & second spouse	
139MV.C3.01b05	0	36	(42)	child of 139MV.c2.0101 & second spouse	
139MV.C3.0306	0	39	47		
139MV.C3.0307	0				
139MV.C3.0308	0	38	(41)		
139MV.C3.0309	0				
139MV.C3.0310	0				
139MV.C4.0101	0	36	42		
139MV.C4.0102	0				
139MV.C4.0103	0				
139MV.D1.0001	2	?	(?)	German	H*ddot*ull et al.(1998)
139MV.d1.0001	1		(?)		
139MV.D2.0101	2	?	(?)		
139MV.D2.0102	2	45	(52)		
139MV.d2.0102	1		(?)		
139MV.D3.0101	1	42	(52)		
139MV.D3.0102	1	?	(49)		
139MV.D3.0103	1		(48)	no information onlast years of life	
139MV.D3.0104	1	43	51	proband	
143IT.A1.0001	1		(?)	Family AD/A, Belgian	Martin et al.(1991), Cruts et al.(1995)
143IT.a1.0001	2		(?)		
143IT.A2.0101	1	?	(49)		
143IT.a2.0101	2		(?)		
143IT.A2.0102	1	?	(34)		
143IT.a2.0102	2		(?)		
143IT.A3.0101	2	?	(43)		
143IT.a3.0101	1		(?)		
143IT.A3.0102	2	34	(40)		
143IT.a3.0102	1		(?)		
143IT.A3.0103	2		(?)		
143IT.A3.0204	1		(?)		
143IT.a3.0204	2		(?)		
143IT.A3.0205	1		(?)		

ID	Sex	AAO	Age censored (at death)	Comments	Reference
143IT.A3.0206	2	32	(39)		
143IT.a3.0206	1		(?)		
143IT.A3.0207	2	?	(41)		
143IT.a3.0207	1		(?)		
143IT.A4.0101	2		(?)		
143IT.a4.0101	1		(?)		
143IT.A4.0102	2	40	(43)		
143IT.A4.0103	1	?	(39)		
143IT.a4.0103	2		(?)		
143IT.A4.0104	1		(?)		
143IT.a4.0104	2		(?)		
143IT.A4.0105	2	?	(42)	autopsy confirmation of AD	
143IT.a4.0105	1		(?)		
143IT.A4.0106	2	?	(47)		
143IT.a4.0106	1				
143IT.A4.0207	2	?	(41)	autopsy confirmation of AD	
143IT.a4.0207	1		(?)		
143IT.A4.0208	2				
143IT.a4.0208	1		(?)		
143IT.A4.0209	1		(?)		
143IT.A4.0210	1		(?)		
143IT.A4.0211	1	?	(43)		
143IT.A4.0212	2		(?)		
143IT.A4.0413	0				
143IT.A4.0614	2	?	(37)		
143IT.A4.0615	1	?	(36)		
143IT.a4.0615	2				
143IT.A4.0616	2		(?)		
143IT.A4.0717	1	31	(40)	autopsy confirmation of AD	
143IT.a4.0717	2				
143IT.A4.0718	2		(?)		
143IT.a4.0718	1				
143IT.A4.0719	2	40	(45)	autopsy confirmation of AD	
143IT.a4.0719	1		(?)		
143IT.A4.0720	1		(?)		
143IT.A4.0721	2	?	(40)		
143IT.a4.0721	1		(?)		
143IT.A5.0101	0				
143IT.A5.0302	1	39	(43)	autopsy confirmation of AD	
143IT.a5.0302	2				
143IT.A5.0303	2				
143IT.a5.0303	1				
143IT.A5.0404	0				
143IT.A5.0505	1	?	(36)		
143IT.a5.0505	2				
143IT.A5.0506	1	?	(38)		
143IT.A5.0507	2	30	(38)		
143IT.A5.0508	1				
143IT.A5.0509	2				
143IT.A5.0610	1				
143IT.A5.0611	2	?	(42)		
143IT.a5.0611	1				
143IT.A5.0612	2				
143IT.A5.0713	1	?	(39)		
143IT.A5.0814	0				

ID	Sex	AAO	Age censored (at death)	Comments	Reference
143IT.A5.1415	2	?	(42)		
143IT.a5.1415	1				
143IT.A5.1416	2	33	(36)		
143IT.a5.1416	1				
143IT.A5.1517	2	26	(36)	autopsy confirmation of AD	
143IT.a5.1517	1		(?)		
143IT.A5.1518	1	31	(35)		
143IT.a5.1518	2				
143IT.A5.1619	0				
143IT.A5.1720	2		(?)		
143IT.a5.1720	1				
143IT.A5.1821	0				
143IT.A5.1922	1	42	(49)		
143IT.a5.1922	2				
143IT.A5.1923	2	39	(46)	autopsy confirmation of AD	
143IT.a5.1923	1				
143IT.A5.1924	1				
143IT.a5.1924	2				
143IT.A5.1925	1	45	(51)		
143IT.a5.1925	2				
143IT.A5.1926	1				
143IT.A5.1927	2	34	(38)	autopsy confirmation of AD	
143IT.a5.1927	1				
143IT.A5.1928	2	37	(44)		
143IT.a5.1928	1				
143IT.A5.1929	1	40	(46)		
143IT.a5.1929	2		(?)		
143IT.A5.1930	2				
143IT.a5.1930	1				
143IT.A5.1931	2	33	(45)	autopsy confirmation of AD	
143IT.a5.1931	1				
143IT.A5.2132	1				
143IT.A5.2133	1	33	(42)		
143IT.a5.2133	2				
143IT.A6.0201	1	31	35		
143IT.A6.0302	0				
143IT.A6.0503	2	32	(37)		
143IT.A6.1104	1				
143IT.A6.1505	2	?	(41)		
143IT.a6.1505	1				
143IT.A6.1506	1				
143IT.a6.1506	2				
143IT.A6.1607	2	?	35		
143IT.a6.1607	1				
143IT.A6.1608	2				
143IT.a6.1608	1				
143IT.A6.1709	2		(?)		
143IT.A6.1810	1		(?)		
143IT.A6.1811	2	?			
143IT.a6.1811	1				
143IT.A6.1812	1				
143IT.A6.2013	0				
143IT.A6.2214	2	?			
143IT.a6.2214	1				
143IT.A6.2315	1				

ID	Sex	AAO	Age censored (at death)	Comments	Reference
143IT.a6.2315	2				
143IT.A6.2316	2	?	(?)		
143IT.A6.2417	0				
143IT.A6.2518	1				
143IT.A6.2519	1				
143IT.A6.2520	2				
143IT.A6.2721	2				
143IT.A6.2721	1				
143IT.A6.2722	2				
143IT.A6.2722	1				
143IT.A6.2723	1				
143IT.A6.2723	2				
143IT.A6.2724	1				
143IT.A6.2724	2				
143IT.A6.2725	2				
143IT.A6.2725	1				
143IT.A6.2726	2				
143IT.A6.2827	2	?			
143IT.a6.2827	1				
143IT.A6.2828	1				
143IT.A6.2829	1				
143IT.A6.2830	1				
143IT.A6.2931	1				
143IT.A6.2932	2				
143IT.A6.2933	2				
143IT.A6.2934	1				
143IT.A6.2935	2				
143IT.A6.3036	0				
143IT.A6.3137	1				
143IT.A6.3338	1				
143IT.A7.0501	2				
143IT.A7.0602	0				
143IT.A7.0703	2				
143IT.A7.0704	1				
143IT.A7.0805	0				
143IT.A7.1106	0				
143IT.A7.1407	0				
143IT.A7.1508	0				
143IT.A7.2109	0				
143IT.A7.2210	0				
143IT.A7.2311	0				
143IT.A7.2412	0				
143IT.A7.2513	0				
143IT.A7.2714	0				
146MI.A1.0001	2		(?)	Family E-M, Swedish	Gustafson et al. (1998)
146MI.a1.0001	1		(?)		
146MI.A2.0101	1	35	(53)		
146MI.a2.0101	2		(?)		
146MI.A3.0101	1		(?)		
146MI.A3.0102	1	43	(58)	autopsy confirmation of AD	
146MI.a3.0102	2		(?)		
146MI.A3.0103	2	35	(44)		
146MI.a3.0103	1		(?)		
146MI.A4.0201	2				
146MI.a4.0201	1				

ID	Sex	AAO	Age censored (at death)	Comments	Reference
146MI.A4.0202	1	48	(51)	autopsy confirmation of AD	
146MI.A4.0303	1		(?)		
146MI.A4.0304	2		(?)		
146MI.A4.0305	1		(?)		
146MI.A4.0306	2		(?)		
146MI.A4.0307	1		(?)		
146MI.A4.0308	1				
146MI.A4.0309	2	49	(56)	autopsy confirmation of AD	
146MI.a4.0309	1		(?)		
146MI.A5.0101	1				
146MI.a5.0101	2				
146MI.A5.0102	2				
146MI.a5.0102	1				
146MI.A5.0903	1				
146MI.a5.0903	2				
146MI.A5.0904	1	46	(55)		
146MI.a5.0904	2				
146MI.a5b.0904	2			second spouse of 146MI.A5.0904	
146MI.A6.0101	0				
146MI.A6.0202	0				
146MI.A6.0303	0				
146MI.A6.0404	0				
146MI.A6.0405	0			child of 146MI.A5.0904 & second spouse	
146MI.B1.0001	0	41	(56)	Danish	Jørgensen et al. (1996)
146MI.b1.0001	0				
146MI.B2.0101	0	42	(50)		
146MI.b2.0101	0				
146MI.B2.0102	0	57	(69)		
146MI.B2.0103	0				
146MI.B2.0104	0		(?)		
146MI.B2.0105	0		(?)		
146MI.B2.0106	0	49	(59)		
146MI.B2.0107	0		67		
146MI.B2.0108	0	42	(53)		
146MI.B3.0101	0	38	(52)		
146MI.b3.0101	0				
146MI.B3.0102	0	42	(50)		
146MI.B3.0303	0				
146MI.B3.0304	0				
146MI.B3.0605	0				
146MI.B3.0606	0				
146MI.B3.0807	0				
146MI.B3.0808	0				
146ML.A1.0001	0	?	(?)	Family FAD4, Italian	Sherrington et al. (1995)
146ML.A1.0002	0	?	(?)		
146ML.A2.0101	0	?	(?)		
146ML.A2.0202	0	?	(?)		
146ML.a2.0202	0			-/-	
146ML.A2.0203	0	?	(?)		
146ML.a2.0203	0			-/-	
146ML.A2.0204	0			-/-	
146ML.A3.0101	0			-/-	
146ML.A3.0102	0	?		+/-	
146ML.A3.0103	0			-/-	

ID	Sex	AAO	Age censored (at death)	Comments	Reference
146ML.A3.0104	0			-/-	
146ML.A3.0105	0			-/-	
146ML.A3.0106	0			-/-	
146ML.A3.0207	0	?		+/-	
146ML.A3.0308	0	?		+/-	
146ML.A3.0309	0			+/-	
146ML.A3.0310	0			+/-	
146ML.A3.0311	0			+/-	
146ML.B1.0001	2	?	(47)	Family AR1, Argentinian	Morelli et al.(1998)
146ML.b1.0001	1				
146ML.B2.0101	2	?	(51)		
146ML.b2.0101	1				
146ML.B2.0102	1		56		
146ML.B2.0103	1	40	(52)	autopsy confirmation of AD	
146ML.B3.0101	1	34	41		
146ML.B3.0102	2	33	(40)	autopsy confirmation of AD	
146ML.B3.0103	0				
146ML.B3.0104	0			+/-	
163HR.A1.0001	1	?	(?)	Japanese	Poduslo et al.(1996)
163HR.a1.0001	2			-/-	
163HR.A2.0101	2	40's		+/-	
163HR.a2.0101	1			-/-	
163HR.A2.0102	1	40's		+/-	
163HR.A2.0103	2	40's		+/-	
163HR.B1.0001	1	?		Japanese	Tanahashi et al.(1995)
163HR.b1.0001	2				
163HR.B2.0101	1	?			
163HR.b2.0101	2				
163HR.B2.0102	1	?			
163HR.b2.0102	2				
163HR.B2.0103	1	?			
163HR.b2.0103	2				
163HR.B3.0101	2	?			
163HR.b3.0101	1				
163HR.B3.0202	1	?			
163HR.b3.0202	2				
163HR.B3.0303	1	?			
163HR.b3.0303	2				
163HR.B4.0101	2	?			
163HR.b4.0101	2				
163HR.B4.0102	1	?			
163HR.b4.0102	1				
163HR.B4.0103	2				
163HR.b4.0103	1				
163HR.B4.0104	2	?		+/-	
163HR.b4.0104	2				
163HR.B4.0205	1	?		+/-	
163HR.B4.0306	1	?			
163HR.B5.0101	2	?			
163HR.B5.0202	1	?		+/-	
163HR.B5.0203	2			-/-	
163HR.B5.0304	1			-/-	
163HR.B5.0405	1			-/-	
163HR.C1.0001	0	?		Family HR-1, German	Poorkaj et al.(1998)
163HR.C2.0101	0	55			

ID	Sex	AAO	Age censored (at death)	Comments	Reference
163HR.C2.0102	0		82	censored age or age at death	
163HR.C2.0103	0	50			
163HR.C2.0104	0		80	censored age or age at death	
163HR.C2.0105	0	49			
163HR.C2.0106	0		46	censored age or age at death	
163HR.C2.0107	0	52			
163HR.C3.0101	0	42		+/1; several at-risk individuals in third generation are negative for mutation, but not identified for confidentiality	
163HR.C3.0102	0	45		+/-	
163HR.C3.0103	0		65	censored age or age at death	
163HR.C3.0304	0	49			
163HR.C3.0305	0	40			
163HR.C3.0506	0	52			
163HR.C3.0507	0		66	censored age or age at death	
163HR.C3.0508	0		68	censored age or age at death	
163HR.C3.0509	0		64	censored age or age at death	
163HR.C3.0710	0	47			
163HR.C3.0711	0	48			
163HR.C4.0201	0				
163HR.C4.0202	0				
163HR.C4.0203	0				
163HR.C4.0204	0				
163HR.C4.0205	0				
163HR.C4.0206	0				
163HR.C4.0407	0				
163HR.C4.0408	0				
163HR.C4.0409	0				
163HR.C4.0410	0				
163HR.C4.0511	0				
163HR.C4.0512	0				
163HR.C4.0513	0				
163HR.C4.0514	0				
163HR.C4.0515	0				
163HR.C4.0616	0	40		+/-	
163HR.C4.0617	0				
163HR.C4.0618	0				
163HR.C4.1019	0				
163HR.C4.1020	0				
163HR.C4.1021	0				
163HR.C4.1022	0				
163HR.C4.1123	0				
163HY.A1.0001	0		(?)	Swedish	Axelman et al.(1998)
163HY.a1.0001	0		(?)		
163HY.A2.0101	0	?	(?)		
163HY.A2.0102	0	?	(?)		
163HY.A2.0103	0		(?)		
163HY.A2.0104	0		(?)		
163HY.A2.0105	0	50	(63)		
163HY.A2.0106	0	65	(75)		
163HY.A2.0107	0		(?)		
163HY.A2.0108	0	50	(73)		
163HY.A2.0109	0		(?)		
163HY.A3.0101	0		(?)		

ID	Sex	AAO	Age censored (at death)	Comments	Reference
163HY.A3.0102	0		(?)		
163HY.A3.0103	0		(?)		
163HY.A3.0104	0		(?)		
163HY.A3.0105	0	56	(66)		
163HY.A3.0106	0	62	(73)		
163HY.A3.0107	0		(?)		
163HY.A3.0208	0		(?)		
163HY.A3.0209	0		(?)		
163HY.A3.0210	0		(?)		
163HY.A3.0211	0		(?)		
163HY.A3.0212	0	60	(72)		
163HY.A3.0213	0	59	(65)		
163HY.A3.0214	0		(?)		
163HY.A3.0315	0		(?)		
163HY.A3.0416	0		(?)		
163HY.A3.0417	0		(?)		
163HY.A3.0418	0		(?)		
163HY.A3.0419	0		(?)		
163HY.A3.0420	0		(?)		
163HY.A3.0521	0		(?)		
163HY.A3.0522	0		(?)		
163HY.A3.0523	0		(?)		
163HY.A3.0524	0		(?)		
163HY.A3.0525	0	?	(?)		
163HY.a3.0525	0		(?)		
163HY.A3.0526	0	64	(83)		
163HY.A3.0527	0		(?)		
163HY.A3.0528	0	48	(59)		
163HY.A3.0529	0	63	(68)		
163HY.A3.0630	0		(?)		
163HY.A3.0631	0	60	(73)		
163HY.A3.0632	0	48	(58)		
163HY.A3.0633	0	51	(60)		
163HY.A3.0834	0		(?)		
163HY.A3.0835	0	57	(69)		
163HY.A3.0936	0				
163HY.a3b.0525	0		(?)	second spouse of 163HY.A3.0525	
163HY.a3c.0525	0		(?)	third spouse of 163HY.A3.0526	
163HY.A4.0101	0		(?)		
163HY.A4.0202	0				
163HY.A4.0303	0		(?)		
163HY.A4.0604	0		(?)		
163HY.A4.0605	0				
163HY.A4.0906	0		(?)		
163HY.A4.1107	0		(?)		
163HY.A4.1208	0	?	(?)		
163HY.A4.1209	0		(?)		
163HY.A4.1810	0		(?)		
163HY.A4.2111	0				
163HY.A4.2212	0				
163HY.A4.2413	0		(?)		
163HY.A4.2414	0				
163HY.A4.24b15	0		(?)	child of 163HY.A3.0525 & second spouse	
163HY.A4.24b16	0	45	(55)	child of 163HY.A3.0525 & second spouse	

ID	Sex	AAO	Age censored (at death)	Comments	Reference
163HY.A4.24c17	0			child of 163HY.A3.0525 & third spouse	
163HY.A4.24c18	0	47	60	child of 163HY.A3.0525 & third spouse	
163HY.A4.24c19	0	44	56	child of 163HY.A3.0525 & third spouse	
163HY.A4.2620	0				
163HY.A4.2621	0				
163HY.A4.2722	0				
163HY.A4.2923	0				
163HY.A4.2924	0				
163HY.A5.0101	0				
163HY.A5.0102	0				
163HY.A5.0803	0	46	53		
163HY.A5.0804	0				
163HY.A5.1405	0				
163HY.A5.1506	0				
163HY.A5.1607	0				
163HY.A5.1608	0				
163HY.A5.1609	0				
163HY.A5.1710	0				
163HY.A5.1711	0				
163HY.A5.1712	0				
163HY.A5.1713	0				
163HY.A5.1814	0				
163HY.A5.1815	0				
163HY.A5.1916	0				
163HY.A6.0301	0				
163HY.A6.0302	0				
163HY.A6.0503	0				
163HY.A6.0704	0				
163HY.A6.0805	0				
163HY.A6.0806	0				
163HY.A6.0907	0				
163HY.A6.0908	0				
163HY.A6.0909	0				
163HY.A6.1010	0				
163HY.A6.1111	0				
163HY.A6.1212	0				
163HY.A6.1413	0				
163HY.A6.1614	0				
165WG.A1.0001	1	?	(?)	Japanese	Higuchi et al.(2000)
165WG.a1.0001	2				
165WG.A2.0101	2	34	(43)		
165WG.a2.0101	1				
165WG.A2.0102	1	34	(53)		
165WG.a2.0102	2				
165WG.A2.0103	1				
165WG.A3.0101	2				
165WG.A3.0102	2		(?)		
165WG.A3.0103	2	37			
165WG.a3.0103	1				
165WG.A3.0204	2	38	41	proband	
165WG.a3.0204	1				
165WG.A3.0205	1				
165WG.A3.0206	2				

ID	Sex	AAO	Age censored (at death)	Comments	Reference
165WG.A4.0301	2				
165WG.A4.0302	2				
165WG.A4.0403	2				
165WG.A4.0404	1				
166LR.A1.0001	2	?	44	Spanish	Ezquerra et al. (2000)
166LR.a1.0001	1				
166LR.A2.0101	2	?	42		
166LR.A2.0102	2	?	42		
166LR.a2.0102	1				
166LR.A2.0103	1	?	38		
166LR.A2.0104	2	44	48		
166LR.A2.0105	1		60	-/-	
166LR.A3.0201	2		37	-/-	
166LR.A3.0202	1	32	33	proband, +/-	
166LR.A3.0203	2		28	+/-	
166LR.A3.0204	1		25	+/-	
169SL.A1.0001	2	?	(?)	Family PERTH-4, Australian	Taddei et al. (1998)
169SL.a1.0001	1		(?)		
169SL.A2.0101	2	39	(42)		
169SL.A2.0102	1		45		
169SL.A2.0103	2	31	(37)	proband	
169SP.A1.0001	2	31	38	proband, +/-, Spanish	Ezquerra et al. (1999)
169SP.a1.0001	1				
169SP.A2.0101	1	33		+/-	
169SP.A2.0102	1	35			
169SP.A2.0103	2	34		+/-	
169SP.A2.0104	2		(18)		
169SP.A2.0105	2		32		
169SP.A2.0106	1		30		
169SP.A2.0107	1		26		
171LP.A1.0001	0	?	(?)	Family Ped 1, Mexican	Ramirez-Dueñas et al. (1998)
171LP.a1.0001	0				
171LP.A2.0101	0	40	69	proband, +/-	
171LP.a2.0101	0			-/-	
171LP.A2.0102	0				
171LP.A2.0103	0				
171LP.A3.0101	0	?	(48)		
171LP.A3.0102	0				
171LP.A3.0103	0				
171LP.A3.0104	0			+/-	
171LP.a3.0104	0			-/-	
171LP.A4.0401	0			-/-	
171LP.A4.0402	0			-/-	
171LP.A4.0403	0			-/-	
171LP.A4.0404	0			-/-	
184ED.A1.0001	2	42	(51)	Family ABCD-1, Japanese	Yasuda et al. (1997)
184ED.a1.0001	1		(?)		
184ED.A2.0101	2	44	(51)	+/-	
184ED.a2.0101	1		(?)		
184ED.A3.0101	1		(?)		
184ED.A3.0102	2			-/-	
184ED.A3.0103	1		(?)		
184ED.A3.0104	2			-/-	
184ED.A3.0105	2	41	(51)		
184ED.A3.0106	2			-/-	

ID	Sex	AAO	Age censored (at death)	Comments	Reference
184ED.A3.0107	1	41	47	+/-	
209GR.A1.0001	2	53	76	Japanese	Sugiyama et al.(1999)
209GR.a1.0001	1				
209GR.A2.0101	1	46	53	proband	
209GR.A2.0102	2	48	50		
209GV.A1.0001	0	41		Family L, German	Poorkaj et al.(1998)
209GV.A2.0101	0	48			
209GV.A2.0102	0		85	censored age or age at death	
209GV.A2.0103	0		86	censored age or age at death	
209GV.A2.0104	0	48			
209GV.A2.0105	0	36			
209GV.A3.0101	0	39		several at-risk individuals in third generation are negative for mutation, but not identified for confidentiality	
209GV.A3.0102	0	39		+/-	
209GV.A3.0103	0	45			
209GV.A3.0104	0		58	censored age or age at death	
209GV.A3.0105	0	30			
209GV.A3.0106	0		56	censored age or age at death	
209GV.A3.0107	0	43			
209GV.A3.0108	0		73	censored age or age at death	
209GV.A3.0109	0	41			
209GV.A3.0110	0		60	censored age or age at death	
209GV.A3.0111	0	44		+/-	
209GV.A3.0412	0		52	censored age or age at death	
209GV.A3.0413	0	40		+/-	
209GV.A3.0414	0	39		+/-	
209GV.A3.0415	0	41		+/-	
209GV.A3.0516	0	41			
209GV.A3.0517	0				
209GV.A3.0518	0				
209GV.A3.0519	0				
209GV.A3.0520	0				
209GV.A3.0521	0				
209GV.A4.0101	0				
209GV.A4.0102	0				
209GV.A4.0203	0				
209GV.A4.0304	0	39		+/-	
209GV.A4.0305	0				
209GV.A4.0306	0				
209GV.A4.0307	0				
209GV.A4.0508	0	47		+/-	
209GV.A4.0509	0				
209GV.A4.0710	0	45		+/-	
209GV.A4.0711	0				
209GV.A4.0712	0				
209GV.A4.0713	0				
209GV.A4.0914	0	36			
209GV.A4.0915	0				
209GV.A4.0916	0				
209GV.A4.0917	0				
209GV.A4.0918	0				
209GV.A4.0919	0				
209GV.A4.1120	0				
209GV.A4.1121	0				

ID	Sex	AAO	Age censored (at death)	Comments	Reference
209GV.A4.1122	0				
209GV.A4.1123	0				
209GV.A4.1124	0				
209GV.A4.1325	0				
209GV.A4.1326	0				
209GV.A4.1427	0				
209GV.A4.1428	0				
209GV.A4.1429	0				
209GV.A4.1530	0				
209GV.A4.1531	0				
209GV.A4.1632	0				
209GV.A4.1633	0				
213IT.A1.0001	1	?	(?)	Family OS-2, Japanese	Kamino et al. (1996)
213IT.a1.0001	2				
213IT.A2.0101	0				
213IT.A2.0102	0	?	(?)		
213IT.A2.0103	0	48		+/-	
213IT.A2.0104	0	42		+/-	
219LP.A1.0001	1	?	(52)	Family MELB-1, Australian	Smith et al. (1999)
219LP.a1.0001	2	?	(67)		
219LP.A2.0101	1				
219LP.A2.0102	1	54	(66)		
219LP.a2.0102	2				
219LP.A2.0103	2				
219LP.A2.0104	1				
219LP.A2.0105	1				
219LP.A2.0106	2				
219LP.A3.0201	1	?	(74)		
219LP.a3.0201	2				
219LP.A3.0202	0				
219LP.A3.0203	0				
219LP.A3.0204	0				
219LP.A3.0205	0				
219LP.A3.0206	0				
219LP.A3.0207	0				
219LP.A3.0208	0				
219LP.A4.0101	2	54	(64)		
219LP.a4.0101	1				
219LP.A4.0102	1	?	(64)		
219LP.a4.0102	2				
219LP.A4.0103	2				
219LP.a4.0103	1				
219LP.A4.0104	1		(?)		
219LP.a4.0104	2				
219LP.A4.0105	2	?	68		
219LP.a4.0105	1				
219LP.A5.0101	2				
219LP.A5.0102	2	53	58		
219LP.A5.0103	1				
219LP.A5.0104	2				
219LP.A5.0105	1				
219LP.A5.0106	2				
219LP.A5.0107	2				
219LP.A5.0108	1				
219LP.A5.0109	2				

ID	Sex	AAO	Age censored (at death)	Comments	Reference
219LP.A5.0110	1				
219LP.A5.0211	2				
219LP.A5.0212	2	?	(54)		
219LP.A5.0213	2	47	49		
219LP.A5.0214	1				
219LP.A5.0315	1				
219LP.A5.0316	1				
219LP.A5.0317	1				
219LP.A5.0418	2				
219LP.A5.0419	2				
219LP.A5.0520	1		(?)		
219LP.A5.0521	1				
219LP.A5.0522	1				
219LP.A5.0523	1				
231AV.A1.0001	2	?	(92)	Family 1072, Caucasian	Cruts et al. (1998)
231AV.a1.0001	1		(?)		
231AV.A1.0002	2		(?)		
231AV.A2.0101	2	75	(?)		
231AV.A2.0102	0			unknown number of sibs	
231AV.B1.0001	1	55	(?)	married 231AV.A1.0002	
231AV.B2.0101	1	56	(?)	married 231AV.A2.0101	
231AV.B2.0102	0			unknown number of sibs	
231AV.B3.0101	0				
231AV.B3.0102	0				
231AV.B3.0103	1	63	(?)	autopsy confirmation of AD	
231AV.B3.0104	2	58		proband	
231AV.B3.0105	0				
231AV.B3.0106	0				
231AV.B3.0107	0				
231AV.B3.0108	0				
231AV.B3.0109	0				
231AV.B3.0110	0				
231AV.B3.0111	0				
233MT.A1.0001	2	?	(?)	Family PERTH-1, Australian	Kwok et al. (1997)
233MT.a1.0001	1				
233MT.A2.0101	2	34		+/-	
233MT.A2.0102	1	33		+/-	
233MT.A2.0103	1	38			
233MT.A2.0104	2			-/-	
233MT.A2.0105	2				
233MT.A3.0101					
233MT.A3.0102					
233MT.A3.0103					
233MT.A3.0204					
233MT.A3.0205					
233MT.A3.0306					
233MT.A3.0307					
233MT.A3.0408					
233MT.A3.0409					
233MT.A3.0410					
233MT.A3.0511					
233MT.A3.0512					
235LP.A1.0001	1	?	(36)	Family SAL 510, French	Campion et al. (1996)
235LP.a1.0001	2	?			
235LP.A2.0101	0	31	(36)	+/-	

ID	Sex	AAO	Age censored (at death)	Comments	Reference
235LP.A2.0102	0	35	40	+/-	
235LP.A2.0103	0	29	33	+/-	
235LP.A2.0104	0			-/-	
235LP.A2.0105	0			-/-	
235LP.A2.0106	0				
235LP.A2.0107	0				
246AE.A1.0001	0	?	(?)	Family FAD1, Caucasian	Sherrington et al. (1995)
246AE.A1.0002	0	?	(?)		
246AE.A1.0003	0	?	(?)		
246AE.A2.0101	0	?	(?)		
246AE.a2.0101	0			-/-	
246AE.A2.0102	0			-/-	
246AE.A2.0203	0		(?)		
246AE.A2.0204	0	?	(?)		
246AE.a2.0204	0			-/-	
246AE.A2.0305	0	?	(?)		
246AE.A3.0101	0	?		+/-	
246AE.A3.0102	0			+/-	
246AE.A3.0303	0			-/-	
246AE.A3.0304	0			-/-	
246AE.A3.0305	0			-/-	
246AE.A3.0406	0	?		+/-	
246AE.A3.0407	0			+/-	
246AE.A3.0408	0			-/-	
246AE.A3.0409	0			-/-	
246AE.A3.0410	0			-/-	
246AE.A3.0411	0			-/-	
246AE.A3.0512	0	?		+/-	
246AE.A3.0513	0			-/-	
250LS.A1.0001	2	?	(58)	Family 184, British	Harvey et al.(1998)
250LS.a1.0001	1		(?)		
250LS.A2.0101	2	51	(66)		
250LS.a2.0101	1		(?)		
250LS.A2.0102	2	?	(Early 60's)		
250LS.A3.0101	0	55	(69)		
250LS.A3.0102	0				
250LS.A3.0103	0	56	(63)		
250LS.A3.0104	0	49	(55)		
250LS.A3.0105	0	50	(61)		
250LS.A3.0106	0				
260AV.A1.0001	2		(?)	Family AM/JPN1, Japanese	Ikeda et al. (1996)
260AV.a1.0001	1		(?)		
260AV.A2.0101	1				
260AV.a2.0101	2				
260AV.A2.0102	2		(?)		
260AV.A2.0103	1	?	(?)		
260AV.a2.0103	2				
260AV.A3.0101	2				
260AV.A3.0102	2				
260AV.A3.0103	2				
260AV.A3.0104	2				
260AV.A3.0105	2				
260AV.A3.0306	2	?	(?)		
260AV.A3.0306	1				
260AV.A3.0307	1	?	(?)	autopsy confirmation of AD	

ID	Sex	AAO	Age censored (at death)	Comments	Reference
260AV.A3.0307	2				
260AV.A3.0308	2				
260AV.A3.0308	1				
260AV.A3.0309	2	?			
260AV.A3.0309	1				
260AV.A3.0310	2	?	(?)	autopsy confirmation of AD	
260AV.A3.0310	1				
260AV.A3.0311	2				
260AV.A3.0311	1				
260AV.A3.0312	2	?	(?)	autopsy confirmation of AD	
260AV.A3.0312	1				
260AV.A3.0313	1	?			
260AV.A3.0313	2				
260AV.A3.0314	2				
260AV.A3.0314	1				
260AV.A4.0601	1	?			
260AV.A4.0602	2				
260AV.A4.0703	1	?			
260AV.A4.0704	1	?			
260AV.A4.0705	2				
260AV.A4.0706	2		(?)		
260AV.A4.0807	2				
260AV.A4.0808	1				
260AV.A4.0809	1				
260AV.A4.0810	1				
260AV.A4.0911	2				
260AV.A4.0912	2				
260AV.A4.1013	2				
260AV.A4.1014	1				
260AV.A4.1115	1				
260AV.A4.1116	1				
260AV.A4.1117	1				
260AV.A4.1218	1				
260AV.A4.1219	2				
260AV.A4.1220	1				
260AV.A4.1321	2				
260AV.A4.1422	1				
260AV.A4.1423	2				
264PL.A1.0001	0	45		Family KG, British	Poorkaj et al.(1998)
264PL.A2.0101	0	43		several at-risk individuals in third generation are negative for mutation, but not identified for confidentiality	
264PL.A2.0102	0		70	censored age or age at death	
264PL.A2.0103	0	43			
264PL.A2.0104	0		62		
264PL.A2.0105	0		60		
264PL.A2.0106	0		72		
264PL.A2.0107	0	45		+/-	
264PL.A2.0108	0		67		
264PL.A2.0109	0	45			
264PL.A3.0101	0				
264PL.A3.0302	0				
264PL.A3.0703	0				
264PL.A3.0704	0				
264PL.A3.0905	0				

ID	Sex	AAO	Age censored (at death)	Comments	Reference
264PL.A3.0906	0				
264PL.A3.0907	0				
282LR.A1.0001	2	?	(58)	Spanish	Aldudo et al . (1998)
282LR.a1.0001	1		60		
282LR.A2.0101	2	40	(60)		
282LR.A2.0102	2		61		
282LR.A2.0103	1	40	(55)		
282LR.A2.0104	2	49	(54)	proband	
282LR.A2.0105	2		54		
285AV.A1.0001	1	?	(?)	Family SD6, Japanese	Ikeda et al. (1996)
285AV.a1.0001	2		(?)		
285AV.A2.0101	2	55	(65)		
285AV.a2.0101	1				
285AV.A2.0102	1				
285AV.A3.0101	2		51		
285AV.A3.0102	2	47	49	proband	
285AV.A3.0103	2		46		
285AV.B1.0001	1		(60)	Family TOH-1, Japanese	Aoki et al.(1997)
285AV.b1.0001	2		(60)		
285AV.B2.0101	2	55	(65)		
285AV.b2.0101	1		(72)		
285AV.B2.0102	1		(?)	died in World War II	
285AV.B3.0101	2		50		
285AV.B3.0102	2	45	48		
285AV.B3.0103	1		46		
286LV.A1.0001	0	?	(?)	Family FAD2, Ashkenazi-Jewish	Sherrington et al. (1995)
286LV.A1.0002	0	?	(?)		
286LV.a1.0002	0				
286LV.A1.0003	0	?	(?)		
286LV.A2.0101	0	?		+/-	
286LV.A2.0102	0	?	(?)		
286LV.a2.0102	0			-/-	
286LV.A2.0203	0			-/-	
286LV.A2.0204	0	?	(?)		
286LV.a2.0204	0			-/-	
286LV.A2.0305	0			-/-	
286LV.A2.0306	0			-/-	
286LV.A2.0307	0			-/-	
286LV.A2.0308	0	?	(?)		
286LV.A3.0201	0	?		+/-	
286LV.A3.0202	0			+/-	
286LV.A3.0203	0			-/-	
286LV.A3.0204	0			-/-	
286LV.A3.0205	0			-/-	
286LV.A3.0406	0			+/-	
286LV.A3.0407	0			-/-	
286LV.A3.0808	0	?		+/-	
286LV.A3.0809	0			+/-	
EX09D.A1.0001	1	45	(56)	Family Finn2, Finnish	Crook et al. (1998), Verkkoniemi et al.(2000)
EX09D.a1.0001	2		(?)		
EX09D.A2.0101	2	48	(53)		
EX09D.A2.0102	2		(?)		
EX09D.A2.0103	1	?	(?)		
EX09D.a2.0103	2		(?)		

ID	Sex	AAO	Age censored (at death)	Comments	Reference
EX09D.A2.0104	1		(?)		
EX09D.A2.0105	1		(?)		
EX09D.A2.0106	1	?	(?)		
EX09D.A2.0107	2		(?)		
EX09D.A2.0108	1	45	(56)		
EX09D.a2.0108	2		(?)		
EX09D.A2.0109	1	?	(?)		
EX09D.A2.0110	1		(?)		
EX09D.A2.0111	1	51	(62)		
EX09D.a2.0111	2				
EX09D.A3.0301	1	?	(?)		
EX09D.A3.0302	2	?	(?)		
EX09D.a3.0302	1				
EX09D.A3.0803	2				
EX09D.a3.0803	1				
EX09D.A3.0804	1	54	(66)		
EX09D.a3.0804	2				
EX09D.A3.0805	1	57	(69)		
EX09D.a3.0805	2				
EX09D.A3.0806	1	54	(64)		
EX09D.a3.0806	2				
EX09D.A3.1107	1		(?)		
EX09D.A3.1108	1		(?)		
EX09D.A3.1109	1	55	(61)		
EX09D.a3.1109	2				
EX09D.A3.1110	1	51	62		
EX09D.a3.1110	2				
EX09D.A3.1111	1				
EX09D.A3.1112	2	49	(54)		
EX09D.a3.1112	1				
EX09D.A3.1113	2	51	57		
EX09D.a3.1113	1				
EX09D.A3.1114	1	49	54		
EX09D.a3.1114	2				
EX09D.A3.1115	2				
EX09D.a3.1115	1				
EX09D.A4.0201	2				
EX09D.A4.0302	1				
EX09D.A4.0303	1				
EX09D.A4.0404	1				
EX09D.A4.0505	2				
EX09D.A4.0506	2				
EX09D.A4.0607	1				
EX09D.A4.0908	2				
EX09D.A4.0909	1				
EX09D.A4.1010	1				
EX09D.A4.1011	2				
EX09D.A4.1212	2				
EX09D.A4.1213	2				
EX09D.A4.1314	1				
EX09D.A4.1315	2				
EX09D.A4.1416	2				
EX09D.A4.1517	1				
EX09D.A4.1518	2				
EX09D.B1.0001	1	?	(?)	Family F74, British	Perez-Tur et al. (1995)

ID	Sex	AAO	Age censored (at death)	Comments	Reference
EX09D.b1.0001	2		(?)		
EX09D.B2.0101	2			-/-	
EX09D.B2.0102	2	42	(?)		
EX09D.b2.0102	1			-/-	
EX09D.B2.0103	1	50	(?)		
EX09D.b2.0103	2			-/-	
EX09D.B3.0201	1	42	(?)		
EX09D.b3.0201	2				
EX09D.B3.0202	2			-/-	
EX09D.B3.0203	2	39		+/-	
EX09D.b3.0203	1			-/-	
EX09D.B3.0304	1	42	(?)	+/-	
EX09D.B3.0305	1	42		+/-	
EX09D.B4.0101	0				
EX09D.B4.0102	0				
EX09D.B4.0103	0				
EX09D.B4.0304	0				
EX09D.B4.0305	0			-/-	
EX09D.C1.0001	2	43	(45)	Finnish	Hiltunen et al.(2000)
EX09D.c1.0001	1		(?)		
EX09D.C2.0101	1	45	(50)	+/-	
EX09D.c2.0101	2			-/-	
EX09D.C2.0102	2			-/-	
EX09D.C2.0103	1	42	(44)	+/-	
EX09D.C2.0104	1	40	(45)	+/-	
EX09D.c2.0104	2			-/-	
EX10D.A1.0001	1	?	(?)	Family TK-1, Japanese	Sato et al. (1997)
EX10D.a1.0001	2		(?)		
EX10D.A2.0101	1	?	(?)		
EX10D.a2.0101	2		(?)		
EX10D.A2.0102	1		(?)		
EX10D.A3.0101	2	?	(?)		
EX10D.a3.0101	1		(?)		
EX10D.A3.0102	1	?	(?)		
EX10D.a3.0102	2				
EX10D.A4.0101	1	?	(?)		
EX10D.a4.0101	2				
EX10D.A4.0102	2		(?)		
EX10D.A4.0103	2				
EX10D.A4.0104	1	?	(?)		
EX10D.A4.0105	1		(?)		
EX10D.A4.0106	2		(?)		
EX10D.A4.0107	2	?	(?)		
EX10D.A4.0208	1	?	(?)		
EX10D.a4.0208	2		(?)		
EX10D.A4.0209	1	?	(?)		
EX10D.a4.0209	2				
EX10D.A4.0210	2				
EX10D.A4.0211	1	?	(?)		
EX10D.a4.0211	2				
EX10D.A4.0212	2		(?)		
EX10D.A4.0213	2				
EX10D.A5.0101	2				
EX10D.A5.0102	2	?		proband, +/-	
EX10D.a5.0102	1				

ID	Sex	AAO	Age censored (at death)	Comments	Reference
EX10D.A5.0103	1		(?)		
EX10D.A5.0104	2			-/-	
EX10D.A5.0105	1		(?)		
EX10D.A5.0106	2			+/-	
EX10D.A5.0107	1			-/-	
EX10D.A5.0108	1			+/-	
EX10D.A5.0109	1		(?)		
EX10D.A5.0810	1			+/-	
EX10D.A5.0911	1		(?)		
EX10D.A5.0912	1				
EX10D.A5.0913	1				
EX10D.A5.1114	1			+/-	
EX10D.A6.0201	1			-/-	
EX10D.a6.0201	2				
EX10D.A6.1002	1			-/-	
EX10D.A6.1003	1			-/-	
EX10D.A7.0101	1			-/-	
EX04D.B1.0001	0	32	(40)	Scottish; deletion isoleucine and methionine of codons 83 and 84 respectively	Steiner et al.(2001)
EX04D.b1.0001	0		(?)		
EX04D.B2.0101	0		(?)		
EX04D.B2.0102	0	38	(46)		
EX04D.B2.0103	0	38	(46)		
EX04D.b2.0103	0		(72)		
EX04D.B3.0301	0	36	(44)		
EX04D.B3.0302	0		60		
EX04D.B3.0303	0		55		
EX04D.B3.0304	0	36	(44)	proband	
EX04D.b3.0304	0		52		
EX04D.B4.0101	0				
EX04D.B4.0102	0				
EX09D.D1.0001	2	53	(58)	Family AusAD-1, Australian; dementia without spastic paraparesis	Smith et al.(2001)
EX09D.d1.0001	1		(?)		
EX09D.D2.0101	2		(?)		
EX09D.d2.0101	1		(?)		
EX09D.D2.0102	2	36	(43)	dementia without spastic paraparesis	
EX09D.d2.0102	1		(?)		
EX09D.D2.0103	2	47	(49)	dementia without spastic paraparesis	
EX09D.d2.0103	1		(?)		
EX09D.D2.0104	1	52	(56)	dementia without spastic paraparesis	
EX09D.D2.0105	1	47	(52)	dementia without spastic paraparesis	
EX09D.d2.0105	2		(?)		
EX09D.D2.0106	1	46	(52)	dementia without spastic paraparesis	
EX09D.d2.0106	2		(?)		
EX09D.D2.0107	1	41	(46)	dementia without spastic paraparesis	
EX09D.d2.0107	2				
EX09D.D2.0108	1		(?)		
EX09D.D2.0109	1				
EX09D.D2.0110	2	39	(47)	dementia without spastic paraparesis	
EX09D.d2.0110	1		(?)		
EX09D.D3.0101	1				
EX09D.D3.0102	1				
EX09D.D3.0103	2				
EX09D.D3.0204	1				

ID	Sex	AAO	Age censored (at death)	Comments	Reference
EX09D.D3.0305	2		(?)		
EX09D.D3.0306	1				
EX09D.D3.0607	2	54	(63)	dementia with spastic paraparesis	
EX09D.D3.0608	2				
EX09D.D3.0609	2	50	(53)	spastic paraparesis without dementia	
EX09D.D3.0610	1	46	57	spastic paraparesis without dementia	
EX09D.D3.0611	1	48	54	spastic paraparesis without dementia	
EX09D.D3.0612	2				
EX09D.D3.0713	1				
EX09D.D3.1014	1	36	(46)	dementia without spastic paraparesis	
EX09D.D3.1015	2				
EX09D.D3.1016	1				
318EG.A1.0001	2	?	(47)	Family 1069, Caucasian	Cruts et al. (1998)
318EG.A2.0101	2		(?)		
318EG.A2.0102	1	57		proband	
318EG.A2.0103	0			unknown number of sibs	
318EG.B1.0001	2	?	(60+)	Family PERTH-5, Australian	Taddei et al. (1998)
318EG.b1.0001	1				
318EG.B2.0101	2	?			
318EG.B2.0102	1	late 50+		proband	
318EG.B2.0103	1				
318EG.C1.0001	2	?	(69)	Swedish	Forsell et al.(1997)
318EG.c1.0001	1		(?)		
318EG.C2.0101	0	60		proband	
318EG.C2.0102	2	68			
318EG.C2.0103	2		84		
318EG.C2.0104	1	60	(?)		
378GE.A1.0001	2	35	(40)	French	Besançon et al.(1997)
378GE.a1.0001	1		(?)		
378GE.A2.0101	2		69		
378GE.A2.0101	1				
378GE.A2.0102	2	38	(40)		
378GE.a2.0102	1				
378GE.A2.0103	2	35	(37)		
378GE.a2b.0102	1			second spouse of 378GE.A2.0102	
378GE.A3.0101	2				
378GE.A3.0202	1	34	46	proband	
378GE.a3.0202	2				
378GE.A3.02b03	2		33	child of 378GE.A2.0102 & second spouse	
378GE.a3.02b03	1				
378GE.A3.02b04	2		31	child of 378GE.A2.0102 & second spouse	
378GE.a3.02b04	1				
378GE.A3.02b05	2		30	child of 378GE.A2.0102 & second spouse	
378GE.a3.02b05	1				
378GE.A4.0201	1				
378GE.A4.0302	1				
378GE.A4.0403	2				
378GE.A4.0404	2				
378GE.A4.0505	2				
384GA.A1.0001	2	?	(44)	Family AD/B, Belgian	Martin et al.(1991), Cruts et al.(1995)
384GA.a1.0001	1		(?)		

ID	Sex	AAO	Age censored (at death)	Comments	Reference
384GA.A2.0101	2		(?)		
384GA.a2.0101	1		(?)		
384GA.A2.0102	2	?	(40)		
384GA.a2.0102	1		(?)		
384GA.A2.0103	2	?	(43)		
384GA.a2.0103	1		(?)		
384GA.A2.0104	2		(?)		
384GA.a2.0104	1		(?)		
384GA.A3.0101	0				
384GA.A3.0202	1		(?)		
384GA.a3.0202	2				
384GA.A3.0203	1	?	(45)		
384GA.a3.0203	2		(?)		
384GA.A3.0204	1	?	(47)		
384GA.a3.0204	2		(?)		
384GA.A3.0205	2				
384GA.a3.0205	1		(?)		
384GA.A3.0206	2	?	(45)		
384GA.a3.0206	1		(?)		
384GA.A3.0207	2	?	(41)		
384GA.a3.0207	1		(?)		
384GA.A3.0208	2	?	(40)		
384GA.a3.0208	1		(?)		
384GA.A3.0209	2		(?)		
384GA.A3.0310	2		(?)		
384GA.a3.0310	1		(?)		
384GA.A3.0311	2	?	(41)		
384GA.a3.0311	1		(?)		
384GA.A3.0312	2				
384GA.a3.0312	1				
384GA.A3.0313	1	?	(44)		
384GA.A3.0314	1		(?)		
384GA.A3.0415	0				
384GA.A4.0201	0				
384GA.A4.0302	1				
384GA.a4.0302	2				
384GA.A4.0303	2	?	(39)		
384GA.a4.0303	1				
384GA.A4.0304	2				
384GA.A4.0305	1				
384GA.a4.0305	2				
384GA.A4.0306	2				
384GA.a4.0306	1				
384GA.A4.0307	1	30	(43)	autopsy confirmation of AD	
384GA.A4.0308	2	39	(42)	autopsy confirmation of AD	
384GA.a4.0308	1				
384GA.A4.0309	1	36	(39)	autopsy confirmation of AD	
384GA.a4.0309	2				
384GA.A4.0310	2	35	(41)	autopsy confirmation of AD	
384GA.a4.0310	1				
384GA.A4.0411	1				
384GA.a4.0411	2				
384GA.A4.0512	0				
384GA.A4.0613	2				
384GA.a4.0613	1		(?)		

ID	Sex	AAO	Age censored (at death)	Comments	Reference
384GA.A4.0614	1	?	(45)		
384GA.a4.0614	2				
384GA.A4.0615	2	?	(44)		
384GA.a4.0615	1				
384GA.A4.0616	2				
384GA.a4.0616	1				
384GA.A4.0717	2	?	(39)		
384GA.a4.0717	1		(?)		
384GA.A4.0718	2				
384GA.a4.0718	1				
384GA.A4.0719	1	?	(42)		
384GA.a4.0719	2				
384GA.A4.0820	2				
384GA.a4.0820	1				
384GA.A4.1021	0				
384GA.A4.1122	1				
384GA.a4.1122	2				
384GA.A4.1123	2	?	(43)		
384GA.a4.1123	1				
384GA.A4.1124	2	?	(42)		
384GA.A4.1125	2	?	(40)		
384GA.A4.1126	1	33	(43)	autopsy confirmation of AD	
384GA.a4.1126	2				
384GA.A4.1127	1	35	(41)	autopsy confirmation of AD	
384GA.a4.1127	2				
384GA.A4.1228	0				
384GA.A5.0201	0				
384GA.A5.0302	1				
384GA.A5.0303	2				
384GA.a5.0303	1				
384GA.A5.0304	2				
384GA.A5.0505	0				
384GA.A5.0606	0				
384GA.A5.0807	2				
384GA.A5.0807	1				
384GA.A5.0808	1				
384GA.A5.0809	2				
384GA.A5.0910	2				
384GA.A5.0911	1				
384GA.A5.1012	2				
384GA.A5.1013	2				
384GA.A5.1014	1				
384GA.A5.1115	0				
384GA.A5.1316	0				
384GA.A5.1417	2				
384GA.A5.1518	1				
384GA.A5.1518	2				
384GA.A5.1519	2				
384GA.A5.1620	0				
384GA.A5.1721	1				
384GA.A5.1721	2				
384GA.A5.1822	0				
384GA.A5.1923	2				
384GA.A5.2024	0				
384GA.A5.2225	0				

ID	Sex	AAO	Age censored (at death)	Comments	Reference
384GA.A5.2326	2				
384GA.A5.2326	1				
384GA.A5.2327	2				
384GA.A5.2628	2				
384GA.A5.2629	2				
384GA.A5.2630	1				
384GA.A5.2631	2				
384GA.A5.2732	2				
384GA.A5.2733	2				
384GA.A5.2734	1				
384GA.A5.2735	2				
384GA.A6.0301	0				
384GA.A6.0702	0				
384GA.A6.1803	0				
384GA.A6.2104	0				
384GA.A6.2605	0				
392LP.A1.0001	2	?	(?)	Italian	Tedde et al.(2000)
392LP.a1.0001	1		(?)		
392LP.A2.0101	2	36	(?)		
392LP.a2.0101	1		(?)		
392LP.A3.0101	1	36	42	proband	
392LP.A3.0102	2	43	45		
392LP.a3.0102	1				
392LP.A4.0201	1				
410CY.A1.0001	0	?	(?)	Family FAD3, Russian-Jewish	Sherrington et al. (1995)
410CY.A1.0002	0		(?)		
410CY.A1.0003	0		(?)		
410CY.A1.0004	0		(?)		
410CY.A2.0101	0	?	(?)		
410CY.A2.0102	0	?	(?)		
410CY.A2.0103	0	?	(?)		
410CY.A2.0104	0			-/-	
410CY.A2.0205	0			-/-	
410CY.A2.0206	0			-/-	
410CY.A2.0307	0			-/-	
410CY.A2.0408	0			-/-	
410CY.A2.0409	0			-/-	
410CY.A3.0101	0	?		+/-	
410CY.A3.0102	0			-/-	
410CY.A3.0203	0			+/-	
410CY.A3.0304	0	?		+/-	
410CY.A3.0305	0			+/-	
410CY.A3.0306	0			+/-	
426AP.A1.0001	0			Family HRX-III (XIII, Scot-1), Scottish	Poorkaj et al.(1998)
426AP.A2.0101	0	41			
426AP.A2.0102	0		88	censored age or age at death	
426AP.A2.0103	0	46			
426AP.A2.0104	0	51			
426AP.A3.0101	0				
426AP.A3.0102	0				
426AP.A3.0303	0	48			
426AP.A3.0304	0	48		+/-	
426AP.A3.0305	0				
426AP.A3.0306	0				

ID	Sex	AAO	Age censored (at death)	Comments	Reference
426AP.A3.0407	0		47	censored age or age at death	
426AP.A3.0408	0	42		+/-	
426AP.A4.0301	0				
426AP.A4.0302	0				
426AP.A4.0303	0				
426AP.A4.0304	0				
426AP.A4.0305	0				
426AP.A4.0306	0				
426AP.A4.0407	0				
426AP.A4.0408	0				

Appendix E

Pedigree database of presenilin-2 gene mutations

The following table summarises the family studies in which the PSEN-2 mutations have been found.

ID	Sex	AAO	Age censored (at death)	Comments	Reference
122TP.A1.0001	2	∼46	(51)	German family	Finckh et al. (2000b)
122TP.a1.0001	1		(46)		
122TP.A2.0101	2	∼45	(48)		
122TP.a2.0101	1		81		
122TP.A3.0101	2	46	50	proband	
141NI.A1.0001	0		(44)	family BE	Levy-Lahad et al. (1995a)
141NI.a1.0001	0		(36)		
141NI.A2.0101	0				
141NI.A2.0102	0				
141NI.A2.0103	0				
141NI.A2.0104	0		76	-/-	
141NI.A2.0105	0	57			
141NI.A2.0106	0	58			
141NI.A2.0107	0	62		+/-	
141NI.B1.0001	1		(76)	"neuropsychiatric disorder of unknown type"; Russian family E	Bird et al. (1988)
141NI.b1.0001	2		(85)	clinical condition unknown	
141NI.B2.0101	2		(∼75)		
141NI.B2.0102	2	62	68	autopsy confirmation of AD	
141NI.B2.0103	1	61	65	autopsy confirmation of AD	
141NI.B2.0104	1		(∼75)		
141NI.B2.0105	1	57	69	autopsy confirmation of AD	
141NI.B2.0106	2		(76)		
141NI.B2.0107	2		(71)	autopsy; Creutzfeldt-Jakob disease (CJD) onset at 70	
141NI.B2.0108	1	51	(65)		
141NI.B3.0101	1				

ID	Sex	AAO	Age censored (at death)	Comments	Reference
141NI.B3.0102	1				
141NI.B3.0103	1				
141NI.B3.0104	1				
141NI.B3.0205	1	50	(58)		
141NI.B3.0206	2		(56)		
141NI.B3.0207	2		40		
141NI.B3.0408	1				
141NI.B3.0409	1				
141NI.B3.0410	1				
141NI.B3.0411	2				
141NI.B3.0412	2				
141NI.B3.0513	1				
141NI.B3.0514	2				
141NI.B3.0515	2				
141NI.B3.0716	1				
141NI.B3.0717	1				
141NI.B3.0718	2				
141NI.B3.0819	2				
141NI.B3.0820	1				
141NI.B3.0821	1				
141NI.C1.0001	0	70		family HD; pedigree incomplete with only affected shown	Levy-Lahad et al. (1995a)
141NI.c1.0001	0				
141NI.C2.0101	0	55			
141NI.C2.0102	0	67			
141NI.C2.0103	0	53			
141NI.C3.0101	0	47			
141NI.C3.0202	0	75		-/-; sporadic AD?	
141NI.C3.0303	0	51			
141NI.C4.0101	0	60		+/-	
141NI.C4.0102	0	52		+/-	
141NI.C4.0303	0	46		+/-	
141NI.C5.0101	0	49		+/-	
141NI.D1.0001	1		(?)	possible dementia; Russian family KS	Bird et al. (1988)
141NI.d1.0001	2		(?)	possible dementia	
141NI.D2.0101	1		(?)	probable dementia	
141NI.D2.0102	1		(?)		
141NI.d2.0102	2		(?)		
141NI.d2b.0102	2		(?)	second spouse of 141NI.D2.0101	
141NI.D2.0103	2		(?)		
141NI.D2.0104	2		(?)		
141NI.D2.0105	2		(?)		
141NI.D3.0101	1		(60)		
141NI.D3.0102	1		(56)		
141NI.D3.0103	1		(44)		
141NI.D3.0104	1	72	(?)		
141NI.D3.0105	1		(62)		
141NI.D3.0106	1		(?)		
141NI.D3.0107	1		(?)		
141NI.D3.0108	2		(?)		
141NI.D3.0109	1		(?)		
141NI.D3.02a10	1		(?)	child of 141NI.D2.0102 & first spouse	
141NI.D3.02a11	1		(73)	Parkinson's disease	
141NI.D3.02a12	2		(?)		
141NI.D3.02a13	2		(?)		

ID	Sex	AAO	Age censored (at death)	Comments	Reference
141NI.D3.02a14	2		(?)		
141NI.D3.02b15	1			child of 141NI.D2.0102 & second spouse	
141NI.D3.02b16	1				
141NI.D3.02b17	2				
141NI.D3.02b18	2				
141NI.D3.02b19	2				
141NI.D3.02b20	2				
141NI.D3.02b21	2				
141NI.D3.02b22	2				
141NI.D4.0101	2		(41–62)		
141NI.D4.0102	2		(41–62)		
141NI.D4.0103	2		(41–62)		
141NI.D4.0104	2		(41–62)		
141NI.D4.0105	2	68	78		
141NI.D4.0106	2		71		
141NI.D4.0107	1		(45)		
141NI.D4.0108	1		61		
141NI.D4.0209	2		(26–62)		
141NI.D4.0210	2		(26–62)		
141NI.D4.0211	2		(26–62)		
141NI.D4.0212	2	68	(75)		
141NI.D4.0213	2		69		
141NI.D4.0314	2	?	(74)		
141NI.D4.0315	1		(69)		
141NI.D4.0316	2	?	(76)		
141NI.D4.0317	1		(65)	probable dementia	
141NI.D4.0318	2		71		
141NI.D4.0419	1		(?)	infant death	
141NI.D4.0420	1		(?)	infant death	
141NI.D4.0421	1	58	76		
141NI.D4.0422	2	68	73	probable dementia	
141NI.D4.0423	1		71		
141NI.D4.0424	1	66	69	probable dementia	
141NI.D4.0425	1		64		
141NI.D4.0426	1		58		
141NI.E1.0001	1		(79)	probable dementia; Russian family H	Bird et al. (1988)
141NI.e1.0001	2		(?)		
141NI.E2.0101	2		(60)	probable dementia	
141NI.E2.0102	1		(89)		
141NI.e2.0102	2		(78)		
141NI.E3.0101	0		(?)		
141NI.E3.0102	0		(?)		
141NI.E3.0103	0		(?)		
141NI.E3.0104	1		(65)		
141NI.E3.0105	1	?	(64)		
141NI.E3.0106	2		(35)		
141NI.E3.0107	1	?	(66)		
141NI.E3.0208	2	?	(76)		
141NI.E3.0209	0		(?)	infant death	
141NI.E3.0210	0		(?)	infant death	
141NI.E3.0211	2	58	(80)	autopsy confirmation of AD	
141NI.E3.0212	1		72		
141NI.E3.0213	1	?	(70)	autopsy confirmation of AD	
141NI.E3.0214	2		70		

ID	Sex	AAO	Age censored (at death)	Comments	Reference
141NI.E3.0215	2		(29)		
141NI.F1.0001	0			family HB	Levy-Lahad et al. (1995a)
141NI.f1.0001	0				
141NI.F2.0101	0				
141NI.F2.0102	0				
141NI.F2.0103	0				
141NI.F3.0101	0			married 141NI.F4.0201	
141NI.F3.0202	0	?			
141NI.F3.0303	0				
141NI.f3.0303	0				
141NI.f3b.0303	0				
141NI.F4.0201	0	55		married 141NI.F3.0101	
141NI.F4.03a02	0	75		+/-; child of 141NI.F3.0303 & first spouse	
141NI.F4.03b03	0	55		+/-; child of 141NI.F3.0303 & second spouse	
141NI.F4.03b04	0	65		+/-; child of 141NI.F3.0303 & second spouse	
141NI.F5.0101	0	72		+/-	
141NI.F5.0102	0	68		+/-	
141NI.F5.0103	0	62			
141NI.G1.0001	0	?	(?)	Volga-German family R	"Levy-Lahad et al. (1995a, 1995b)"
141NI.g1.0001	0		(?)		
141NI.G2.0101	0	43	(?)		
141NI.g2.0101	0		(?)		
141NI.G2.0102	0		(?)		
141NI.G2.0103	0		(73)		
141NI.G2.0104	0		(?)		
141NI.G3.0101	0	52	(?)		
141NI.g3.0101	0		(50)		
141NI.G3.0102	0	60	(?)		
141NI.g3.0102	0		(81)		
141NI.G3.0103	0		(43)		
141NI.g3.0103	0		(88)		
141NI.G3.0104	0		(92)		
141NI.G3.0105	0		(85)		
141NI.G4.0101	0	67	(?)		
141NI.G4.0102	0	45	(?)		
141NI.G4.0103	0		85		
141NI.G4.0104	0	44	(?)		
141NI.g4.0104	0				
141NI.G4.0105	0		(50)	clinical condition unknown	
141NI.G4.0106	0	49	(?)		
141NI.G4.0106	0				
141NI.G4.0107	0	40	(?)	autopsy confirmation of AD	
141NI.G4.0108	0	50	(?)		
141NI.G4.0109	0	56	(?)	autopsy confirmation of AD	
141NI.G4.0110	0	43	(?)		
141NI.G4.0111	0	45	(?)	autopsy confirmation of AD	
141NI.G4.0112	0		70		
141NI.G4.0113	0	45	(?)	autopsy confirmation of AD	
141NI.G4.0114	0	54	(?)		
141NI.G4.0215	0	64	(?)	autopsy confirmation of AD	
141NI.G4.0216	0	54	(?)		
141NI.G4.0217	0		(42)		

ID	Sex	AAO	Age censored (at death)	Comments	Reference
141NI.G4.0318	0	55			
141NI.G4.0319	0	47			
141NI.G4.0320	0		(81)		
141NI.G5.0401	0	53			
141NI.G5.0402	0		54		
141NI.G5.0403	0	46			
141NI.G5.0604	0	45			
141NI.H1.0001	2	58	(66)	Russian family W	Bird et al. (1988)
141NI.h1.0001	1		(62)		
141NI.H2.0101	1	53	(72)	autopsy confirmation of AD	
141NI.H2.0102	1		78		
141NI.H2.0103	2	57	(62)		
141NI.H2.0104	2		66		
141NI.H2.0105	1		74		
141NI.H2.0106	2	50	58		
141NI.H2.0107	1		(62)		
141NI.H2.0108	2		65		
141NI.H2.0109	1		(18)		
141NI.I1.0001	0	76	(?)	family WFL	Levy-Lahad et al. (1995a)
141NI.i1.0001	0		(53)		
141NI.I2.0101	0	60			
141NI.I2.0102	0	?			
141NI.I2.0103	0	?			
141NI.I2.0104	0	?			
141NI.I2.0105	0		76		
141NI.I2.0106	0	62			
239MI.A1.0001	2		(33)	obligate carrier; Italian family	Finckh et al. (2000b)
239MI.a1.0001	1		(79)		
239MI.A1.0002	2	?	(56)		
239MI.A2.0101	1		68	+/-	
239MI.A2.0102	1		67	-/-	
239MI.A2.0103	1	58	(65)	"+/-; proband, autopsy confirmation of AD"	
239MI.A2.0104	2		58	+/-	
239MI.A2.0105	1	50	56	+/-	
239MI.A2.0106	1	44	54	+/-	
239MV.A1.0001	0	?	(75)	Italian FLO10; possible misture of late-onset and early-onset familial AD	Sherrington et al. (1996)
239MV.a1.0001	0		(?)		
239MV.A2.0101	0	?	(?)		
239MV.A2.0102	0		(?)	obligate carrier	
239MV.A3.0101	0	88			
239MV.A3.0102	0	68			
239MV.a3.0102	0				
239MV.A3.0103	0	84			
239MV.a3.0103	0				
239MV.A3.0104	0	72			
239MV.A3.0105	0				
239MV.a3.0105	0	49	(?)		
239MV.A4.0201	0				
239MV.A4.0202	0				
239MV.A4.0303	0				
239MV.A4.0504	0	48			
239MV.A4.0505	0	45			

Appendix F

Pedigree database of amyloid precursor protein gene mutations

The following table summarises the family studies in which the APP mutations have been found.

ID	Sex	AAO	Age censored (at death)	Comments	Reference
000APP.A1.0001	1		(?)	German family; mutation not identified	Frommelt et al. (1991)
000APP.a1.0001	2		(?)		
000APP.A2.0101	2	?	(?)	Suspected EOAD	
000APP.a2.0101	1		(?)		
000APP.A2.0102	2		(?)		
000APP.A2.0103	1				
000APP.a2.0103	2				
000APP.A2.0104	2		(?)		
000APP.A2.0105	1		(?)		
000APP.A2.0106	2				
000APP.A2.0107	2	?	(?)		
000APP.a2.0107	1		(?)		
000APP.A3.0101	1	?	(?)		
000APP.a3.0101	2		(?)		
000APP.A3.0102	2				
000APP.A3.0103	1		(?)		
000APP.A3.0104	1				
000APP.A3.0305	2				
000APP.A3.0306	2				
000APP.A3.0707	1		(?)		
000APP.A3.0708	2		(?)		
000APP.A3.0709	2		(?)		
000APP.a3.0709	1	?	(?)		
000APP.A4.0101	2	?	(?)		
000APP.a4.0101	1				
000APP.A4.0102	2		(?)		

ID	Sex	AAO	Age censored (at death)	Comments	Reference
000APP.A4.0103	2		(?)		
000APP.A4.0104	1	48	(54)		
000APP.a4.0104	2				
000APP.A4.0105	1		(?)		
000APP.a4.0105	2				
000APP.A4.0106	1		(?)		
000APP.A4.0107	2	?	(?)		
000APP.A4.0308	0		(?)		
000APP.A4.0309	0		(?)		
000APP.A4.0310	0		(?)		
000APP.A4.0911	1	?	(?)		
000APP.a4.0911	2		(?)		
000APP.A4.0912	2		(?)		
000APP.a4.0912	1		(?)		
000APP.A4.0913	1		(?)		
000APP.A4.0914	1	?	(?)		
000APP.a4.0914	2		(?)		
000APP.A4.0915	1	?	(?)		
000APP.a4.0915	2				
000APP.A4.0916	2	?	(?)		
000APP.A5.0101	2	45	(54)	daughter of 000APP.A4.0101 with previous spouse	
000APP.A5.0102	2	45	(57)		
000APP.A5.0103	2				
000APP.A5.0104	2				
000APP.A5.0105	1	44			
000APP.a5.0105	2				
000APP.A5.0206	2		(?)	daughter of 000APP.A4.0102 with first spouse	
000APP.A5.0207	2		(?)	daughter of 000APP.A4.0102 with first spouse	
000APP.A5.0208	1				
000APP.A5.0209	1				
000APP.A5.0210	1				
000APP.A5.0211	1				
000APP.A5.0212	2				
000APP.A5.0213	1				
000APP.A5.0314	1				
000APP.A5.0315	2				
000APP.A5.0316	1				
000APP.A5.0417	2				
000APP.A5.0518	1				
000APP.A5.0519	1				
000APP.A5.0620	1				
000APP.A5.0621	1				
000APP.A5.0722	2				
000APP.A5.1123	1		(?)		
000APP.A5.1124	2	50	(55)		
000APP.a5.1124	1		(?)		
000APP.A5.1125	1		(?)		
000APP.A5.1126	2				
000APP.A5.1127	2	56			
000APP.a5.1127	1				
000APP.A5.1128	2		(?)		
000APP.A5.1129	2				
000APP.A5.1230	1		(?)		

ID	Sex	AAO	Age censored (at death)	Comments	Reference
000APP.a5.1230	2				
000APP.A5.1431	1	46	(54)		
000APP.a5.1431	2		(?)		
000APP.a5b.1431	2			second spouse of 000APP.A5.1431	
000APP.A5.1432	2	39	(41)		
000APP.a5.1432	1				
000APP.A5.1433	1	?	(?)		
000APP.a5.1433	2				
000APP.A5.1534	2	?	(?)		
000APP.a5.1534	1				
000APP.A5.1535	1				
000APP.A6.0101	2		(?)		
000APP.A6.0102	2				
000APP.A6.0203	1				
000APP.A6.0204	1				
000APP.A6.0305	2				
000APP.A6.0506	2				
000APP.A6.0507	2				
000APP.A6.1508	2				
000APP.A6.1509	1				
000APP.A6.1610	1				
000APP.A6.1611	1				
000APP.A6.1712	2				
000APP.A6.2013	2				
000APP.A6.2014	2				
000APP.A6.2115	2				
000APP.A6.2116	1				
000APP.A6.2217	1				
000APP.A6.2218	1				
000APP.A6.2219	2				
000APP.A6.2420	1	49			
000APP.A6.2421	2				
000APP.A6.2422	2				
000APP.A6.2623	1				
000APP.A6.2624	1				
000APP.A6.2725	2				
000APP.A6.2726	2				
000APP.A6.2727	2				
000APP.A6.2828	1				
000APP.A6.2829	1				
000APP.A6.3030	1				
000APP.A6.3031	1				
000APP.A6.31a32	1	44		child of 000APP.A5.1431 & first spouse	
000APP.A6.31b33	2			child of 000APP.A5.1431 & second spouse	
000APP.A6.31b34	2			child of 000APP.A5.1431 & second spouse	
000APP.A6.31b35	1			child of 000APP.A5.1431 & second spouse	
000APP.A6.3236	1				
000APP.A6.3237	2				
000APP.A6.3238	2		(?)		
000APP.A6.3239	2	39			
000APP.A6.3240	1				
000APP.A6.3241	2				

ID	Sex	AAO	Age censored (at death)	Comments	Reference
000APP.A6.3242	2				
000APP.A6.3243	1				
000APP.A6.3244	2				
000APP.A6.3245	2				
000APP.A6.3246	2				
000APP.A6.3247	2				
000APP.A6.3348	1				
000APP.A6.3349	2				
000APP.A6.3450	1				
000APP.A6.3451	2				
000APP.A7.0301	2				
000APP.A7.0402	2				
000APP.A7.1203	1				
000APP.A7.1204	1				
000APP.A7.2005	2				
000APP.A7.2106	1				
000APP.A7.2107	2				
670KN.A1.0001	1	?	(?)	"Lys670Asn/Met671Leu mutation; Swedish family, F139"	Mullan et al. (1992)
670KN.a1.0001	2		(?)		
670KN.A2.0101	2	?	(?)		
670KN.a2.0101	1		(?)		
670KN.A2.0102	1		(?)		
670KN.A2.0103	1		(?)		
670KN.A2.0104	2	?	(?)		
670KN.A2.0104	1		(?)		
670KN.A2.0105	2		(?)		
670KN.A2.0106	1	?	(?)		
670KN.A2.0107	1	?	(?)		
670KN.A2.0108	1	?	(?)		
670KN.A3.0101	2	?	(?)		
670KN.a3.0101	1		(?)		
670KN.A3.0102	2	?		+/-	
670KN.A3.0403	1			-/-	
670KN.A3.0404	2	?		+/-	
670KN.A3.0405	1	?		+/-	
670KN.A3.0406	2			-/-	
670KN.A3.0407	2	?	(?)		
670KN.A3.0408	1		(?)		
670KN.A3.0409	2		(?)		
670KN.A4.0101	1	?		+/-	
670KN.A4.0102	1			-/-	
670KN.A4.0103	1			-/-	
670KN.B1.0001	1	?	(?)	"Lys670Asn/Met671Leu mutation; Swedish family, F144"	Mullan et al. (1992)
670KN.b1.0001	2		(?)		
670KN.B2.0101	2	?	(?)		
670KN.b2.0101	1		(?)		
670KN.B2.0102	2	?	(?)		
670KN.b2.0102	1		(?)		
670KN.B2.0103	1			-/-	
670KN.B2.0104	1	?	(?)		
670KN.b2.0104	2			-/-	
670KN.B2.0105	1	?	(?)		
670KN.b2.0105	2			-/-	
670KN.B3.0101	1			-/-	

ID	Sex	AAO	Age censored (at death)	Comments	Reference
670KN.B3.0102	2			-/-	
670KN.B3.0103	1			+/-	
670KN.B3.0104	1	?		+/-	
670KN.b3.0104	2				
670KN.B3.0105	1			-/-	
670KN.B3.0106	1			+/-	
670KN.B3.0207	2	?		+/-	
670KN.B3.0408	1			-/-	
670KN.B3.0409	1			+/-	
670KN.B3.0510	2			+/-	
670KN.B3.0511	1			-/-	
670KN.B4.0401	1			-/-	
692AG.A1.0001	0	?	(?)	Dutch family 1302; pedigree disguised and only non-affected and patients shown	Hendriks et al. (1992)
692AG.A2.0101	0		(?)		
692AG.A2.0102	0	?	(?)		
692AG.A2.0103	0	?	(?)		
692AG.A2.0104	0	?	(?)		
692AG.A2.0105	0	?	(?)		
692AG.A2.0106	0		(?)		
692AG.A3.0201	0			-/-	
692AG.A3.0202	0			-/-	
692AG.A3.0303	0	?	(?)		
692AG.A3.0304	0		(?)	cerebral haemorrhage	
692AG.A3.0405	0	?	(?)		
692AG.A3.0406	0	?	(?)		
692AG.A3.0407	0	?	(?)		
692AG.A3.0508	0	?	(?)	-/-	
692AG.A3.0509	0			-/-	
692AG.A3.0510	0			-/-	
692AG.A3.0511	0		(?)	cerebral haemorrhage	
692AG.A4.0301	0			+/-; cerebral haemorrhage	
692AG.A4.0502	0	?		+/-	
692AG.A4.0503	0			+/-; cerebral haemorrhage	
692AG.A4.0604	0	?		+/-	
692AG.A4.0705	0	?		+/-	
693EG.A1.0101	1	75	(?)	SB family	Kamino et al. (1992)
693EG.a1.0101	2		(55)		
693EG.A2.0101	2		(73)		
693EG.A2.0102	2		(67)		
693EG.A2.0103	2	65	(?)		
693EG.A2.0104	1	55	(?)		
693EG.a2.0104	2		(83)		
693EG.A3.0401	2	56	(?)	+/-	
693EG.A3.0402	1	61		-/-	
693EG.A3.0403	1		68	-/-	
693EG.A3.0404	2		62	-/-	
693EG.A3.0405	1		59	-/-	
713AT.A1.0001	2		88	+/- ;French family with double mutation: Ala713Thr + silent change at Val715	Carter et al. (1992)
713AT.A1.0002	1		(76)	inferred presence of double mutation	
713AT.a1.0002	2		(83)	mutation is either non-pathogenic polymorphism or incomplete penetrant	

ID	Sex	AAO	Age censored (at death)	Comments	Reference
713AT.A2.0201	0		>62	+/-	
713AT.A2.0202	0		>62		
713AT.A2.0203	0		>62	+/-	
713AT.A2.0204	2	59	64	+/-	
713AT.A2.0205	0		<62		
713AT.A2.0206	0		<62	+/-	
713AT.A2.0207	0		<62	+/-	
713AV.A1.0001	2			schizophrenia; Non-AD family with schizophrenia	Jones et al. (1992)
713AV.a1.0001	1		(?)		
713AV.A2.0101	2		(?)	deaf and blind in middle age	
713AV.a2.0101	1		(?)		
713AV.A2.0102	1		(?)		
713AV.A3.0101	2			proband; +/-; schizophrenia	
713AV.A3.0102	1		(?)	-/-	
714TI.A1.0001	2		(48)	Austrian family AD156	Kumar-Singh et al. (2000)
714TI.a1.0001	1		(78)		
714TI.A2.0101	2	38	(49)		
714TI.a2.0101	1				
714TI.A3.0101	2	33	(41)		
714TI.A3.0102	2	34	42		
715VM.A1.0001	1		(40)	Italian family 074	Ancolio et al. (1999)
715VM.a1.0001	2			-/-	
715VM.A1.0002	1	60	73	+/-	
715VM.A1.0003	1	52	(66)		
715VM.A1.0004	1		(71)		
715VM.A1.0005	2		(70)		
715VM.A2.0101	2	41	44	proband	
715VM.A2.0102	0				
715VM.A2.0103	0		37		
716IV.A1.0001	2	?	(?)		Eckman et al. (1997)
716IV.a1.0001	1		(?)		
716IV.A2.0101	2	early 50's	(early 60's)		
716IV.a2.0101	1		(80)		
716IV.A3.0101	2	53	58		
716IV.A3.0102	2	53	55		
717VG.A1.0001	1	?	(?)	Family F19	Chartier-Harlin et al. (1991)
717VG.a1.0001	2		(?)		
717VG.A2.0101	2	?	(?)		
717VG.a2.0101	1		(?)		
717VG.A2.0102	1	?	(?)		
717VG.a2.0102	2		(?)		
717VG.A3.0101	0				
717VG.A3.0102	0	?	(?)		
717VG.A3.0203	0				
717VG.A3.0204	0				
717VG.A3.0205	0				
717VG.A3.0206	0	?			
717VG.A3.0207	0	?			
717VG.A3.0208	0	?			
717VG.A3.0209	0				
717VG.A3.0210	0	?	(?)		
717VG.A3.0211	0	?	(?)		
717VG.A3.0212	0	?			
717VG.A3.0213	0	?			

ID	Sex	AAO	Age censored (at death)	Comments	Reference
717VI.A1.0001	1		(?)	Australian family (Welsh origin)	Brooks et al. (1995)
717VI.a1.0001	2		(?)		
717VI.A2.0101	1	48	(54)		
717VI.a2.0101	2		(?)		
717VI.A3.0101	0	48	62	proband; +/-	
717VI.A3.0102	0	46	61	+/-	
717VI.A3.0103	0	51	(59)	+/-	
717VI.A3.0104	0		56	-/-	
717VI.A3.0105	0		42	+/-	
717VI.B1.0001	1		(?)	clinical condition unknown; French family R03	Campion et al. (1996b)
717VI.b1.0001	2		(?)	clinical condition unknown	
717VI.B2.0101	1		(<40)	Obligate carrier, age of death < 40	
717VI.B2.0102	1		(<40)	Obligate carrier, age of death < 40	
717VI.B3.0101	1		(<40)	Obligate carrier, age of death < 40	
717VI.B3.0202	2	?	(?)		
717VI.B4.0101	2			-/-	
717VI.B4.0102	1			-/-	
717VI.B4.0103	1	?		+/-	
717VI.B4.0204	1	?		+/-	
717VI.B4.0205	2	?	(?)		
717VI.B4.0206	2	?	(?)		
717VI.B4.0207	1			-/-	
717VI.B4.0208	1			-/-	
717VI.B4.0209	2			-/-	
717VI.B4.0210	1			-/-	
717VI.C1.0001	2	60	(66)		Finckh et al. (2000b)
717VI.c1.0001	1		(60)		
717VI.C2.0101	1		65		
717VI.C2.0102	2		63		
717VI.C2.0103	2	∼50	57	proband; +/-	
717VI.C2.0104	1	∼50	55		
717VI.C2.0105	1	∼47	52		
717VI.D1.0001	1	?	(?)	Family F23	Groate et al. (1991)
717VI.d1.0001	2		(?)		
717VI.D2.0101	1	?	(?)		
717VI.d2.0101	2		(?)		
717VI.D2.0102	1	?	(?)		
717VI.d2.0102	2		(?)	sister of 717VI.d2.0101	
717VI.D3.0101	0	?			
717VI.D3.0102	0	?			
717VI.D3.0103	0	?			
717VI.D3.0104	0	?			
717VI.D3.0105	0	?			
717VI.D3.0106	0				
717VI.D3.0107	0				
717VI.D3.0108	0				
717VI.D3.0109	0				
717VI.D3.0110	0				
717VI.D3.0211	0	?			
717VI.D3.0212	0				
717VI.D3.0213	0				
717VI.E1.0001	2	?	(?)	Japanese family	Matsumura et al. (1996)
717VI.e1.0001	1		(?)		
717VI.E2.0101	2	61	(77)		

ID	Sex	AAO	Age censored (at death)	Comments	Reference
717VI.e2.0101	1		(?)		
717VI.E2.0102	2		early 70's		
717VI.e2.0102	1		(?)		
717VI.E2.0103	2		early 70's		
717VI.e2.0103	1		(?)		
717VI.E3.0101	2	55	(64)		
717VI.e3.0101	1				
717VI.E3.0102	2	55	60	proband	
717VI.e3.0102	1				
717VI.E3.0203	1				
717VI.E3.0204	2				
717VI.E3.0205	2				
717VI.E3.0206	2				
717VI.E3.0307	2				
717VI.E3.0308	2				
717VI.E3.0309	1				
717VI.E4.0201	2				
717VI.E4.0202	1				
717VI.E4.0803	2				
717VI.e4.0803	1				
717VI.E4.0804	1				
717VI.F1.0001	2	65	(68)	Italian family FLO12	Sorbi et al. (1993)
717VI.f1.0001	1		(?)		
717VI.F2.0101	1	58	(61)	sibship incomplete	
717VI.f2.0101	2		89	-/-	
717VI.F2.0102	1	63	(70)		
717VI.f2.0102	2		(?)		
717VI.F3.0101	2		63	-/-	
717VI.F3.0102	1	58	61	+/-	
717VI.F3.0103	2	54	58	+/-	
717VI.f3.0103	1		64	-/-	
717VI.F3.0204	1	55	57	+/-; sibship incomplete	
717VI.F3.0205	1		61	-/-	
717VI.F4.0301	0		< 30	+/-	
717VI.F4.0302	0		< 30	-/-	
717VI.F4.0303	0		< 30	+/-	
717VI.G1.0001	2	50	(55)	Italian family FLO13	Sorbi et al. (1993)
717VI.g1.0001	1		(?)		
717VI.G2.0101	2	52	65	+/-; sibship incomplete	
717VI.g2.0101	1		67	-/-	
717VI.G2.0102	1	52	(64)		
717VI.g2.0102	2		81	-/-	
717VI.G2.0103	2	52	(64)		
717VI.g2.0103	1		(?)		
717VI.G3.0101	0		<45	+/-	
717VI.G3.0102	0		<45	+/-	
717VI.G3.0103	0		<45	-/-	
717VI.G3.0204	0		<45	+/-	
717VI.G3.0205	0		<45	-/-	
717VI.G3.0206	0		<45	-/-	
717VI.G3.0307	0		<50	-/-	
717VI.G3.0308	0		<50	-/-	
717VI.G3.0309	2	48	51	+/-	
717VI.G3.0310	2	46	47	+/-	

ID	Sex	AAO	Age censored (at death)	Comments	Reference
717VI.G3.0311	0		<50	-/-	
717VI.H1.0001	1	?	(?)	Italian family FLO33	Sorbi et al. (1995)
717VI.h1.0001	2		(?)		
717VI.H2.0101	2	?	(?)		
717VI.H2.0101	1		(?)		
717VI.H2.0102	1		(?)		
717VI.H2.0103	1	?	(?)		
717VI.h2.0103	2		(?)		
717VI.H3.0101	1	?	(?)		
717VI.h3.0101	2				
717VI.H3.0102	1	?	(?)		
717VI.h3.0102	2				
717VI.H3.0203	2				
717VI.H3.0204	1	?	(?)		
717VI.h3.0204	2		(?)		
717VI.H3.0205	1		(?)		
717VI.H3.0206	1	?	(?)		
717VI.h3.0206	2				
717VI.H3.0207	2	?	(?)		
717VI.h3.0207	1				
717VI.H4.0101	2				
717VI.H4.0102	1		60	+/-; asymptomatic	
717VI.H4.0203	1				
717VI.H4.0204	1	54	?	+/-	
717VI.h4.0204	2				
717VI.H4.0405	2				
717VI.H4.0406	2	44	?	+/-	
717VI.H4.0407	2				
717VI.h4.0407	1				
717VI.H4.0408	1			+/-	
717VI.H4.0409	1	?	(?)		
717VI.H4.0610	1	37	?	+/-	
717VI.H4.0611	1				
717VI.H4.0612	2	38	?	+/-	
717VI.h4.0612	1				
717VI.H4.0713	2				
717VI.H4.0714	1	45	?	+/-	
717VI.h4.0714	2				
717VI.H5.0401	2				
717VI.H5.0402	1				
717VI.H5.0703	2				
717VI.H5.0704	1			+/-	
717VI.H5.1205	2			+/-	
717VI.H5.1206	2			+/-	
717VI.H5.1407	2			+/-	
717VL.A1.0001	2	?	($\sim$ 50)	American	Murrell et al. (2000)
717VL.a1.0001	1		(?)		
717VL.A2.0101	2	39	(49)		
717VL.a2.0101	1		(?)		
717VL.A2.0102	1		(?)		
717VL.A2.0103	1		(?)		
717VL.A2.0104	1		(?)		
717VL.A2.0105	1		(?)		
717VL.A2.0106	2		(?)		
717VL.A2.0107	2		(?)		

ID	Sex	AAO	Age censored (at death)	Comments	Reference
717VL.A2.0108	2		(?)		
717VL.A3.0101	2				
717VL.A3.0102	1	38	(40)		
717VL.a3.0102	2				
717VL.A4.0201	2	38	44	proband	
717VL.a4.0201	1		(?)		
717VL.a4b.0201	1			second spouse of 717VL.A4.0201	
717VL.A4.0202	2		40	-/-	
717VL.A4.0203	1	35	38	+/-	
717VL.a4.0203	2				
717VL.A4.0204	1		39		
717VL.A4.0205	2		36	-/-	
717VL.A4.0206	2		30	+/-	
717VL.A5.01a01	1			child of 717VL.A4.0201 & first spouse	
717VL.A5.01b02	1			child of 717VL.A4.0201 & second spouse	
717VL.A5.0303	1				
717VL.A5.0304	1				
717VL.A5.0305	2				
717VF.A1.0001	1	?	(?)		Murrell et al. (1991)
717VF.a1.0001	2		(?)		
717VF.A2.0101	1				
717VF.A2.0102	1	41	(?)		
717VF.a2.0102	2				
717VF.A2.0103	1		(?)		
717VF.a2.0103	2				
717VF.A2.0104	2	42	(?)		
717VF.A2.0104	1				
717VF.A2.0105	2				
717VF.A2.0106	1				
717VF.A2.0107	1				
717VF.A2.0108	2	45	(?)		
717VF.A2.0108	1				
717VF.A2.0109	2				
717VF.A3.0201	1				
717VF.A3.0202	1				
717VF.A3.0203	2				
717VF.A3.0304	0				
717VF.A3.0305	0				
717VF.A3.0306	0				
717VF.A3.0307	0				
717VF.A3.0408	1				
717VF.A3.0409	1	?		proband	
717VF.a3.0409	2				
717VF.a3b.0409	2			second spouse of 717VF.A3.0409	
717VF.A3.0410	1				
717VF.A3.0411	1				
717VF.A3.0412	1				
717VF.A3.0813	2				
717VF.A3.0814	2				
717VF.A4.09a01	2			child of 717VF.A3.0409 & first spouse	
717VF.A4.09a02	2			child of 717VF.A3.0409 & first spouse	
717VF.A4.09b03	1			child of 717VF.A3.0409 & second spouse	
723LP.A1.0001	1		(?)	Australian family	Kwok et al. (2000)
723LP.a1.0001	2		(?)		

ID	Sex	AAO	Age censored (at death)	Comments	Reference
723LP.A2.0101	2		(?)		
723LP.A2.0102	1		(?)		
723LP.A2.0103	1	?	(?)		
723LP.a2.0103	2		(?)		
723LP.A3.0301	2	?	(?)		
723LP.A3.0302	2			-/-	
723LP.A3.0303	2			-/-	
723LP.A3.0304	2	?	(?)		
723LP.A3.0304	1			-/-	
723LP.A4.0201	2				
723LP.A4.0202	1			"tested, result not disclosed"	
723LP.A4.0303	1		(?)		
723LP.A4.0404	1	40		proband; +/-	
723LP.A4.0405	1			"tested, result not disclosed"	

Appendix G

The Critical Illness Insurance Model

Gutiérrez and Macdonald (2003) obtained the following model for CI insurance based on medical studies and population data. Full references can be found in that paper.

(a) Rates of onset were found for:

(i) *Cancer (excluding non-malignant skin cancers)*: For males:

$$\begin{aligned} \mu_x^c &= \exp(-11.25 + 0.105x) \quad (x < 51) \\ \mu_x^c &= \exp(0.2591585 - 0.01247354x + 0.0001916916x^2 - 8.952933 \times 10^{-7}x^3) \\ &\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad (x \geq 60) \end{aligned}$$

with linear interpolation between ages 51 and 60, and for females:

$$\begin{aligned} \mu_x^c &= \exp(-10.78 + 0.123x - 0.00033x^2) \quad (x < 53) \\ \mu_x^c &= -0.01545632 + 0.0003805097x \quad (x \geq 53). \end{aligned}$$

(ii) *Heart Attack*: For males:

$$\begin{aligned}\mu_x^h &= \exp(-13.2238 + 0.152568x) \quad (x < 44)\\ \mu_x^h &= (-0.01245109 + 0.000315605x) \quad (x > 49)\end{aligned}$$

with linear interpolation between ages 44 and 49, and for females:

$$\mu_x^h = \left(0.598694\left(\frac{0.15317^{15.6412}\exp(-0.15317x)x^{14.6412}}{\Gamma(15.6412)}\right)\right).$$

(iii) *Stroke*: For males:

$$\mu_x^s = \exp(-16.9524 + 0.294973x - 0.001904x^2 + 0.00000159449x^3)$$

and for females:

$$\mu_x^s = \exp(-11.1477 + 0.081076x).$$

(b) 28-day survival factors for heart attack and stroke victims were taken from Dinani et al. (2000) (this relates to the common contractual condition, that payment depends on surviving for 28 days). Let p_x^h and p_x^s be the 28-day survival probabilities after the first-ever heart attack or stroke, respectively, and $q_x^h = 1 - p_x^h$, $q_x^s = 1 - p_x^s$ the corresponding mortality rates. From Dinani et al. (2000), $q_x^h = 0.21$ at ages 20–80 for females, and q_x^h for males is given in Table G.32. From the same source, $p_x^s = (0.9 - 0.2x)/0.9$ for both males and females.

Table G.32: 28-Day mortality rates ($q_x^h = 1 - p_x^h$) following heart attack. Based on Dinani et al. (2000).

age	q_x^h	age	q_x^h	age	q_x^h	age	q_x^h
20–39	0.15	47–52	0.18	58–59	0.21	65–74	0.24
40–42	0.16	53–56	0.19	60–61	0.22	75–79	0.25
43–46	0.17	57	0.20	62–64	0.23	80+	0.26

(c) Other minor causes of CI insurance claims amount to about 15% of those arising from cancer, heart attack and stroke. Therefore the aggregate rate of CI claims is:

$$\mu_x^{CI} = 1.15(\mu_x^c + p_x^h \times \mu_x^h + p_x^s \times \mu_x^s).$$

(d) Population mortality rates (English Life Tables No.15) were adjusted to exclude deaths which would have followed a CI insurance claim.

Bibliography

Åsberg, A., Hveem, K., Thorstensen, K., Ellekjaer, E., Kannelønning, K., Fjøsne, U., Halvorsen, T. B., Smethurst, H.-B. G., Sagen, E., and Bjerve, S. (2001). Screening for hemochromatosis: high prevalence and low mobility in an unselected population of 65,238 persons. *Scandinavian Journal of Gastroenterology*, 36:1108–1115.

ABI (1997). Genetic testing: ABI Code of Practice. Association of British Insurers.

Adams, P. C. (1999). Role of genetic testing and liver biopsy in the diagnosis of hemochromatosis. *Current Gastroenterology Reports*, 1:27–29.

Adams, P. C., Brissot, P., and Powell, L. W. (2000). EASL International Consensus Conference on Haemochromatosis (Part II. Expert document). *Journal of Hepatology*, 33:487–496.

Adams, P. C. and Chakrabarti, S. (1998). Genotypic/phenotypic correlations in genetic hemochromatosis: evolution of diagnostic criteria. *Gastroenterology*, 114:319–323.

Aldudo, J., Bullido, M. J., Arbizu, T., Oliva, R., and Valdivieso, F. (1998). Identification of a novel mutation (Leu282Arg) of the human presenilin 1 gene in Alzheimer's disease. *Neuroscience Letters*, 240:174–176.

Aldudo, J., Bullido, M. J., Arbizu, T., and Valdivieso, F. (1999). DGGE method for the mutational analysis of the coding and proximal promoter regions of the Alzheimer's disease presenilin-1 gene: 2 novel mutations. *Human Mutation*, 14:433–439.

Alloul, K., Sauriol, L., Kennedy, W., Laurier, C., Tessier, G., Novosel, S., and Contandriopoulos, A. (1998). Alzheimer's disease: a review of the disease, its epidemiology and economic impact. *Archives of Gerontology and Geriatrics*, 27:189–221.

Ancolio, K., Dumanchin, C., Barelli, H., Warter, J. M., Brice, A., Campion, D., Frébourg, T., and Checler, F. (1999). Unusual phenotypic alteration of β amyloid precursor protein (βAPP) maturation by a new Val-715 $\rightarrow$ Met mutation responsible for probable early-onset Alzheimer's disease. *Proceedings of the National Academy of Science, USA*, 96:4119–4124.

Andersen, P. K., Borgan, Ø., Gill, R. D., and Keiding, N. (1993). *Statistical models based on counting processes*. Springer-Verlag, New York.

Andrews, N. C. (1999). Disorders of iron metabolism. *The New England Journal of Medicine*, 341(26):1986–1995.

Aoki, M., Abe, K., Oda, N., Ikeda, M., Tsuda, T., Kanai, M., Shoji, M., St. George-Hyslop, P. H., and Itoyama, Y. (1997). A presenilin-1 mutation in a family with Alzheimer's disease and distinctive abnormalities on cranial MRI. *Neurology*, 48:1118–1120.

Axelman, K., Basun, H., and Lannfelt, L. (1998). Wide range of onset in a family with Alzheimer's disease and a His163Tyr mutation in the presenilin-1 gene. *Archives of Neurology*, 55:698–702.

Ball, D. W. (1996). *Genetic mechanisms in multiple endocrine neoplasia type 2*, chapter Clinical manifestations of multiple endocrine neoplasia type 2, pages 1–20. Landes Company.

Barton, J. C., McDonnell, S. M., Adams, P. C., Brissot, P., Powell, L. W., Edwards, C. Q., Cook, J. D., and Kowdley, K. V. (1998). Management of hemochromatosis. Hemochromatosis Management Working Group. *Annal of Internal Medicine*, 129(11):932–939.

Barton, J. C., Sawada-Hirai, R., Rothenberg, B. E., and Acton, R. T. (1999). Two

novel missense mutations of the HFE gene (I105T and G93R) and identification of the S65C mutation in Alabama hemochromatosis probands. *Blood Cells, Molecules, and Diseases*, 25(9):146–154.

Bassett, M. L., Leggett, B. A., Halliday, J. W., Webb, S., and Powell, L. W. (1997). Analysis of the cost of population screening for haemochromatosis using biochemical and genetic markers. *Journal of Hepatology*, 27:517–524.

Beard, C. M., Kokmen, E., Sigler, C., Smith, G. E., Petterson, T., and O'brien, P. C. (1996). Cause of death in Alzheimer's disease. *Annals of Epidemiology*, 6(3):195–200.

Beard, C. M., Sheps, S. G., Kurland, L. T., Carney, J. A., and Lie, J. T. (1983). Occurrence of pheochromocytoma in Rochester, Minnesota, 1950–1979. *Mayo Clinic Proceddings*, 58:802–804.

Bertram, L., Blacker, D., Mullin, K., Keeney, D., Jones, J., Basu, S., Yhu, S., Mclnnis, M. G., Go, R. C. P., Vekrellis, K., Selkoe, D. J., Saunders, A. J., and Tanzi, R. E. (2000). Evidence for genetic linkage of Alzheimer's disease to chromosome 10q. *Science*, 290:2302–2303.

Besançon, R., Lorenzi, A., Cruts, M., Radawiec, S., Sturtz, F., Broussolle, E., Chazot, G., van Broeckhoven, C., Chamba, G., and Vandenberghe, A. (1997). Missense mutation in exon 11 (codon 378) of the presenilin-1 gene in a French family with early-onset Alzheimer's disease and transmission study by mismatch enhanced allele specific amplification. *Human Mutation (Mutation in Brief)*, 141:online.

Beutler, E., Felitti, V. J., Koziol, J. A., Ho, N. J., and Gelbart, T. (2002). Penetrance of 845G⟶A (C282Y) HFE hereditary haemochromatosis mutation in the USA. *Lancet*, 359:211–218.

Beutler, E., Gelbart, T., West, C., Lee, P., Adams, M., Blackstone, R., Pockros, P., Kosty, M., Venditti, C. P., Phatak, P. D., Seese, N. K., Chorney, K. A., Ten Elshof, A. E., Gerhard, G. S., and Chorney, M. (1996). Mutation analysis in hereditary hemochromatosis. *Blood cells, molecules & diseases*, 22:187–194.

Bird, T. D., Lampe, T. H., J., N. E., Miner, G. W., Sumi, S. M., and Schellenberg, G. D. (1988). Familial Alzheimer's disease in American descendants of the Volga Germans: Probable genetic founder effect. *Annals of Neurology*, 23:25–31.

Bird, T. D., Levy-Lahad, E., Poorkaj, P., Sharma, V., Nemens, E., Lahad, A., Lampe, T. H., and Schellenberg, G. D. (1996). Wide range in age of onset for chromosome 1–related familial Alzheimer's disease. *Annals of Neurology*, 40(6):932–936.

Blacker, D., Wilcox, M. A., Laird, N. M., Rodes, L., Horvath, S. M., Go, R. C. P., Perry, R., Watson, B. J., Bassett, S. S., Mclnnis, M. G., Albert, M. S., Hyman, B. T., and Tanzi, R. D. (1998). Alpha-2 macroglobulin is genetically associated with Alzheimer's disease. *Nature Genetics*, 19:357–360.

Boteva, K., Vitek, M., Mitsuda, H., de Siva, H., Xu, P. T., Small, G., and Gilbert, J. R. (1996). Mutation analyisis of presenilin 1 gene in Alzheimer's disease. *Lancet*, 347:130–131.

Brackenridge, R. D. C. and Elder, W. J., editors (1998). *Medical Selection of Life Risks*. Stockton Press, New York.

Bradley, L. A., Johnson, D. D., Palomaki, G. E., Haddow, J. E., Robertson, N. H., and Ferrie, R. M. (1998). Hereditary haemochromatosis mutation frequencies in the general population. *Journal of Medical Screening*, 5(1):34–36.

Brandi, M. L., Gagel, R. F., Angeli, A., Bilezikian, J. P., Beck-Peccoz, P., Bordi, C., Conte-Devolx, B., Falchetti, A., Gheri, R. G., Libroia, A., Lips, C. J. M., Lombardi, G., Mannelli, M., Pacini, F., Ponder, B. A. J., Raue, F., Skogseid, B., Tamburrano, G., Thakker, R. V., Thompson, N. W., Tomassetti, P., Tonelli, F., Wells, S. A. J., and Marx, S. J. (2001). Guidelines for diagnosis and therapy of MEN Type 1 and Type 2. *The Journal of Clinical Endocrinology & Metabolism*, 86:5658–5671.

Brooks, W. S., Martins, R. N., De Voecht, J., Nichlson, G. A., Schofield, P. R., Kwok, J. B. J., Fisher, C., Yeung, L. U., and van Broeckhoven (1995). A mutation in

codon 717 of the amyloid precursor protein gene in an Australian family with Alzheimer's disease. *Neuroscience Letters*, 199:183–186.

Campion, D., Brice, A., Dumanchin, C., Puel, M., Baulac, M., De La Sayette, V., Hannequin, D., Duyckaerts, C., Michon, A., Martin, C., Moreau, V., Penet, C., Martinez, M., Clerget-Darpoux, F., Agid, Y., and Frebourg, T. (1996a). A novel presenilin 1 mutation resulting in familial Alzheimer's disease with an onset age of 29 years. *NeuroReport*, 7:1582–1584.

Campion, D., Brice, A., Hannequin, D., Charbonnier, F., Dubois, B., Martin, C., Michon, A., Penet, C., Bellis, M., calenda, A., Martinez, M., Agid, Y., Clerget-Darpoux, F., Frebourg, T., Thomas-Anterion, C., Puel, M., Pasquier, F., Ledoze, F., Moreaud, O., and Mallet, J. (1996b). No founder effect in three novel Alzheimer's disease families with APP 717 Val→Ile mutation. *Journal of Medical Genetics*, 33:661–664.

Campion, D., Brice, A., Hannequin, D., Tardieu, S., Dubois, B., Calenda, A., E., B., C., P., J., T., Martinez, M., Bellis, G., Mallet, J., Agid, Y., and Clerget-Darpoux, F. (1995a). A large pedigree with early-onset Alzheimer's disease: clinical, neuropathological, and genetic characterization. *Neurology*, 45:80–85.

Campion, D., Dumanchin, C., Hannequin, D., Dubois, B., Belliard, S., Puel, M., Thomas-Anterion, C., Michon, A., Martin, C., Charbonnier, F., Raux, G., Camuzat, A., Penet, C., Mesnage, V., Martinez, M., Clerget-Darpoux, F., Brice, A., and Frebourg, T. (1999). Early-onset autosomal dominant Alzheimer disease: prevalence, genetic heterogeneity, and mutation spectrum. *American Journal of Human Genetics*, 65:664–670.

Campion, D., Flaman, J. M., Brice, A., Hannequin, D., Dubois, B., Martin, C., Moreau, V., Charbonnier, F., Didierjean, O., Tardieu, S., Penet, C., Puel, M., Pasquier, F., Le Doze, F., Bellis, G., Calenda, A., Heilig, R., Martinez, M., Mallet, J., Bellis, M., Clerget-Darpoux, F., Agid, Y., and Frebourg, T. (1995b). Mutations of the presenilin 1 gene in families with early-onset Alzheimer's disease. *Human Molecular Genetics*, 4(12):2373–2377.

Carter, D. A., Desmarais, E., Bellis, M., Campion, D., Clerget-Darpoux, F., Brice, A., Agid, Y., Jaillard-Serradt, A., and Mallet, J. (1992). More missense in amyloid gene. *Nature Genetics*, 2:255–256.

Cervenakova, L., Brown, P., Sandoval, F., Foncin, J.-F., Garruto, R., Polincky, R. J., Nee, L., and Goldfarb, L. (1996). Identification of presenilin-1 gene point mutations in early-onset Alzheimer's disease families. *American Journal of Human Genetics*, 59(Suppl):A252.

Chapman, J., Asherov, A., Wang, N., Treves, T. A., Korczyn, A. D., and Goldfarb, L. G. (1995). Familial Alzheimer's disease associated with S182 codon 286 mutation. *Lancet*, 346:1040.

Chartier-Harlin, M. C., Crawford, F., Houlden, H., Warren, A., Hughes, D., Fidani, L., Goate, A., Rossor, M., Roques, P., Hardy, J., and Mullan, M. (1991). Early-onset Alzheimer's disease caused by mutations at codon 717 of the β-amyloid precursor protein gene. *Nature*, 353:844–846.

Clark, R. F., Hutton, M., Fuldner, R. A., Froelich, S., Karran, E., Talbot, C., Crook, R., Lendon, C., Prihar, G., He, C., Korenblat, K., Martinez, A., Wragg, M., Busfield, F., Behrens, M. I., Myers, A., Norton, J., Morris, J., Mehta, N., Pearson, C., Lincoln, C., Baker, M., Duff, K., Zehr, C., Perez-Tur, J., Houlden, H., Ruiz, A., Ossa, J., Lopera, F., Arcos, M., Madrigal, L., Collinge, J., Humphreys, C., Ashworth, A., Sarner, S., Fox, N., Harvey, R., Kennedy, A., Roques, P., Cline, R. T., Phillips, C. A., Venter, J. C., Forsell, L., Axelman, K., Lilius, L., Johnston, J., Cowburn, R., Viitanen, M., Winblad, B., Kosik, K., Haltia, M., Poyhonen, M., Dickson, D., Mann, D., Neary, D., Snowdon, J., Lantos, P., Lannfelt, L., Rossor, M., Roberts, G. W., Adams, M. D., Hardy, J., and Goate, A. u. D. C. G. (1995). The structure of the presenilin 1 (S182) gene and identification of six novel mutations in early onset AD families. *Nature Genetics*, 11:219–222.

Cras, P. (2001). Recent developments in Alzheimer's disease. *Acta Clinica Belgica*, 56(5):269–278.

Crook, R., Ellis, R., Shanks, M., Thal, L. J., Perez-Tur, J., Baker, M., Hutton, M.,

Haltia, T., Hardy, J., and Galasko, D. (1997). Early-onset Alzheimer's disease with a presenilin-1 mutation at the site corresponding to the Volga German presenilin-2 mutation. *Annals of Neurology*, 42:124–128.

Crook, R., Verkkoniemi, A., Perez-Tur, J., Mehta, N., Baker, M., Houlden, H., Farrer, M., Hutton, M., Lincoln, S., Hardy, J., Gwinn, K., Somer, M., Paetau, A., Kalimo, H., Ylikoski, R., Pöyhönen, M., Kucera, S., and Haltia, M. (1998). A variant of Alzheimer's disease with spastic paraparesis and unusual plaques due to deletion of exon 9 of presenilin 1. *Nature Medicine*, 4(4):452–455.

Crosbie, D. (2000). Protection of genetic information: an international comparison. Report to the Human Genetics Commission, London.

Cruts, M., Backhovens, H., Wang, S. Y., van Gassen, G., Theuns, J., De Jonghe, C., Wehnert, A., De Voecht, J., de Winter, G., Cras, P., Bruyland, M., Datson, N., Weissenbach, J., den Dunnen, J. T., Martin, J. J., Hendriks, L., and van Broeckhoven, C. (1995). Molecular genetic analysis of familial early-onset Alzheimer's disease linked to chromosome 14q24.3. *Human Molecular Genetics*, 4(12):2363–2371.

Cruts, M., Hendriks, L., and van Broeckhoven, C. (1996). The presenilin genes: a new gene family involved in Alzheimer's disease. *Human Molecular Genetics*, 5(Review):1449–1455.

Cruts, M. and van Broeckhoven, C. (1998). Presenilin mutations in Alzheimer's disease. *Human Mutation*, 11:183–190.

Cruts, M., van Duijn, C. M., Backhovens, H., van den Broeck, M., Wehnert, A., Serneels, S., Sherrington, R., Hutton, M., Hardy, J., St. George-Hyslop, P. H., Hofman, A., and van Broeckhoven, C. (1998). Estimation of the genetic contribution of presenilin-1 and -2 mutations in a population-based study of presenile Alzheimer disease. *Human Molecular Genetics*, 7(1):43–51.

Czech, C., Tremp, G., and Pradier, L. (2000). Presenilins and Alzheimer's disease: biological functions and pathogenic mechanisms. *Progress in Neurobiology*, 60:363–384.

Dartigues, J. F. and Letenneur, L. (2000). Genetic epidemiology of Alzheimer's disease. *Current Opinion in Neurology*, 13:385–389.

Daykin, C. D., Akers, D. A., Macdonald, A. S., McGleenan, T., Paul, D., and Turvey, P. (2003). Genetics and insurance — some social policy issues. Presented to the Institute of Actuaries and the Faculty of Actuaries.

De Jonghe, C., Cruts, M., Rogaeva, E. A., Tysoe, C., Singleton, A., Vanderstichele, H., Meschino, W., Dermaut, B., Vanderhoeven, I., Backhovens, H., Vanmechelon, E., Morris, C. M., Hardy, J., Rubinsztein, D. C., St. George-Hyslop, P. H., and van Broeckhoven, C. (1999). Aberrant splicing in the presenilin-1 intron 4 mutation causes presenile Alzheimer's disease by increased Aβ42 secretion. *Human Molecular Genetics*, 8:1539–1540.

De Jonghe, C., Kumar-Singh, S., Cruts, M., Kleinert, R., Vanderstichele, H., Vanmechelen, E. J. M., Kroisel, P., and Van Broeckhoven, C. (2000). Unusual Aβ amyloid deposition in Alzheimer's disease due to an APP T714I mutation at the γ42-secretase site. *Neurobiology of Aging*, 21(Suppl):S200.

Delbridge, L. and Robinson, B. (1998). Genetic and biochemical screening for endocrine disease: III. costs and logistics. *World Journal of Surgery*, 22:1212–1217.

Delbridge, L. W., Younes, N. A., Guinea, A. I., Reeve, T. S., Clifton-Bligh, P., and Robinson, B. G. (1998). Surgery for primary hyperthyroidism 1962–1996: indications and outcomes. *Medical Journal of Australia*, 168:153–156.

Dinani, A., Grimshaw, D., Robjohns, N., Somerville, S., Spry, A., and Staffurth, J. (2000). A critical review. Report of the Citical Ilness Halthcare Sudy Goup (unpublished manuscript). *The Staple Inn Actuarial Society.*

Doble, A. (2001). Protection of human genetics information. *Australian Actuarial Journal*, 8(2):263–319.

Dumanchin, C., Brice, A., Campion, D., Hannequin, D., Martin, C., Moreau, V., Agid, Y., Martinez, M., Clerget-Darpoux, F., Frebourg, T., and the

French Alzheimer's Disease Study Group (1998). De novo presenilin 1 mutations are rare in clinically sporadic, early onset Alzheimer's disease cases. *Journal of Medical Genetics*, 35:672–673.

Easton, D. F., Ponder, M. A., Cummings, T., Gagel, R. F., Hansen, H. H., Reichlin, S., Tashjian, A. H. J., Telenius-Berg, M., and Ponder, B. A. (1989). The clinical and screening age-at-onset distribution for the MEN-2 syndrome. *American Journal of Human Genetics*, 44(2):208–215.

Eckman, C. B., Mehta, N. D., Crook, R., Perez-Tur, J., Prihar, G., Pfeiffer, E., Graff-Radford, N., Hinder, P., Yager, D., Zenk, B., Refolo, L. M., Prada, C. M., Younkin, S. G., Hutton, M., and Hardy, J. (1997). A new pathogenic mutation in the APP gene (I716V) increases the relative proportion of Aβ42(43). *Human Molecular Genetics*, 6(12):2087–2089.

Elandt-Johnson, R. C. (1973). Age-at-onset distribution in chronic diseases. a life table approach to analysis of family data. *Journal of Chronic Disability*, 26:529–545.

Emilien, G., Ponchon, M., Caldas, C., Isacson, O., and Maloteaux, J.-M. (2000). Impact of genomics on drug discovery and clinical medicine. *Quarterly Journal of Medicine*, 93.

Eng, C., Clayton, D., Schuffenecker, I., Lenoir, G., Cote, G., Gagel, R. F., van Amstel, H. K., Lips, C. J., Nishisho, I., Takai, S. I., Marsh, D. J., Robinson, B. G., Frank-Raue, K., Raue, F., Xue, F., Noll, W. W., Romei, C., Pacini, F., Fink, M., Niederle, B., Zedenius, J., Nordenskjold, M., Komminoth, P., Hendy, G. N., Mulligan, L. M., and et al. (1996). The relationship between specific RET proto-oncogene mutations and disease phenotype in multiple endocrine neoplasia type 2. international RET mutation consortium analysis. *Journal of American Medical Association*, 276(19):1575–1579.

ESHG (2001). Genetic information and testing in insurance and employment: technical, social and ethical issues. European Society of Human Genetics Public and Professional Policy Committee.

Ezquerra, M., Carnero, C., Blesa, R., Gelpí, J. L., Ballesta, F., and Oliva, R. (1999). A presenilin 1 mutation (Ser169Pro) associated with early-onset AD and myoclonic seizures. *Neurology*, 52:566–570.

Ezquerra, M., Carnero, C., Blesa, R., and Oliva, R. (2000). A novel presenilin 1 mutation (Leu166Arg) associated with early-onset Alzheimer's disease. *Archives of Neurology*, 57:485–488.

Fargion, S., Mandelli, C., Piperno, A., Cesana, B., Fracanzani, A. L., Fraquelli, M., Bianchi, P. A., Fiorelli, G., and Conte, D. (1992). Survival and prognostic factors in 212 Italian patients with genetic hemochromatosis. *Hepatology*, 15:655–659.

Farlow, M. R., Murrell, J. R., Hulette, C. M., and Ghetti, B. (2000). Hereditary lateral sclerosis and Alzheimer disease associated with mutation at codon 261 of the presenilin (PS1) gene. *Neurobiology of Aging*, 21(Suppl):S62.

Farrer, L. A. (2001). Intercontinental epidemiology of Alzheimer's disease: a global approach to bad gene hunting. *Journal of the American Medical Association*, 285(6):796–798.

Fidani, L., Rooke, K., Chartier-Harlin, M. C., Hughes, D., Tanzi, R., Mullan, M., Roques, P., Rossor, M., Hardy, J., and Goate, A. (1992). Screening for mutations in the open reading frame and promoter of the β-amyloid precursor protein gene in familial Alzheimer's disease: identification of a further family with APP717 Val→Ile. *Human Molecular Genetics*, 1(3):165–168.

Finckh, U., Alberici, A., Antoniazzi, M., Benussi, L., Fedi, V., Giannini, C., Gal, A., Nitsch, R. M., and Binetti, G. (2000a). Variable expression of familial Alzheimer's disease with presenilin 2 mutation M239I. *Neurology*, 54:2006–2008.

Finckh, U., Müller-Thomsen, T., Mann, U., Eggers, C., Markseiner, J., Meins, W., Binetti, G., Alberici, A., Hock, C., Nitsch, R. M., and Gal, A. (2000b). High prevalence of pathogenic mutations in patients with early-onset dementia detected by sequence analyses of four different genes. *American Journal of Human Genetics*, 66:110–117.

Finckh, U., M*ü*ller-Thomsen, T., Mann, U., Eggers, C., Markseiner, J., Meins, W., Binetti, G., Alberici, A., Sonderegger, W., Hock, C., Nitsch, R. M., and Gal, A. (2000c). High frequency of mutations in four different disease genes in early-onset dementia. *Annals of the New York Academy of Sciences*, 920:100–106.

Fischer, E.-P. and Berberich, K. (1999). *Impact of modern genetics on insurance*. Publications of the Cologne Re, No. 42.

Fleming, T. R. and Harrington, D. P. (1991). *Counting processes and survival analysis*. John Wiley, New York.

Fogarty, M. (1999). Genetic testing, Alzheimer's disease, and long-term care insurance. *Genetic Testing*, 3(1):133–137.

Forsell, C., Froelich, S., Axelman, K., Vestling, M., Cowburn, R. F., Lilius, L., Johnston, J. A., Engvall, B., Johansson, K., Dahlkild, A., Ingelson, M., St. George-Hyslop, P. H., and Lannfelt, L. (1997). A novel pathogenic mutation (Leu262Phe) found in the presenilin 1 gene in early-onset Alzheimer's disease. *Neuroscience Letters*, 234:3–6.

Fox, N. C., Kennedy, A. M., Harvey, R. J., Lantos, P. L., Roques, P. K., Collinge, J., Hardy, J., Hutton, M., Stevens, J. M., Warrington, E. K., and Rossor, M. N. (1997). Clinicopathological features of familial Alzheimer's disease associated with the M139V mutation in the presenilin 1 gene. pedigree but not mutation specific age at onset provides evidence for a further genetic factor. *Brain*, 120:491–501.

Fraser, P. E., Yang, D.-S., Yu, G., Lévesque, L., Nishimura, M., Arawaka, S., Serpell, L. C., Rogaeva, E., and St George-Hyslop, P. (2000). Presenilin structure, function and role in Alzheimer disease. *Biochimica et Biophysica Acta*, 1502:1–15.

Frommelt, P., Schnabel, R., K*ü*hne, W., Nee, L. E., and Polinsky, R. J. (1991). Familial Alzheimer's disease: a large, multigeneration German kindred. *Alzheimer Disease and Associated Disorders*, 5(1):36–43.

Funato, H., Enya, M., Yoshimura, M., Morishima-Kawashima, M., and Ihara, Y. (1999). Presence of sodium dodecyl sulfate-stable amyloid beta-protein dimers in

the hippocampus CA1 not exhibiting neurofibrillary tangle formation. *American Journal of Pathololology*, 155(1):23–28.

GAIC (2000). First Annual Report. Genetics and Insurance Committee, Department of Health, London.

Gard, P. (1998). *Human Endocrinology*. Taylor & Francis Ltd, London.

Gifford, R. W., Manger, W. M., and Bravo, E. L. (1994). Pheochromocytoma. *Edocrinology and Metabolism Clinics of North America*, 23:387–404.

Goate, A., Chartier-Harlin, M.-C., Mullan, M., Brown, J., Crawford, F., Fidani, L., Giuffra, L., Haynes, A., Irving, N., James, L., Mant, R., Newton, P., Rooke, K., Roques, P., Talbot, C., Pericak-Vance, M., Roses, A., Williamson, R., Rossor, M., Owen, M., and Hardy, J. (1991). Segregation of a missense mutation in the amyloid precursor protein gene with familial Alzheimer's disease. *Nature*, 349:704–706.

Gómez-Isla, T., Wasco, W., Pettingell, W. P., Gurubhagavatula, S., Schmidt, S. D., Jondro, P. D., McNamara, M., Rodes, L. A., DiBlasi, T., Growdon, W. B., Seubert, P., Schenk, D., Growdon, J. H., Hyman, B. T., and Tanzi, R. E. (1997). A novel presenilin-1 mutation: increased β-amyloid and neurofibrillary changes. *Annals of Neurology*, 41:809–813.

Goretzki, P. E., Höppner, W., Dotzenrath, C., Clark, O. H., Simon, D., Cupisti, K., Schulte, H., and Röher, H. D. (1998). Genetic and biochemical screening for endocrine disease. *World Journal of Surgery*, 22:1202–1207.

Gui, E. H. and Macdonald, A. S. (2002a). Early-onset Alzheimer's disease, critical illness insurance and life insurance. *Genetics and Insurance Research Centre Research Report, Heriot-Watt University*, 02(02):1–31.

Gui, E. H. and Macdonald, A. S. (2002b). A Nelson-Aalen estimate of the incidence rates of early-onset Alzheimer's disease associated with the presenilin-1 gene. *ASTIN Bulletin*, 32:1–42.

Gustafson, L., Brun, A., Englund, E., Hagnell, O., Nilsson, K., Stensmyr, M., Ohlin, A.-K., and Abrahamson, M. (1998). A 50-year perspective of a family with chromosome-14-linked Alzheimer's disease. *Human Genetics*, 102(3):253–257.

Gutiérrez, C. and Macdonald, A. S. (2002a). Huntington's disease and insurance i: A model of Huntington's disease. *Genetics and Insurance Research Centre Research Report, Heriot-Watt University*, 02(03):1–28.

Gutiérrez, C. and Macdonald, A. S. (2002b). Huntington's disease and insurance ii: Critical illness and life insurance. *Genetics and Insurance Research Centre Research Report, Heriot-Watt University*, 02(04):1–33.

Gutiérrez, M. C. and Macdonald, A. S. (2003). Adult polycystic kidney disease and critical illness insurance. *To appear, North American Actuarial Journal*.

Hanson, E. H., Imperatore, G., and Burke, W. (2001). HFE gene and hereditary hemochromatosis: a HuGE review. Human Genome Epidemiology. *American Journal of Epidemiology*, 154(3):193–206.

Hardy, J. (1997). Amyloid, the presenilins and Alzheimer's disease. *Trends in Neuroscience*, 20(4):154–159.

Hardy, J., Mullan, M., Chartier-Harlin, M.-C., Brown, J., Goate, A., Rossor, M., Collinge, J., Roberts, G., Luthert, P., Lantos, P., Naruse, S., Kaneko, K., Tsuji, S., Miyatake, T., Shimizu, T., Kojima, T., Nakano, I., Yoshioka, K., Sakaki, Y., Miki, T., Katsuya, T., Ogihara, T., Roses, A., Pericak-Vance, M., Haan, J., Roos, R., Lucotte, G., and Favid, F. (1991). Molecular classfication of Alzheimer's disease. *The Lancet*, 337:1342–1343.

Harper, P. S. (1997). *Genetics Society and Clinical Practice*, chapter Genetic Testing and Insurance, pages 49–66. BIOS Scientific Publishers Ltd, Oxford.

Harper, P. S. and Newcombe, R. G. (1992). Age at onset and life table risks in genetic counselling for Huntington's disease. *Journal of Medical Genetics*, 29:239–242.

Harvey, R. J. (1998). Young onset dementia: Epidemiology, clinical symptoms, family burden, support and outcome. Technical report, Imperial College of Science, Technology and Medicine. Funded by NHS Executive (North Thames).

Harvey, R. J., Ellison, D., Hardy, J., Hutton, M., Roques, P. K., Collinge, J., Fox, N. C., and Rossor, M. N. (1998). Chromosome 14 familial Alzheimer's disease: the clinical and neuropathological characteristics of a family with a leucine → serine (L250S) substitution at codon 250 of the presenilin 1 gene. *Journal of Neurology, Neurosurgery and Psychiatry*, 64:44–49.

HCSTC (1995). House of Commons Science and Technology Committee, Third report — Human genetics: the science and its consequences. HC41. HMSO, London.

HCSTC (2001). House of Commons Science and Technology Committee, Fifth report — Genetics and insurance. HC174. T.S.O., London.

Heitjan, D. F. (1994). Ignorability in general incomplete-data models. *Biometrika*, 81:701–708.

Hendriks, L., van Duijn, C. M., Cras, P., Cruts, M., van Hul, W., van Harskamp, F., Warren, A., McInnis, M. G., Antonarakis, S. E., Martin, J.-J., Hofman, A, ., and van Broeckhoven, C. (1992). Presenilin dementia and cerebral haemorrhage linked to a mutation at codon 692 of the β-amyloid precursor protein gene. *Nature Genetics*, 1:218–221.

Heshmati, H. M. and Hofbauer, L. C. (1997). Multiple endocrine neoplasia type 2: recent progress in diagnosis and management. *European Journal of Endocrinology*, 137:572–578.

Heyman, A., Wilkinson, W. E., Hurwitz, B. J., Helms, M. J., Haynes, C. S., Utley, C. M., and Gwyther, L. P. (1987). Early-onset Alzheimer's disease: clinical predictors of institutionalization and death. *Neurology*, 37:980–984.

HGAC (1997). The implications of genetic testing for insurance. Human Genetics Advisory Commission, London.

HGC (2000). Whose hands on your genes? Human Genetics Commission, London.

HGC (2002). Inside information — balancing interests in the use of personal genetic data. Human Genetics Commission, London.

Higuchi, S., Yoshino, A., Matsui, T., Matsushita, S., Satoh, A., Iimura, T., Ishikawa, M., Arai, H., and Shirakura, K. (2000). A novel PS1 mutation (W165G) in a Japanese family with early-onset Alzheimer's disease. *Alzheimer's Reports*, 3(4):227–231.

Hiltunen, M., Helisalmi, S., Mannermaa, A., Alafuzoff, I., Koivisto, A. M., Lehtovirta, M., Pirskanen, M., Sulkava, R., Verkkoniemi, A., and Soininen, H. (2000). Identification of a novel 4.6-kb genomic deletion in presenilin-1 gene which results in exclusion of exon 9 in a Finnish early onset Alzheimer's disease family: an Alu core sequence-stimulated recombination ? *European Journal of Human Genetics*, 8:259–266.

Hosmer, D. W. and Lemeshow, S. (1999). *Applied survival analysis: regression modelling of time to event data*. John Wiley & Sons, Inc., New York.

Hougaard, P. (2000). *Analysis of multivariate survival data*. Springer-Verlag, New York.

Hüll, M., Fiebich, B. L., Dykierek, P., Schmidtke, K., Nitzsche, E., Orszagh, M., Deuschl, G., Moser, E., Schumacher, M., Lucking, C., Berger, M., and Bauer, J. (1998). Early-onset Alzheimer's disease due to mutations of the presenilin-1 gene on chromosome 14: a 7-year follow-up of a patient with a mutation at codon 139. *European Archives of Psychiatry and Clinical Neurosciences*, 248:123–129.

Hutton, M., Busfield, F., Wragg, M., Crook, R., Perez-Tur, J., Clark, R. F., Prihar, G., Talbot, C., Phillips, H., Wright, K., Baker, M., Lendon, C., Duff, K., Martinez, A., Houlden, H., Nichols, A., Karran, E., Roberts, G., Roques, P., Rossor, M., Venter, J. C., Adams, M. D., Cline, R. T., Phillips, C. A., Fuldner, R. A., Hardy, J., and Goate, A. (1996). Complete analysis of the presenilin 1 gene in early onset Alzheimer's disease. *Neuroreport*, 7:801–805.

Ikeda, M., Sharma, V., Mark Sumi, S., Rogaeva, E. A., Poorkaj, P., Sherrington, R., Nee, L., Tsuda, T., Oda, N., Watanabe, M., Aoki, M., Shoji, M., Abe, K., Itoyama, Y., Hirai, S., Schellenberg, G. D., Bird, T. D., and St. George-Hyslop, P. H. (1996). The clinical phenotype of two missense mutations in the presenilin 1 gene in Japanese patients. *Annals of Neurology*, 40:912–917.

Ishii, K., Lippa, C., Tomiyama, T., Miyatake, F., Ozawa, K., Tamaoka, A., Hasegawa, T., Fraser, P. E., Shoji, S., Nee, L. E., Pollen, D. A., St George-Hyslop, P. H., Ii, K., Ohtake, T., Kalaria, R. N., Rossor, M. N., Lantos, P. L., Cairns, N. J., Farrer, L. A., and Mori, H. (2001). Distinguishable effects of presenilin-1 and APP717 mutations on amyloid plaque deposition. *Neurobiology of Aging*, 22(3):367–376.

Iwatsubo, T. (1998). Aβ42, presenilin and Alzheimer's disease. *Neurobiology of Aging*, 19(Suppl 1):S11–S13.

Jacquier, M., Arango, D., Torres, O., Cruts, M., Serrano, M., Matallana, M., Cano, C., and van Broeckhoven, C. (2000). Presenilin mutations in a Colombian familial and sporadic sample. *Neurobiology of Aging*, 21(Suppl):S176.

Jones, C. T., Morris, S., Yates, C. M., Moffoot, A., Sharpe, C., Brock, D. J. H., and St. Clair, D. (1992). Mutation in codon 713 of the β amyloid precursor protein gene presenting with schizophrenia. *Nature Genetics*, 1:306–309.

Jørgensen, P., Bus, C., Pallisgaard, N., Bryder, M., and Jørgensen, A. L. (1996). Familial Alzheimer's disease co-segregates with a Met146Ile substitution in presenilin-1. *Clinical Genetics*, 50:281–286.

Jouanolle, A. M., Gandon, G., Jezequel, P., Blayau, M., Campion, M. L., Yaouanq, J., Mosser, J., Fergelot, P., Chauvel, B., Bouric, P., Carn, G., Andrieux, N., Gicquel, I., Le Gall, J. Y., and David, V. (1996). Haemochromatosis and HLA-H. *Nature Genetics*, 14:251–252.

Kahn, M. A., Cote, G. J., and Gagel, R. F. (1996). RET protooncogene mutational analysis in multiple endocrine neoplasia syndrome type 2B: case report and review

of the literature. *Oral Surgical, Oral Medicine, Oral Pathology, Oral Radiology, Endodontics*, 82(3):288–294.

Kamimura, K., Tanahashi, H., Yamanaka, H., Takahashi, K., Asada, T., and Tabira, T. (1998). Familial Alzheimer's disease genes in Japanese. *Journal of the Neurological Sciences*, 160:76–81.

Kamino, K., Orr, H. T., Payami, H., Wijsman, E. M., Alonso, M. E., Pulst, S. M., Anderson, L., O'dahl, S., Nemens, E., White, J. A., Sadovnick, A. D., Ball, M. J., Kaye, J., Warren, A., McInnis, M., Antonarakis, S. E., Korenberg, J. R., Sharma, V., Kukull, W., Larson, E., Heston, L. L., Martin, G. M., Bird, T. D., and Schellenberg, G. D. (1992). Linkage and mutation analysis of familial Alzheimer disease kindreds for the APP gene region. *American Journal of Human Genetics*, 51:998–1014.

Kamino, K., Sato, S., Sakaki, Y., Yoshiiwa, A., Nishiwaki, Y., Takeda, M., Tanabe, H., Nishimura, T., Ii, K., St. George-Hyslop, P. H., Miki, T., and Ogihara, T. (1996). Three mutations of presenilin 1 gene in early-onset Alzheimer's disease families. *Neuroscience Letters*, 208:195–198.

Klein, J. P. and Moeschberger, M. L. (1997). *Survival analysis: Techniques for censored and truncated data*. Springer-Verlag, New York.

Koch, C. A., Vortmeyer, A. O., Huang, S. C., Alesci, S., Zhuang, Z., and Pacak, K. (2001). Genetic aspects of pheochromocytoma. *Endocrine Regulations*, 35:43–52.

Kokmen, E., Beard, C. M., Offord, K. P., and Kurland, L. T. (1989). Prevalence of medically diagnosed dementia in a defined United States population : Rochester, Minnesota, January 1, 1975. *Neurology*, 39:773–776.

Kowalska, A., Forsell, C., Florczak, J., Pruchnik-Wolinska, D., Modestowicz, R., Paprzycki, W., Wender, M., and Lannfelt, L. (1999). A Polish pedigree with Alzheimer's disease determined by a novel mutation in exon 12 of the presenilin 1 gene: clinical and molecular characterization. *Folia Neuropathologica*, 37(1):415–424.

Kowdley, K. V., Tait, J. F., Bennett, R. L., and Motulsky, A. G. (2000). Hereditary hemochromatosis. *Gene Reviews*, www.geneclinics.org/profiles/hemochromatosis/.

Kumar-Singh, S., De Jonghe, C., Cruts, M., Kleinert, R., Wang, R., Mercken, M., De Strooper, B., Vanderstichele, H., Löfgren, A., Vanderhoeven, I., Backhovens, H., Vanmechelen, E., Kroisel, P. M., and van Broeckhoven, C. (2000). Nonfibrillar diffuse amyloid deposition due to a γ_{42} secretase site mutation points to an essential role for N-truncated Aβ_{42} in Alzheimer's disease. *Human Molecular Genetics*, 9(18):2589–2598.

Kwok, J. B. J., Li, Q.-X., Hallupp, M., Whyte, S., Ames, D., Beyreuther, K., Masters, C. L., and Schofield, P. R. (2000a). Novel Leu723Pro amyloid precursor protein mutation increases amyloid β42(43) peptide levels and induces apoptosis. *Annals of Neurology*, 47:249–253.

Kwok, J. B. J., Smith, M. J., Brooks, W. S., Kril, J., Mclean, C., Hallupp, M., and Schofield, P. R. (2000b). Variable presentation of Alzheimer's disease and/or spastic paraparesis phenotypes in pedigrees with a novel PS-1 exon 9 gene deletion or exon 9 splice acceptor mutations. *Neurobiology of Aging*, 21(Suppl):S25.

Kwok, J. B. J., Taddei, K., Hallupp, M., Fisher, C., Brooks, W. S., Broe, G. A., Hardy, J., Fulham, M. J., Nicholson, G. A., Stell, R., St. George-Hyslop, P. H., Fraser, P. E., Kakulas, B., Clarnette, R., Relkin, N., Gandy, S. E., Schofield, P. R., and Martins, R. N. (1997). Two novel (M233T and R278T) presenilin-1 mutations in early-onset Alzheimer's disease pedigrees and preliminary evidence for association of presenilin-1 mutations with a novel phenotype. *NeuroReport*, 8:1537–1542.

Lao, J. I., Beyer, K., Fernández-Novoa, L., and Cacabelos, R. (1998). A novel mutation in the predicted TM2 domain of the presenilin 2 gene in a Spanish patient with late-onset Alzheimer's disease. *Neurogenetics*, 1:293–296.

Learoyd, D. L., Delbridge, L. W., and Robinson, B. G. (2000). Multiple endocrine neoplasia. *The Australia and New Zealand Journal of Medicine*, 30:675–682.

Lemaire, J., Subramanian, K., Armstrong, K., and Asch, D. A. (2000). Pricing term insurance in the presence of a family history of breast or ovarian cancer. *North American Actuarial Journal*, 4:75–87.

Lendon, C. and Craddock, N. (2001). Susceptibility gene(s) for Alzheimer's disease on chromosome 10. *Trends in Neurosceinces*, 24(10):557–559.

Lendon, C. L., Martinez, A., Behrens, I. M., Kosik, K. S., Madrigal, L., Norton, J., Neuman, R., Myers, A., Busfield, F., Wragg, M., Arcos, M., Arango Viana, J. C., Ossa, J., Ruiz, A., Goate, A. M., and Lopera, F. (1997). E280A PS-1 mutation causes Alzheimer's disease but age of onset is not modified by ApoE alleles. *Human Mutation*, 10:186–195.

Levy, E., Carman, M. D., Fernandez-Madrid, I. J., Power, M. D., Lieberburg, I., van Duinen, S. G., Bots, G. T. A. M., Luyendijk, W., and Frangione, B. (1990). Mutation of the Alzheimer's disease amyloid gene in hereditary cerebral hemorrhage, Dutch type. *Science*, 248:1124–1126.

Levy-Lahad, E., Wasco, W., Poorkaj, P., Romano, D. M., Oshima, J., Pettingell, W. H., Yu, C., Jondro, P. D., Schmidt, S. D., Wang, K., Crowley, A. C., Fu, Y.-H., Guenette, S. Y., Galas, D., Nemens, E., Wijsman, E. M., Bird, T. D., Schellenberg, G. D., and Tanzi, R. E. (1995a). Candidate gene for the chromosome 1 familial Alzheimer's disease locus. *Science*, 269:973–977.

Levy-Lahad, E., Wijsman, E. M., Nemens, E., Anderson, L., B., G. K. A., Weber, J. L., Bird, T. D., and Schellenberg, G. D. (1995b). A familial Alzheimer's disease locus on chromosome 1. *Science*, 269:970–973.

Lewinski, A., Ferenc, T., Sporny, S., and Jarzab, B. (2000). Thyroid carcinoma : diagnostic and therapeutic approach; genetic background (review). *Endocrine Regulations*, 34:99–113.

Lippa, C. F., Swearer, J. M., Kane, K. J., Nochlin, D., Bird, T. D., Ghetti, B., Nee, L. E., St. George-Hylsop, P. H., Pollen, D. A., and Drachman, D. A. (2000). Familial Alzheimer's disease: site of mutation influences clinical phenotype. *Annals of Neurology*, 48:376–379.

Lips, C., Landsvater, R. M., Hoppener, J., Geerdink, R. A., Blijham, G., Jansen-Schillhorn van Veen, J. M., van Gils, A., de Wit, M. J., Zewald, R. A., Berends, M., Beemer, F. A., Brouwers-Smalbraak, J., Jansen, R., Ploos van Amstel, H. K., van Vroonhoven, T., and Vroom, T. M. (1994). Clinical screening as compared with DNA analysis in families with multiple endocrine neoplasia type 2A. *The New England Journal of Medicine*, 331(13):828–835.

LISA (1997). Underwriting and genetic testing. Draft Policy of the Life, Investment and Superannuation Association of Australia on Genetic Testing.

Macdonald, A. S. (1996). An actuarial survey of statistical models for decrement and transition data III: Counting process models. *British Actuarial Journal*, 2:703–726.

Macdonald, A. S. (1997). How will improved forecasts of individual lifetimes affect underwriting? *Philosophical Transactions of the Royal Society*, 352:1067–1075. With discussion in British Actuarial Journal, 3: 1009-1075.

Macdonald, A. S. (1999). Modeling the impact of genetics on insurance. *North American Actuarial Journal*, 3(1):83–101.

Macdonald, A. S. (2002). Genetics and health costs: Some actuarial models. *Law, Probability and Risk*, 1:97–118.

Macdonald, A. S. (2003a). Genetics and insurance: What have we learned so far? *To appear, Scandinavian Actuarial Journal*.

Macdonald, A. S. (2003b). Moratoria on the use of genetic tests and family history for mortgage-related life insurance. *To appear, British Actuarial Journal*.

Macdonald, A. S. and Pritchard, D. J. (2000). A mathematical model of Alzheimer's disease and the ApoE gene. *ASTIN Bulletin*, 30:69–110.

Macdonald, A. S. and Pritchard, D. J. (2001). Genetics, Alzheimer's disease and long-term care insurance. *North American Actuarial Journal*, 5(2):54–78.

Macdonald, A. S., Waters, H. R., and Wekwete, C. T. (2003a). The genetics of breast and ovarian cancer I: A model of family history. *Scandinavian Actuarial Journal*, 1:1–27.

Macdonald, A. S., Waters, H. R., and Wekwete, C. T. (2003b). The genetics of breast and ovarian cancer II: A model of critical illness insurance. *Scandinavian Actuarial Journal*, 1:28–50.

Macdonald, A. S. and Yang, S. Y. (2003a). Highly penetrant genetic disorders: an atlas for critical illness insurance. *Genetics and Insurance Research Centre Research Report, Heriot-Watt University*, 03(01):1–26.

Macdonald, A. S. and Yang, S. Y. (2003b). Tables of representative premiums for critical illness insurance policies in the presence of model genetic disorders. Occasional Actuarial Research Document No. 42, Faculty and Institute of Actuaries.

Martin, J. J., Gheuens, J., Bruyland, M., Cras, P., Vandenberghe, A., Masters, C. L., Beyreuther, K., Dom, R., Ceuterick, C., Lübke, U., van Heuverswijn, H., De Winter, G., and van Broeckhoven, C. (1991). Early-onset Alzheimer's disease in 2 large Belgian families. *Neurology*, 41:62–68.

Matsumura, Y., Kitamura, E., K., M., Yamamoto, Y., Furuyama, J., and Sugihara, T. (1996). Japanese siblings with missense mutation (717Val→Ile) in amyloid precursor protein of early-onset Alzheimer's disease. *Neurology*, 46:1721–1723.

McDonnell, S. M., Hover, A., Gloe, D., Ou, C.-Y., Cogswell, M. E., and Grummer-Strawn, L. (1999). Population-based screening for hemochromatosis using phenotypic and DNA testing among employees of health maintenance organizations in Springfield, Missouri. *The American Journal of Medicine*, 107:30–37.

McGleenan, T. (2001). Insurance and genetic information. Technical report, Association of British Insurers. ABI research report series No.3.

Meiser, B. and Dunn, S. (2000). Psychological impact of genetic testing for Huntington's disease: an update of the literature. *Journal of Neurology, Neurosurgery, and Psychiatry*, 69:574–578.

Merryweather-Clarke, A. T., Pointon, J. J., and Shearman, J. D.and Robson, K. J. (1997). Global prevalence of putative haemochromatosis mutations. *Journal of Medical Genetics*, 34(4):275–278.

Modlin, I. M., Farndon, J. R., Shepherd, A., Johnston, I. D., Kennedy, T. L., Montgomery, D. A., and Welbourn, R. B. (1979). Phaeochromocytomas in 72 patients: clinical and diagnostic features, treatment and longterm results. *British Journal of Surgery*, 66(7):456–465.

Moley, J. F. (1995). Medullary thyroid cancer. *The Surgical clinics of North America*, 75:405–420.

Morelli, L., Prat, M. I., Levy, E., Mangone, C. A., and Castano, E. M. (1998). Presenilin 1 Met146Leu variant due to an a → t transversion in an early-onset familial Alzheimer's disease pedigree from Argentina. *Clinical Genetics*, 53:469–473.

Mullan, M., Crawford, F., Axelman, K., Houlden, H., Lilius, L., Winblad, B., and Lannfelt, L. (1992). A pathogenic mutation for probable Alzheimer's disease in the APP gene at the N-terminus of β-amyloid. *Nature Genetics*, 1:345–347.

Mullan, M., Tsuji, S., Miki, T., Katsuya, T., Naruse, S., K., K., Shimizu, T., Kojima, T., Nakano, I., Ogihara, T., and et al. (1993). Clinical comparison of Alzheimer's disease in pedigrees with the codon 717 Val⟶Ile mutation in the amyloid precursor protein gene. *Neurobiology of Aging*, 14(5):407–419.

Murrell, J., Farlow, M., Ghetti, B., and Benson, M. D. (1991). A mutation in the amyloid precursor protein associated with hereditary Alzheimer's disease. *Science*, 254:97–99.

Murrell, J. R., Hake, A. M., Quaid, K. A., Farlow, M. R., and Ghetti, B. (2000). Early-onset Alzheimer disease caused by a new mutation (V717L) in the amyloid precursor protein gene. *Archives of Neurology*, 57:885–887.

Naruse, S., Igarashi, S., Kobayashi, H., Aoki, K., Inuzuka, T., Kaneko, K., Shimizu,

T., Iihara, K., Kojima, T., Miyatake, T., and Tsuji, S. (1991). Mis-sense mutation Val→Ile in exon 17 of amyloid precursor protein gene in Japanese familial Alzheimer's disease. *The Lancet*, 337:978–979.

Newcombe, R. G. (1981). A life table for onset of Huntington's chorea. *Annals of Human Genetics*, 45:375–385.

Newton, G., editor (1998). *Research directions in Alzheimer's disease*, number Suppl. 2 in Wellcome News.

Niederau, C., Fischer, R., P*ü*rschel, A., Stremmel, W., H*ä*ussinger, D., and Strohmeyer, G. (1996). Long-term survival in patients with hereditary hemochromatosis. *Gastroenterology*, 110:1107–1119.

Nilsberth, C., Westlind-Danielsson, A., Eckman, C. B., Forsell, C., Axelman, K., Luthman, J., Younkin, S. G., and N*Š*slund, J. (2000). The Arctic APP mutation (E693G) causes Alzheimer's disease through a novel mechanism: increased amyloid βprotfibril formation and decreased amyloid βlevels in plasma and conditioned media. *Neurobiology of Aging*, 21(S59):265.

Nochlin, D., Bird, T. D., Nemens, E. J., Ball, M. J., and Mark Sumi, S. (1998). Amyloid angiopathy in a Volga German family with Alzheimer's disease and a presenilin-2 mutation (N141I). *Annals of Neurology*, 43:131–135.

Norberg, R. (1995). Differential equations for moments of present values in life insurance. *Insurance: Mathematics and Economics*, 17:171–180.

Nussbaum, B. L., McInnes, R. R., and Willard, H. F. (2001). *Thompson & Thompson genetics in medicine*. W. B. Saunders Company, 6th edition.

Orlandi, F., Caraci, P., Mussa, A., Saggiorato, E., Pancani, G., and Angeli, A. (2001). Treatment of medullary thyroid carcinoma: an update. *Endocrine-related Cancer*, 8:135–147.

Palmer, M. S., Beck, J. A., Campbell, T. A., Humphries, C. B., Rogues, P. K., Fox, N. C., Harvey, R., Rossor, M. N., and Collinge, J. (1999). Pathogenic presenilin

1 mutations (P436S and I143F) in early-onset Alzheimer's disease in the U. K. *Human Mutation*, 13(3):256.

Panegyres, P. K., Goldblatt, J., Walpole, I., Connor, C., Liebeck, T., and Harrop, K. (2000). Genetic testing for Alzheimer's disease. *The Medical Journal of Australia*, 172:339–343.

Pasternak, J. J. (1999). *An introduction to human molecular genetics*. Fitzgerald Science Press, Bethesda, Maryland.

Peacock, M. L., Murman, D. L., Sima, A. A. F., Warren, J. T., Roses, A. D., and Fink, J. K. (1994). Novel amyloid precursor protein gene mutation (codon 665 Asp) in a patient with late-onset Alzheimer's disease. *Annals of Neurology*, 35:432–438.

Peacock, M. L., Warren, J. T., Roses, A. D., and Fink, J. K. (1993). Novel polymorphism in the A4 region of the amyloid precursor protein gene in a patient without Alzheimer's disease. *Neurology*, 43:1254–1256.

Perez-Tur, J., Croxton, R., Wright, K., Phillips, H., Zehr, C., Crook, R., Hutton, M., Hardy, J., Karran, E., Roberts, G. W., Lancaster, S., and Haltia, T. (1996). A further presenilin 1 mutation in the exon 8 cluster in familial Alzheimer's disease. *Neurodegeneration*, 5:207–212.

Perez-Tur, J., Froelich, S., Prihar, G., Crook, R., Baker, M., Duff, K., Wragg, M., Busfield, F., Lendon, C., Clark, R. F., Roques, P., Fuldner, R. A., Johnston, J., Cowburn, R., Forsell, C., Axelman, K., Lilius, L., Houlden, H., Karran, E., Roberts, G. W., Rossor, M., Adams, M. D., Hardy, J., Goate, A., Lannfelt, L., and Hutton, M. (1995). A mutation in Alzheimer's disease destroying a splice acceptor site in the presenilin-1 gene. *NeuroReport*, 7:297–301.

Poduslo, S. E., Herring, K., and Neal, M. (1996). A presenilin 1 mutation in an early onset Alzheimer's family: no association with presenilin 2. *Neuroreport*, 7:2018–2020.

Pointon, J. J., Wallace, D., Merryweather-Clarke, A. T., and Robson, K. J. (2000). Uncommon mutations and polymorphisms in the hemochromatosis gene. *Genetic Testing*, 4:151–161.

Ponder, B. A. (1997). *The Genetic Basis of Human Cancer*, chapter Multiple Endocrine Neoplasia Type 2, page 476. McGraw-Hill, New York.

Poorkaj, P., Sharma, V., Anderson, L., Nemens, E., Alonso, M. E., Orr, H., White, J., Heston, L., Bird, T. D., and Schellenberg, G. D. (1998). Missense mutations in the chromosome 14 familial Alzheimer's disease presenilin 1 gene. *Human Mutation*, 11:216–221.

Prihar, G., Verkkoniem, A., Perez-Tur, J., Crook, R., Lincoln, S., Houlden, H., Somer, M., Paetau, A., Kalimo, H., Grover, A., Myllykangas, L., Hutton, M., Hardy, J., and Haltia, M. (1999). Alzheimer's disease PS-1 exon 9 deletion defined. *Nature Medicine*, 5:1090.

Pritchard, D. J. (2002). *The genetics of Alzheimer's disease, modelling disability and adverse selection in the long-term care insurance market*. PhD thesis, Heriot-Watt University.

Queralt, R., Ezquerra, M., Castellvi, M., Lleo, A., Blesa, R., and Oliva, R. (2001). Detection of the presenilin 1 gene mutation (M139T) in early-onset familial Alzheimer's disease in Spain. *Neuroscience Letters*, 299:239–241.

Ramirez-Dueñas, M. G., Rogaeva, E. A., Leal, C. A., Lin, C., Ramirez-Casillas, G. A., Hernandez-Romo, J. A., St. George-Hyslop, P. H., and Cantu, J. M. (1998). A novel Leu171Pro mutation in presenilin-1 gene in a Mexican family with early-onset Alzheimer disease. *Annals Génét*, 41(3):149–153.

Randolph, G. W. (2000). Medullary carcinoma of the thyroid. *Cancer Control*, 7(3):253–261.

Raux, G., Gantier, R., Martin, C., Pothin, Y., Brice, A., Frebourg, T., and Campion, D. (2000a). A novel presenilin 1 missense mutation (L153V) segregating with early-onset autosomal dominant Alzheimer's disease. *Human Mutation*, 16:95.

Raux, G., Gantier, R., Thomas-Anterion, C., Boulliat, J., Verpillat, P., Hannequin, D., Brice, A., Frebourg, T., and Campion, D. (2000b). Dementia with prominent frontotemporal features associated with L113P presenilin 1 mutation. *Neurology*, 55:1577–1579.

Reznik-Wolf, H., Machado, J., Haroutunlan, V., DeMarco, L., Walter, G. F., Chapman, Y., Goldman, B., Davidson, M., Johnston, J., Lannfelt, L., Dani, S. U., and Friedman, E. (1996a). Somatic mutational anaylsis of the APP and presenilin 1 genes in Alzheimer's disease patients brains using denaturing gradient gel electrophoresis (DGGE). *Neurobiology of Aging*, 17(Suppl):S14.

Reznik-Wolf, H., Treves, T. A., Davidson, M., Aharon-Peretz, J., St. George-Hyslop, P. H., Chapman, J., Korczyn, A. D., Goldman, B., and Friedman, E. (1996b). A novel mutation of presenilin 1 in familial Alzheimer's disease in Israel detected by denaturing gradient gel electrophoresis. *Human Genetics*, 98:700–702.

Roberts, A. G., Whatley, S. D., Morgan, R. R., Worwood, M., and Elder, G. H. (1997). Increased frequency of the haemochromatosis Cys282Tyr mutation in sporadic porphyria tarda. *Lancet*, 349:321–323.

Rocca, W. A., Amaducci, L. A., and Schoenberg, B. S. (1986). Epidemiology of clinically diagnosed Alzheimer's disease. *Annals of Neurology*, 19:415–424.

Rogaev, E. I., Sherrington, R., Rogaeva, E. A., Levesque, G., Ikeda, M., Liang, Y., Chi, H., Lin, C., Holman, K., Tsuda, T., Mar, L., Sorbi, S., Nacmias, B., Piacentini, S., Amaducci, L., Chumakov, I., Cohen, D., Lannfelt, L., Fraser, P. E., Rommens, J. M., and St. George-Hyslop, P. H. (1995). Familial Alzheimer's disease in kindreds with missense mutations in a gene on chromosome 1 related to the Alzheimer's disease type 3 gene. *Nature*, 376:775–778.

Rogaeva, E. A., Fafel, K. C., Song, Y. Q., Medeiros, H., Sato, C., Liang, Y., Richard, E., Rogaev, E. I., Frommelt, P., Sadovnick, A. D., Meschino, W., Rockwood, K., Boss, M. A., Mayeux, R., and St. George-Hyslop, P. H. (2001). Screening for PS1 mutations in a referral-based series of AD cases. 21 novel mutations. *Neurology*, 57:621–625.

Romero, I., Jørgensen, P., Bolwig, G., Fraser, P. E., Rogaeva, E., Mann, D., Havsager, A.-M., and Jørgensen, A. L. (1999). A presenilin-1 Thr116Asn substitution in a family with early-onset Alzheimer's disease. *NeuroReport*, 10:2255–2260.

Rossor, M. N., Fox, N. C., Beck, J., Campbell, T. C., and Collinge, J. (1996). Incomplete penetrance of familial Alzheimer's disease in a pedigree with a novel presenilin-1 gene mutation. *The Lancet*, 347:1560.

Russo, C., Schettini, G., Saido, T. C., Hulette, C., Lippa, C., Lannselt, L., Ghetti, B., Ganbetti, P., Tabaton, M., and Teller, J. K. (2000). Presenilin-1 mutations in Alzheimer's disease. *Nature*, 405:531–532.

Samaan, N. A., Hickey, R. C., and Shutts, P. E. (1988). Diagnosis, localization and management of pheochromocytoma. pitfall and follow-up in 41 patients. *Cancer*, 62:2451–2460.

Sandbrink, R., Zhang, D., Schaeffer, S., Masters, C. L., Bauer, J., Förstl, H., and Beyreuther, K. (1996). Missense mutations of the PS-1/S182 gene in German early-onset Alzheimer's disease patients. *Annals of Neurology*, 40(2):265–266.

Sato, S., Kamino, K., Miki, T., Doi, A., Li, K., St. George-Hyslop, P. H., Ogihara, T., and Sakaki, Y. (1997). Splicing mutation of presenilin-1 gene for early-onset familial Alzheimer's disease. *Human Mutation*, Suppl. 1:S91–S94.

Schoenberg, B. S., Anderson, D. W., and Haerer, A. F. (1985). Severe dementia, prevalence and clinical features in a biracial US population. *Archives of Neurology*, 42:740–743.

Sheps, S. G., Jiang, N. S., Klee, G. G., and van Heerden, J. A. (1990). Recent developments in the diagnosis and treatment of pheochromocytomas. *Mayo Clinic Proceedings*, 64:88–95.

Sherrington, R., Froelich, S., Sorbi, S., Campion, D., Chi, H., Rogaeva, E. A., Levesque, G., Rogaev, E. I., Lin, C., Liang, Y., Ikeda, M., Mar, L., Brice, A., Agid, Y., Percy, M. E., Clerget-Darpoux, F., Piacentini, S., Marcon, G., Nacmias, B., Amaducci, L., Frebourg, T., L., L., Rommens, J. M., and St. George-Hyslop,

P. H. (1996). Alzheimer's disease associated with mutations in presenilin 2 is rare and variable penetrant. *Human Molecular Genetics*, 5:985–988.

Sherrington, R., Rogaev, E. I., Liang, Y., Rogaeva, E. A., Levesque, G., Ikeda, M., Chi, H., Lin, C., Li, G., Holman, K., Tsuda, T., Mar, L., Foncin, J.-F., Bruni, A. C., Montesi, M. P., Sorbi, S., Rainero, I., Pinessi, L., Nee, L., Chumakov, I., Pollen, D., Brookes, A., Sanseau, P., Polinsky, R. J., Wasco, W., Da Silva, H. A. R., Haines, J. L., Pericak-Vance, M. A., Tanzi, R. E., Roses, A. D., Fraser, P. E., Rommens, J. M., and St. George-Hyslop, P. H. (1995). Cloning of a gene bearing missense mutations in early-onset familial Alzheimer's disease. *Nature*, 375:754–760.

Siegelman, M., Mohabeer, A., Fahey III, T. J., Tomlinson, G., C., M., Jafari, S., Noll, W. W., Thibodeau, S. N., and Dawson, D. B. (1997). Rapid, nonradioactive screening for mutations in exons 10, 11, and 16 of the RET protooncogene associated with inherited medullary thyroid carcinoma. *Clinical Chemistry*, 43(3):453–457.

Smith, C. (1998). Huntington's chorea: A mathematical model for life insurance. *Unpublished manuscript, Swiss Re, Zurich*.

Smith, M. J., Gardner, R. J. M., Knight, M. A., Forrest, S. M., Beyreuther, K., Storey, E., McLean, C. A., Cotton, R. G. H., Cappal, R., and Masters, C. L. (1999). Early-onset Alzheimer's disease caused by a novel mutation at codon 219 of the presenilin-1 gene. *NeuroReport*, 10:503–507.

Smith, M. J., Kwok, J. B. J., Mclean, C. A., Kril, J. J., Broe, G. A., Nicholson, G. A., Cappai, R., Hallupp, M., Cotton, R. G. H., Masters, C. L., Schofield, P. R., and Brooks, W. S. (2001). Variable phenotype of Alzheimer's disease with spastic paraparesis. *Annals of Neurology*, 49:125–129.

Sorbi, S., Nacmias, B., Forleo, P., Piacentini, S., and Amaducci, L. (1993). APP717 and Alzheimer's disease in Italy. *Nature Genetics*, 4:10.

Sorbi, S., Nacmias, B., Forleo, P., Piacentini, S., Sherrington, R., Rogaev, E. St.

George-Hyslop, P. H., and Amaducci, L. (1995). Missense mutation of S182 gene in Italian families with early-onset Alzheimer's disease. *Lancet*, 346:439–440.

St. George-Hyslop, P. H. (1998). Role of genetics in tests of genotype, status, and disease progression in early-onset Alzheimer's disease. *Neurobiology of Aging*, 19(2):133–137.

St. George-Hyslop, P. H. (2000). Molecular genetics of Alzheimer's disease. *Biological Psychiatry*, 47:183–199.

St. John Sutton, M. G., Sheps, S. G., and Lie, J. T. (1981). Prevalence of clinically unsuspected pheochromocytoma. review of a 50-year autopsy series. *Mayo Clinic Proceedings*, 56:354–360.

Steinbart, E. J., Smith, C. O., Poorkaj, P., and Bird, T. D. (2001). Impact of DNA testing for early-onset familial Alzheimer diusease and frontotemporal dementia. *Archives of Neurology*, 58(11):1828–1831.

Steiner, H., Revesz, T., Neumann, M., Romig, H., Grim, M. G., Pesold, B., Kretzschmar, H. A., Hardy, J., Holton, J. L., Baumeister, R., Houlden, H., and Haass, C. (2001). A pathogenic presenilin-1 deletion causes abberant A-beta-42 production in the absence of congophilic amyloid plaques. *Journal of Bioliogical Chemistry*, 276(46):7233–7239.

Strachan, T. and Read, A. P. (1999). *Human molecular genetics*. BIOS Scientific Publishers, Oxford, 6th edition.

Subramanian, K., Lemaire, J., Hershey, J. C., Pauly, M. V., Armstrong, K., and Asch, D. A. (2000). Estimating adverse selection costs from genetic testing for breast and ovarian cancer: The case of life insurance. *Journal of Risk and Insurance*, 66:531–550.

Sudbery, P. (2002). *Human Molecular Genetics*. Pearson Education, Prentice Hall, 2nd edition.

Sugiyama, N., Suzuki, K., Matsumura, T., Kawanishi, C., Onishi, H., Yamada, Y., Iseki, E., and Kosaka, K. (1999). A novel missense mutation (G209P) in exon 8

of the presenilin 1 gene in a Japanese family with presenile familial Alzheimer's disease. *Human Mutation*, 14(1):90–93.

Sulkava, R., Wikstrom, J., Aromaa, A., Raitasalo, R., Lehtinen, V., Lahtela, K., and Palo, J. (1985). Prevalence of severe dementia in Finland. *Neurology*, 35:1025–1029.

Taddei, K., Kwok, J. B. J., Kril, J. J., Halliday, G. M., Creasey, H., Hallupp, M., Fisher, C., Brooks, W. S., Chung, C., Andrews, C., Masters, C. L., Schofield, P. R., and Martins, R. N. (1998). Two novel presenilin-1 mutations (Ser169Leu and Pro436Gln) associated with very early onset Alzheimer's disease. *NeuroReport*, 9:3335–3339.

Tanahashi, H., Kawakatsu, S., Kaneko, M., Yamanaka, H., Takahashi, K., and Tabira, T. (1996). Sequence analysis of presenilin-1 gene mutation in Japanese Alzheimer's disease patients. *Neuroscience Letters*, 218:139–141.

Tanahashi, H., Mitsunaga, Y., Takahashi, K., Tasaki, H., Watanabe, S., and Tabira, T. (1995). Missense mutation of S182 gene in Japanese familial Alzheimer's disease. *Lancet*, 346:440.

Taylor, S. D. (1994). Demand for predictive genetic testing for Huntington's disease in Australia, 1987 to 1993. *Medical Journal of Australia*, 161:351–354.

Tedde, A., Forleo, P., Nacmias, B., Piccini, C., Bracco, L., Piacentini, S., and Sorbi, S. (2000). A presenilin-1 mutation (Leu392Pro) in a familial AD kindred with psychiatric symptoms at onset. *Neurology*, 55:1590–1591.

Terreni, L., Valeria, C., Calella, A. M., Gavazzi, A., Alberoni, M., Grimaldi, L. M., Mariani, C., and Forloni, G. (2000). A novel missense mutation (L219F) in exon 8 of the presenilin 1 gene in an Italian family with presenile familial Alzheimer's disease. *Neurobiology of Aging*, 21(Suppl):S176–S177.

Thakker, R. V. (1998). Editorial: Multiple endocrine neoplasia - syndromes of the twentieth century. *Journal of Clinical Endocrinology and Metabolism*, 83(8):2617–2620.

Therneau, T. M. and Grambsch, P. M. (2000). *Modeling Survival Data: Extending the Cox Model*. Springer.

Toogood, A. A., Eng, C., Smith, D. P., Ponder, B. A., and Shalet, S. M. (1995). No mutation at codon 918 of the RET gene in a family with multiple endocrine neoplasia type 2B. *Clinical Endocrinology*, 43(6):759–762.

Tysoe, C., Whittaker, J., Xuereb, J., Cairns, N. J., Cruts, M., van Broeckhoven, C., Wilcock, G., and Rubinsztein, D. C. (1998). A presenilin-1 truncating mutation is present in two cases with autopsy-confirmed early-onset Alzheimer's disease. *American Journal of Human Genetics*, 62:70–76.

van Duijn, C. M., Clayton, D., Chandra, V., Fratiglioni, L., Graves, A. B., Heyman, A., Jorm, A. F., Kokmen, E., Kondo, K., Mortimer, J., Rocca, W. A., Shalat, S. I., Soininen, H., and Hofman, A. (1991a). Familial aggregation of Alzheimer's disease and related disorders: a collaborative re-analysis of case-control studies. *International Journal of Epidemiology*, 20(Suppl 2):S13–S20.

van Duijn, C. M., de Knijff, P., Cruts, M., Wehnert, A., Havekes, L. M., Hofman, A., and Van Broeckhoven, C. (1994). Apolipoprotein e4 allele in a population-based study of early-onset Alzheimer's disease. *Nature Genetics*, 7:74–78.

van Duijn, C. M., Hendriks, L., Cruts, M., Hardy, J. A., Hofman, A., and van Broeckhoven, C. (1991b). Amyloid precursor protein gene mutation in early-onset Alzheimer's disease. *The Lancet*, 337:978.

van Heerden, J. A., Sheps, S. G., Hamberger, B., Sheedy, P. F., Poston, J. G., and ReMine, W. H. (1982). Current status and changing trends. *Surgery*, 91:367–373.

Venables, W. N. and Ripley, B. D. (1999). *Modern Applied Statistics with S-PLUS*. Springer, 3rd edition.

Venter, J. C., Adams, M. D., Myers, E. W., Li, P. W., Mural, R. J., Sutton, G. G., Smith, H. O., Yandell, M., Evans, C. A., Holt, R. A., Gocayne, J. D., Amanatides, P., Ballew, R. M., Huson, D. H., Wortman, J. R., Zhang, Q., Kodira, C. D., Zheng, X. H., Chen, L., Skupski, M., Subramanian, G., Thomas, P. D., Zhang, J., Miklos,

G. L. G., Nelson, C., Broder, S., Clark, A. G., Nadeau, J., McKusick, V. A., Zinder, N., Levine, A. J., Roberts, R. J., Simon, M., Slayman, C., Hunkapiller, M., Bolanos, R., Delcher, A., Dew, I., Fasulo, D., Flanigan, M., Florea, L., Halpern, A., Hannenhalli, S., Kravitz, S., Levy, S., Mobarry, C., Reinert, K., Remington, K., Abu-Threideh, J., Beasley, E., Biddick, K., Bonazzi, V., Brandon, R., Cargill, M., Chandramouliswaran, I., Charlab, R., Chaturvedi, K., Deng, Z., Francesco, V. D., Dunn, P., Eilbeck, K., Evangelista, C., Gabrielian, A. E., Gan, W., Ge, W., Gong, F., Gu, Z., Guan, P., Heiman, T. J., Higgins, M. E., Ji, R.-R., Ke, Z., Ketchum, K. A. Lin, X., Lu, F., Merkulov, G. V., Milshina, N., Moore, H. M., Naik, A. K., Narayan, V. A., Neelam, B., Nusskern, D., Rusch, D. B., Salzberg, S., Shao, W., Shue, B., Sun, J., Wang, Z. Y., Wang, A., Wang, X., Wang, J., Wei, M.-H., Wides, R., Xiao, C., Yan, C., Yao, A., Ye, J., Zhan, M., Zhang, W., Zhang, H., Zhao, Q., Zheng, L., Zhong, F., Zhong, W., Zhu, X. C., Zhao, S., Gilbert, D., Baumhueter, S., Spier, G., Carter, C., Cravchik, A., Woodage, T., Ali, F., An, H., Awe, A., Baldwin, D., Baden, H., Barnstead, M., Barrow, I., Beeson, K., Busam, D., Carver, A., Center, A., ML., C., Curry, L., Danaher, S., Davenport, L., Desilets, R., S., D., Dodson, K., Doup, L., Ferriera, S., Garg, N., Gluecksmann, A., Hart, B., Haynes, J., Haynes, C., C., H., Hladun, S., Hostin, D., Houck, J., Howland, T., C., I., Johnson, J., Kalush, F., Kline, L., Koduru, S., Love, A., Mann, F., May, D., McCawley, S., McIntosh, T., I., M., Moy, M., Moy, L., Murphy, B., Nelson, K., C., P., Pratts, E., Puri, V., Qureshi, H., Reardon, M., Rodriguez, R., YH., R., Romblad, D., Ruhfel, B., R., S., Sitter, C., Smallwood, M., Stewart, E., Strong, R., E., S., Thomas, R., NN., T., Tse, S., Vech, C., Wang, G., Wetter, J., Williams, S., Williams, M., Windsor, S., E., W.-D., Wolfe, K., Zaveri, J., Zaveri, K., JF., A., R., G., MJ., C., KV., S., Karlak, B., Kejariwal, A., Mi, H., Lazareva, B., Hatton, T., Narechania, A., Diemer, K., Muruganujan, A., Guo, N., Sato, S., Bafna, V., Istrail, S., Lippert, R., Schwartz, R., Walenz, B., S., Y., Allen, D., Basu, A., Baxendale, J., Blick, L., M., C., Carnes-Stine, J., Caulk, P., YH., C., Coyne, M., Dahlke, C., Mays, A., Dombroski, M., Donnelly, M., Ely, D., Esparham, S., Fosler, C., Gire, H., Glanowski, S., K., G., Glodek, A., Gorokhov, M., Graham, K., Gropman, B., Harris, M., Heil, J., Henderson, S.,

Hoover, J., D., J., Jordan, C., Jordan, J., Kasha, J., Kagan, L., C., K., Levitsky, A., Lewis, M., Liu, X., Lopez, J., Ma, D., Majoros, W., McDaniel, J., Murphy, S., Newman, M., T., N., Nguyen, N., Nodell, M., Pan, S., Peck, J., M., P., Rowe, W., Sanders, R., Scott, J., Simpson, M., T., S., Sprague, A., Stockwell, T., Turner, R., Venter, E., Wang, M., Wen, M., Wu, D., Wu, M., Xia, A., Zandieh, A., and Zhu, X. (2001). The sequence of the human genome. *Science*, 291(5507):1304–1351.

Verkkoniemi, A., Somer, M., Rinne, J. O., Myllykangas, L., Crook, R., Hardy, J., Viitanen, M., Kalimo, H., and Haltia, M. (2000). Variant Alzheimer's disease with spastic paraparesis: clinical characterization. *Neurology*, 54:1103–1109.

Wallin, G., Bondesson, A. G., Farnebo, L. O., Hallengren, B., Hamberger, B., Jansson, S., Nilsson, O., Nordenskjöld, M., Smeds, S., Svensson, K. A., Wihlborg, O., and Zedenius, J. (2001). Hereditary thyroid cancer can be cured by prophylactic surgery. *Lakartidningen*, 98(25):3024–3028.

Warren, V., Brett, P., Macdonald, A. S., Plumb, R. H., and Read, A. P. (1999). *Genetic tests and future need for long-term care in the UK: report of a Work Group of the Continuing Care Conference Genetic Tests and Long-term Care Study Group*. Continuing Care Conference, London.

Wasco, W., Pettingell, W. P., Jondro, P. D., Schmidt, S. D., Gurubhagavatula, S., Rodes, L., Diblasi, T., Romano, D. M., Guenette, S. Y., Kovacs, D. M., Growdon, J. H., and Tanzi, R. E. (1995). Familial Alzheimer's chromosome 14 mutations. *Nature Medicine*, 1(9):848.

Wekwete, C. T. (2002). *Genetics and Critical Illness Insurance Underwriting: Models for Breast Cancer and Ovarian Cancer and for Coronary Heart Disease*. PhD thesis, Heriot-Watt University.

Wiesner, G. L. and Snow-Bailey, K. (2003). Multiple endocrine neoplasia type 2. *Gene Reviews*, www.geneclinics.org/profiles/men2/.

Wilkie, A. D. (2000). Report by the independent actuary on the application by the Association of British Insurers to the Genetics and Insurance Committee

for approval to use genetic test results for insurance risk assessment — use of Huntington's disease test in life insurance. *Genetics and Insurance Committee, Department of Health*.

Willis, G., Fellows, I. W., and Wimperis, J. Z. (2000). Deaths attributed to haemochromatosis are rare in Britain. *British Medical Journal*, 320:1146.

Wilson, G. N. (2000). *Clinical Genetics: A Short Course*. Wiley-Liss, New York.

Wisniewski, T., Dowjat, W. K., Buxbaum, J. D., Khorkova, O., Efthimiopoulos, S., Kulczycki, J., Lojkowska, W., Weigiel, J., Wisniewski, H. M., and Frangione, B. (1998). A novel Plish presenilin-1 mutation (P117L) is associated with familial Alzheimer's disease and leads to death as early as the age of 28 years. *NeuroReport*, 9:217–221.

Worwood, M. (2001). What is the role of genetic testing in diagnosis of haemochromatosis ? *Annals of Clinical Biochemistry*, 38:3–19.

Yasuda, M., Maeda, K., Hashimoto, M., Yamashita, H., Ikejiri, Y., Bird, T. D., Tanaka, C., and Schellenberg, G. D. (1999). A pedigree with a novel presenilin mutation at a residue that is not conserved in presenilin 2. *Archives of Neurology*, 56:65–69.

Yasuda, M., Maeda, K., Ikejiri, Y., Kawamata, T., Kuroda, S., and Tanaka, C. (1997). A novel missense mutation in the presenilin-1 gene in a familial Alzheimer's disease pedigree with abundant amyloid angiopathy. *Neuroscience Letters*, 232:29–32.

Yasuda, M., Maeda, S., Kawamata, T., Tamaoka, A., Yamamoto, Y., Kuroda, S., Maeda, K., and Tanaka, C. (2000). Novel presenilin-1 mutation with widespread cortical amyloid deposition but limited cerebral amyloid angiopathy. *Journal of Neurology, Neurosurgery and Psychiatry*, 68:220–223.

Younkin, S., Scheuner, D., Song, X., Eckman, C., Citron, M., Suzuki, N., Bird, T. D., Hardy, J., Hutton, M., Lannfelt, L., Levy-Lahad, E., Peskind, E., Poorkaj, P., Schellenberg, G., Tanzi, R., Viitanen, M., Wasco, W., and Selkoe, D. (1996).

The presenilin 1 and 2 mutations linked to familial Alzheimer's disease increase the extracelluar concentration of amyloid β protein (Aβ) ending at Aβ42(43). *Neurobiology of Aging*, 17:S38 Abstract.

Zick, C. D., Smith, K. R., Mayer, R. N., and Botkin, J. R. (2000). Genetic testing, adverse selection, and the demand for life insurance. *American Journal of Medical Genetics*, 93:29–39.

Zimmern, R. (2001). What is genetic information? *Genetics Law Monitor*, 1(5):–13.