Cerebellar ataxia: A clinical and genetic study in South Wales

A thesis submitted in partial fulfilment
of the requirement for the degree of Doctor of Medicine (MD)

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Declaration

This work has not previously been accepted in substance for any degree and is not being concurrently submitted in candidature for any degree.

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Statement 1

This thesis is the result of my own investigations, except where otherwise stated. Other sources are acknowledged by explicit references. A bibliography is appended.

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To Clare, Thomas and James...

Acknowledgements

This work would not have been possible without the help and encouragement of many people. I would like to thank my principal supervisor, Dr. Neil Robertson, for giving me the opportunity to work in full-time research in the first place, for the many invaluable discussions and advice throughout the course of this research, for his helpful comments on the drafts of papers and this thesis, and for his encouragement, generosity and support throughout my time in research — it has been a most enjoyable, informative and rewarding experience. Dr. Huw Morris as my co-supervisor has been a constant source of support and encouragement, and has been the main facilitator in the collaborative effort to organise and perform the genetic analysis that underpins much of this work. I thank them both for their reviews and comments — their suggestions and corrections have resulted in a dramatically improved work. I must take responsibility for any remaining errors.

I would like to thank my colleagues from the Department of Psychological Medicine, Cardiff University, including Dr. Nigel Williams and Dr. Elisa Majounie. They arranged and performed all of the genetic analyses — the project would not have been possible without them. Dr. Jeremy Hobart (Peninsula Medical School, Plymouth) has provided advice and support on the assessment and evaluation of rating scales, and his comments on this material were invaluable. I wish to thank my colleagues within the Departments of Neurology in Cardiff and Swansea for their assistance in patient recruitment and referral, and I must extend my gratitude to the many patients and families that have generously given their time and resources altruistically to support this work.

This project was initiated in 1999 by Professor Mark Wiles and Dr. Jenny Thomas who developed the first ascertainment, recruitment and assessment protocols, had them accepted by relevant research and ethics organisations, and fur-

thermore saw seven patients as part of a pilot study. The project was subsequently taken on by Dr. Neil Robertson and Dr. Mustapha Muzaimi who invested much time and effort in successfully extending the project to the wider Cardiff region, visiting a total of 78 patients together with the creation of a serum and DNA bank. The work involved in getting this project started should not be underestimated, and I owe a debt of gratitude to all involved in those early days. While the ascertainment and assessment protocols have been subsequently updated and refashioned to focus on contemporary research priorities, I have, where possible, included historic clinical data in addition to data acquired at new patient visits to facilitate analysis of natural history and disease progression in this population-based sample. Such inclusion has made analysis more complex as changes in investigator, different data collection protocols and missing data must be included as potential sources of bias requiring more specialist statistical methods, but the advantages of including such data outweigh any disadvantages. Indeed, while I have made every effort to re-visit all those patients seen previously, several patients decided they did not wish to continue participation, others could not be traced and eleven patients had died (10 from Dr. Muzaimi's group and one from Dr. Thomas'). In these cases, I have used historic data in analysis and so must thank my colleagues for their permission to use their data in this way.

I must also give credit to the significant effort of others in creating the open source software used in the creation of this work. Sophisticated and powerful typesetting facilities were provided by LaTeX 2$_\varepsilon$ which made the creation of a long complex document as straightforward and efficient as possible. All statistical analysis was performed using R[104] (`http://www.r-project.org/`). This is an independent open-source implementation of the S language, powerful and flexible statistical software with excellent graphical facilities. The integration of R with LaTeX 2$_\varepsilon$ was possible using Sweave providing typeset text intermixed with statistical analysis. Indeed, this entire project is dynamically generated with all figures and charts and most tables generated directly and algorithmically from data held in a database so that all analyses are based on the most contemporary data

available. Two different sophisticated relational database systems were used with PostgreSQL (`http://www.postgresql.org`) acting as the main data repository with Filemaker (`http://www.filemaker.com`) used for data entry and project/patient management. Family pedigree charts are generated dynamically using Madeline V2.0[142] directly from the database and flow charts and results of cluster analysis are drawn dynamically using Graphviz (`http://www.graphviz.org/`). Map data are used with permission of the relevant copyright holder(s) with patient locations added using conversion of postcodes to ordnance survey grid references. Throughout the project, TextMate (`http://www.macromates.com`) has supported my writing; it is a superb and effective text editor. All project work, documentation and data has been held in a versioned repository using Subversion (`http://subversion.tigris.org`) allowing every change and every piece of text to be tracked and logged.

<div align="center">*</div>

Finally, I must give special thanks to my wife Clare. None of this work would have been possible without her many sacrifices — Clare has supported me throughout this research and put up with being husband-less for countless weekends and late-nights!

Preface

"Spinocerebellar degenerations, pyramidal tract degenerations, 'system' degenerations and such like constitute a large field of disorders, the study of which, in the Editors' view, has not progressed much beyond the descriptive level... Perhaps only a neurologist can experience those particular feelings of inadequacy which manifest themselves when one is called upon to assume the care of a patient with amyotrophic lateral sclerosis, or progressive spinal muscular atrophy, Strümpell-Lorrain's disease[1], bulbar paralysis, or olivopontocerebellar degeneration."

P.J. Vinken, G.W.Bruyn and J.M.B.V de Jong, 1975

It is illuminating to read the foreword to volumes 21 and 22 of Vinken and Bruyn's *Handbook of Clinical Neurology*.[124] The text from 1975 is almost as applicable today as it was then, despite the great advances in molecular medicine. Our knowledge of the neurodegenerative disorders has increased dramatically, and yet we remain with only a cursory glimpse into the underlying pathogenesis of this complex and burdensome group of conditions.

This work documents a study of cerebellar ataxia in South Wales, a well-defined geographical region of the United Kingdom. We have used systematic and intensive ascertainment to recruit patients from general practitioners, neurologists and geneticists to derive contemporary epidemiological estimates. Each patient was assessed on multiple occasions to derive detailed cross-sectional and longitudinal estimates of important disease parameters with DNA and serum samples taken to create a valuable population-based resource for current and future

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[1]Now better known as Hereditary Spastic Paraplegia

work. To take advantage of this resource, we have forged close collaborative links with other researchers from institutions across the United Kingdom.

Chapter 1 introduces the fundamental concepts involved in the study of this heterogeneous and variable condition with an overview of the range of disorders that may cause cerebellar ataxia in clinical practice.

Chapter 2 describes the materials and methods common to all projects within this work and documents case ascertainment and data collection and storage with detailed descriptions of core epidemiological and statistical methods.

The systematic genetic investigation of patients with cerebellar ataxia in South Wales is documented in Chapter 3 together with detailed epidemiological estimates of disease prevalence for different disorders within this region. We highlight the wide geographical and ethnic variability observed in similar studies of different populations and investigate the possible causes of these differences by looking at high-normal allele frequencies in the background population in Wales. The significance of high-normal allele frequencies is investigated further in Chapter 4, in which we perform a case-control study of sporadic ataxia to determine whether high-normal repeats are a risk factor for the development of ataxia.

During this research we were surprised to identify four separate families with dentatorubral pallidoluysian atrophy (DRPLA), a disease thought to be found "almost exclusively among the Japanese".[145] Chapter 5 details the clinical characteristics of the families and offers a number of hypotheses to explain the origins of this disorder in the UK. Chapter 6 is a detailed systematic review of non-Asian cases of DRPLA, and includes data from our local cases together with published case reports from the literature.

Chapter 7 documents the clinical phenotype of patients with cerebellar ataxia from South Wales with particular emphasis on important clinical features and natural history. We have used a number of standardised questionnaires and assessment tools during this research, as outlined in Chapter 2. In Chapter 8 we assess the psychometric properties of the ataxia rating scale: International Cooperative Ataxia Rating Scale (ICARS).

Chapter 9 attempts to formulate a rational diagnostic strategy for the investigation of patients with chronic progressive cerebellar ataxia and finally, Chapter 10 provides a high-level summary together with conclusions drawn from all relevant

chapters and highlights opportunities for future work.

Appendix A documents the range of published abstracts, presentations and papers that have resulted from this work. Much of the material from Chapters 1 and 11 have been published as a review article (Appendix A.1.1). The work and data from Chapter 3 has been submitted for publication (Appendix A.1.3). The data presented in Chapter 4 has been published (Appendix A.1.4) but this chapter includes an expanded analysis. The material from Chapters 5 and 6 have been presented and published at a wide variety of meetings (see Appendices A.1.2, A.2.2 and A.2.4) and have won a national prize (Sir Charles Symonds Prize: Best Platform Presentation at the ABN). Chapter 7 has been submitted for publication (Appendix A.1.5), presented at a national meeting (Appendix A.2.1) with earlier data presented at a regional neuroscience research meeting (Appendix A.2.3). Material from Chapter 8 is to be submitted for publication in due course.

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"To call in the statistician after the experiment is done may be no more than asking him to perform a post-mortem examination: he may be able to say what the experiment died of."

Sir Ronald Aylmer Fisher, 1938

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Abbreviations

ABN   Association of British Neurologists
ADCA   autosomal dominant cerebellar ataxia
ADL   activities of daily living
ANOVA   analysis of variance

CAG   CAG; codon encoding glutamine
CNS   central nervous system

DNA   deoxyribonucleic acid
DRPLA   dentatorubral pallidoluysian atrophy

EA   episodic ataxia
EOCA   early-onset cerebellar ataxia

FA   Friedreich's ataxia
FAIS   Freidreich's ataxia impact scale
FHM   familial hemiplegia migraine
FXTAS   fragile-X associated tremor ataxia syndrome

GP   general practitioner

HD   Huntington's disease
HES   hospital episode statistics
HRS   Haw River syndrome

ICARS	International Cooperative Ataxia Rating Scale
ICD	International classification of diseases
LHB	local health board
LOCA	late-onset cerebellar ataxia
LOFA	late-onset Friedreich's ataxia
LREC	local research and ethics committee
MERRF	myoclonus epilepsy with ragged-red fibres
MJD	Machado-Joseph disease
MMSE	mini-mental state examination
MPI	master patient index
MS	multiple sclerosis
MSA	multiple system atrophy
NHS	national health service
NHSAR	NHS administrative register
NSTS	NHS strategic tracing service
PCR	polymerase chain reaction
PEDW	patient episode database for Wales
SCA	spinocerebellar ataxia
SD	standard deviation
SF-36	short-form 36 item questionnaire
SNP	single nucleotide polymorphism
SQL	structured query language
TNR	trinucleotide repeat
UK	United Kingdom
VLOFA	very-late onset Friedreich's ataxia

Abstract

We have performed a population-based cross-sectional and longitudinal epidemiological survey in South Wales to systematically investigate patients with late-onset cerebellar ataxia (LOCA) for known heritable causes. Furthermore, we have investigated potential causes of geographical and ethnic variability of disease prevalence, examined genetic risk factors of sporadic disease, reviewed clinical phenotypes and natural history and assessed methods of rating disease severity.

The minimum prevalence of LOCA is 11.33 per 100,000 and we have identified SCA6, DRPLA and Friedreich's ataxia to be important genetic causes of ataxia within this region. There was a significant difference between Welsh and Japanese control chromosomes at common loci and in a pattern that mirrors the relative importance of different expansions when Asian and Caucasian series are compared suggesting that there may some evidence of an association between disease prevalence and high-normal repeats. However, there was not a systematic difference between Caucasian series, suggesting other factors, such as founder effects and ascertainment bias are more important.

Patients with LOCA commonly demonstrate significant disease progression with time, becoming decreasingly ambulant and increasingly dependent. Furthermore, sporadic LOCA is clinically heterogeneous with evidence of a subset of patients with defined extra-cerebellar symptoms and signs who, despite having a shorter disease duration, are less ambulant, more disabled and have a significantly worse prognosis. Our work on ICARS suggests that total ICARS score satisfied fundamental psychometric criteria with adequate scaling assumptions, targeting and reliability but highlighted important deficiencies in ICARS subscales, with particular problems with assessments of speech and ocular ataxia. Finally, while the identification of DRPLA was unexpected, we have demonstrated the broad clinical phenotype of DRPLA and therefore suggest that it should be considered in the differential diagnosis of a wide spectrum of neurological disease especially if there is a dominant family history of dementia or movement disorders.

CHAPTER 1

Introduction

1.1   Cerebellar ataxia

Ataxia is a term used to describe a condition characterised by disordered or inco-ordinate movement and is commonly caused by diseases affecting the cerebellum and its connections within the central nervous system (CNS). Ataxia caused by cerebellar dysfunction is a dominant feature in a wide spectrum of overlapping heterogeneous clinical disorders[51] and may also be mimicked by a variety of isolated or combined neurological deficits including loss of muscular strength, altered tone, diminished sensation or the intrusion of involuntary movements. Ataxia may present either as a pure cerebellar syndrome or associated with significant cognitive, pyramidal, extra-pyramidal, sensory and autonomic dysfunction, and can also be the presenting feature of a more widespread neurodegenerative disorder. It is therefore not surprising that the investigation of cerebellar ataxia often poses considerable diagnostic challenges for the treating physician, and has been made increasingly complex by advances in molecular genetics and immunology that allow access to a bewildering array of novel investigations.

Diseases resulting in cerebellar ataxia are commonly classified as hereditary, symptomatic or idiopathic sporadic. For patients with an acute or sub-acute disease onset, initial investigations will usually readily identify a symptomatic cause (Table 9.1, page 181). However, patients with chronic progressive LOCA frequently pose the greatest diagnostic challenge despite recent rapid advances in molecular genetics leading to an increasing number of available diagnostic investigations. In particular, genetic testing is now routinely available for many of the spinocerebellar ataxia (SCA) mutations (Table 1.1) but these disorders frequently have overlapping clinical features resulting in considerable practical diagnostic difficulties for clinicians and, despite extensive investigation, many families and a majority of sporadic patients remain undiagnosed.

1.1.1   Extent of the problem

Cerebellar ataxia is not rare: Hospital episode statistics (HES) for England and Wales (2005/6) suggest admission figures similar to disorders such as myasthenia gravis, idiopathic intracranial hypertension and bacterial meningitis, and three

SCA subtype	Gene/protein	Phenotype	Mutation
Diagnostic test commonly available in clinical practice			
SCA1	ATXN1/Ataxin 1	ADCA I	CAG repeat
SCA2	ATXN2/Ataxin 2	ADCA I	CAG repeat
SCA3	ATXN3/Ataxin 3	ADCA I	CAG repeat
SCA6	CACNA1A/CACNA1A	ADCA III	CAG repeat
SCA7	ATXN7/Ataxin 7	ADCA II	CAG repeat
SCA12	PPP2R2B/PPP2R2B	ADCA I	CAG repeat
SCA17	TBP/TBP	ADCA I	CAG repeat
DRPLA	ATN1/Atrophin 1	ADCA I	CAG repeat
Test not available routinely†			
SCA5	SPTBN2/β-III spectrin	ADCA III	Deletion/missense
SCA8	KLHLIAS/Kelch-like 1	ADCA I	CTG repeat
SCA10	ATXN10/Ataxin 10	ADCA I	ATTCT repeat
SCA11	TTBK2 exon 12[55]	ADCA III	Insertion
SCA13	KCNC3/KCNC3	ADCA I	Missense
SCA14	PRKCG/PRKCG-γ	ADCA III	Missense
SCA27	FGF14/FGF14	ADCA I	Missense
EA1	KCNA1/K$^+$ channel	EA	Missense
EA2	CACNA1A/PQ-type Ca$^{2+}\alpha$-1A	EA	Missense
EA5	CACNB4/Ca^{2+} channel β4	EA	Missense
EA6	SCL1A3	EA/Migraine	Missense
Gene not yet identified or published			

ADCA I:
    SCA15, SCA16 and SCA26.
ADCA III:
    SCA4, SCA18, SCA19, SCA20, SCA21, SCA22,
    SCA23, SCA24, SCA25, SCA27 and SCA28
Episodic:
    EA3, EA4

Table 1.1: Summary of known SCA mutations. Adapted from [27]. The designation SCA9 is reserved and has not been used. †These tests may be available in research laboratories.

times that of Huntington's disease (HD) (`http://www.hesonline.nhs.uk`). However, these statistics are likely to significantly underestimate the true extent of the problem as cerebellar disease frequently occurs as a feature of other primary neurological disorders such as multiple sclerosis (MS), stroke and CNS

tumours. Accurate epidemiological statistics for incidence and prevalence are scarce and highly variable largely as a result of ascertainment bias, differing inclusion criteria, variable aetiological classification and founder effects. Contemporary estimates of the prevalence of autosomal dominant cerebellar ataxia (ADCA) in the UK lie between 0.31–8.0 /100,000[21,66,86] and 1.2–41.0/100,000 worldwide.[9,95,98]

Prevalence estimates for sporadic idiopathic LOCA are limited, but a minimum prevalence of 10.8/100,000 has been suggested for the UK.[86] These data suggest there are at least 10,000 cases of familial and sporadic LOCA in the UK alone, with the majority of both familial and sporadic cases having no defined aetiology.

1.2 Genetic causes of ataxia

1.2.1 Classification

Over twenty-eight distinct loci are considered responsible for dominant spinocerebellar ataxia (Table 1.1) and the most common of these are trinucleotide repeat (TNR) disorders. Many are caused by CAG repeats coding for glutamine that result in an abnormally long polyglutamine (polyQ) tract and are characterised macroscopically by progressive neurodegeneration in distinct brain areas and microscopically by the presence of polyQ-containing protein aggregates forming cellular inclusions.[171] In addition, TNR disorders are characterised by meiotic instability resulting in intergenerational expansion and clear genotype-phenotype correlations in which longer repeat lengths are associated with more severe disease. These factors result in the phenomenon of anticipation, in which severity of disease increases for each generation. Repeat lengths at SCA loci can be widely variable but there is usually a pathogenic threshold below which patients are either asymptomatic (normal) or at risk of repeat length instability (termed intermediate-length alleles); the latter may result in affected offspring and complicates genetic counselling. In addition, it is suggested that high-normal repeat lengths may act as a reservoir for new expansion and that this may account for the widely observed geographical and ethnic variability in disease prevalence.[137] Individuals with re-

peat lengths above a pathogenic threshold will usually manifest clinical symptoms and signs, although variable penetrance and a more elderly age at onset may also complicate pre-symptomatic counselling for expansions at some loci.

Analysis of the common spinocerebellar mutations results in a positive identification in 39–64% of dominant and 11-38% of non-dominant families, but only 1–19% of sporadic late-onset cases.[62,77,103,120,137] Remaining patients are considered "idiopathic sporadic" but there is considerable overlap with other neurodegenerative disorders and within five years 29–33% of cases will meet diagnostic criteria for possible or probable multiple system atrophy (MSA).[1,35]

A clinical classification of ADCA was introduced by Harding in 1982,[49] with a division into ADCA I,II and III based on the presence of extracerebellar features, a pigmentary retinopathy or a pure cerebellar syndrome respectively. Whilst this classification is still useful in clinical characterisation and can help with an increasing choice of diagnostic tests, it has now been superseded by a genetic classification based on the underlying genetic disorder (Table 1.1). While most SCA mutations identified to date are dynamic repeat expansions, others are either untranslated repeats, deletions or missense mutations. The five main pathogenetic mechanisms of inherited ataxias are abnormal protein folding (e.g., SCA1), mitochondrial (e.g., Friedreich's ataxia), defective DNA repair (e.g., ataxia telangiectasia), channelopathies (e.g., EA1) and metabolic (e.g., inherited vitamin E deficiency).[24] Individual SCA-subtypes are difficult to distinguish clinically because of marked phenotypic variability and overlap.

SCA1

SCA1 is described as a highly variable pancerebellar syndrome with ataxia of gait, stance and limbs.[118] Patients frequently demonstrate dysarthria together with gaze-evoked nystagmus and broken smooth ocular pursuit and may later develop slow saccades, ophthalmoplegia, pyramidal signs and choreiform movements. The CAG repeat was first described in 1993.[96]

SCA2

Slow saccades and depressed or absent reflexes are thought to distinguish SCA2 from SCA1 and SCA3,[37] with electrophysiological studies demonstrating an axonal neuropathy with reduced sensory action potentials and evidence of denervation.

SCA3

SCA3, also known as Machado-Joseph disease (MJD), is the most frequent identified SCA subtype in most studies (Chapter 1.2.2). The clinical phenotype is highly variable with a combination of cerebellar, pyramidal and extrapyramidal features. Like other SCA subtypes, the phenotype is also dependent on disease duration with ophthalmoplegia, amyotrophy, swallowing and sphincter disturbance evolving with time.[28] Pseudo-exophthalmos, faciolingual myokymia and dystonia were considered characteristic of SCA3 but are now known to be present in other disorders.[118] Sleep disturbance and restless legs have subsequently been described.[119]

SCA6

SCA6 is considered a "pure" cerebellar ataxia with few extrapyramidal features and usually an older age at onset than other SCA subtypes with a slow progressive disease course (ADCA III).[116] SCA6 is allelic to both EA-2 (episodic ataxia type 2) and familial hemiplegia migraine (FHM) but is associated with a repeat expansion rather than a point mutation.[34] However, occasionally episodic symptoms are described together with some mild extracerebellar features, such as a peripheral neuropathy.

SCA7

SCA7 is now known to be the predominant underlying molecular defect in most cases of ADCA II, although at least one family has been reported with a similar clinical phenotype without the SCA7 expansion.[38] It is characterised by cerebellar ataxia and visual loss caused by pigmentary macular degeneration. The first

sign of retinal disease is dyschromatopsia or reduced central visual acuity[118] and while visual dysfunction can precede the onset of ataxia, occasionally patients may be ataxic for up to twenty years before manifesting visual symptoms and signs.[154] In addition, SCA7 is frequently associated with marked anticipation that can result in apparently sporadic disease with a child manifesting the disease before the parent.[127]

SCA8

SCA8 was the first dominant ataxia to be identified that was caused by a transcribed but untranslated CTG repeat and is described as a relatively pure, slowly progressive cerebellar ataxia.[70,84] However, there has been much subsequent controversy with markedly reduced penetrance described even in the original families.[84] Indeed, further study has identified SCA8 expansions in apparently unaffected control populations,[167] raising doubt on the utility of diagnostic testing and advising extreme caution in performing and interpreting results for presymptomatic patients.

SCA10

SCA10 is described in Mexican families and characterised by cerebellar ataxia and seizures linked to a pentanucleotide (ATTCT) repeat on chromosome 22.[78] There have been subsequent reports from Brazil,[105] and is commonly assumed to be principally restricted to these populations after limited systematic surveys from other regions.[11,110]

SCA12

SCA12 is a rare cause of cerebellar ataxia with a prominent upper limb tremor usually described with or without head tremor.[53]

SCA17

First described in 1999,[68] SCA17 is characterised by ataxia together with a HD-like phenotype of dementia, dystonia and chorea.[4,129]

DRPLA

DRPLA is a rare, autosomal dominant, clinically heterogeneous neurodegenerative disorder characterised clinically by a variable combination of progressive dementia, ataxia, chorea, myoclonus, epilepsy and psychiatric disturbance and pathologically by combined degeneration of dentatorubral and pallidoluysian systems. DRPLA was first described in 1946 in a brother and sister from Belgium with dementia, ataxia and chorea and more completely defined as a disease entity in 1958 in a Yugloslavian man with ataxia, chorea, dystonia and characteristic pathological findings.[125,141] Despite these early European reports, DRPLA has since been thought to have a marked ethnic predilection with reports primarily from Japan highlighting the broad clinical variability and familial recurrence and subsequently demonstrating the underlying molecular defect.[57,67,89,91,135,136] The disease is caused by a $(CAG)_n$ expansion in *atrophin-1* (ATN1) on chromosome 12p13.31 and is characterised by intergenerational instability and a clear correlation between age of onset and repeat length.[67,169]

However since diagnostic molecular testing has become widely available, there have been reports of affected families from outside Japan suggesting DRPLA may not be as geographically restricted as previously thought. Estimates of disease frequency are limited, but DRPLA is commonly tested as part of the investigation of families with dominantly inherited SCA and in patients with a HD-like phenotype and these data highlight the wide regional variability of genetic aetiologies in these groups of patients (Figure 1.1). In Japan the estimated population prevalence of DRPLA is 0.2–0.7 per 100,000[59] where it accounts for 13.9% of families with dominant ataxia.[77,90,94,137,159] DRPLA accounts for only 0.4% of dominant ataxia in European series in which SCA1, SCA2 and SCA7 are relatively more common.[6,11,32,62,72,103,122] No comparable prevalence estimates from non-Asian series are available but between 1989 and 2007, 27 families have been reported in published literature.[31] In the UK, 12 families have been described to date comprising 48 individuals with the majority being isolated case series or reports, but two families were identified as part of a laboratory based audit of generic SCA requests and one after molecular re-investigation of 115 families with a HD-like phenotype.[19,72]

Our studies describing the clinical and genetic features of DRPLA in Wales and non-Asian series are described in Chapters 5 and 6

FA

Friedreich's ataxia (FA), the commonest genetic cause of ataxia, is an autosomal recessive disease with an onset usually below the age of 25.[47,117] FA was first described in 1863 by Nicholaus Friedreich and is typically associated with progressive gait and limb ataxia with dysarthria, loss of position and vibration sensation, absent deep tendon reflexes and pathological extensor plantar responses.[47] In addition, patients may have hypertrophic cardiomyopathy, diabetes mellitus, optic atrophy, deafness and skeletal deformities such as scoliosis and pes cavus.[117] FA is commonly caused by a homozygous expanded GAA TNR in the frataxin gene with such expansion causing inhibition of frataxin expression, although rarely, patients may be compound heterozygotes for expansions and deleterious point mutations.[15] In common with the dominant trinucleotide disorders, there is a correlation between TNR length and severity of disease.

Since the identification of the underlying molecular defect, it is now known that the clinical spectrum is broader than that defined by classical criteria, and includes patients with disease onset over the age of 25 with retained tendon reflexes.[117] Indeed, designations such as late-onset Friedreich's ataxia (LOFA) and very-late onset Friedreich's ataxia (VLOFA) are now used to describe patients with an atypical age at onset, frequently with a less aggressive disease course and fewer extracerebellar complications.[81,97]

FXTAS

Fragile-X associated tremor ataxia syndrome (FXTAS) is caused by a premutation in the *FMR1* gene and was first described in 2001 in five elderly men.[46] Initially thought to affect only men, it has subsequently been described in women albeit in a less severe form.[45] It is characterised by an intention tremor with gait ataxia together with additional features such as parkinsonism, dementia, neuropathy and autonomic failure.[7]

1.2.2   Geographical and ethnic variability

While there are many inherited causes of ataxia, formulation of a rational diagnostic strategy is complicated by marked variation in the relative importance of these disorders in different populations (Figure 1.1 and Tables 3.5 and 3.6 — see page 59). However, most data are limited to clinic or laboratory based samples which may not be representative of the indigenous population and direct comparison between studies is complicated by variable inclusion criteria and different investigative panels. The majority of studies have included analysis of SCA1,2,3,6 and DRPLA but analysis of rare, controversial or more recently elucidated loci has been variable and in particular the significance of SCA8, SCA10, SCA12 and SCA17 in clinical practice remains unclear. Notwithstanding these limitations, most studies confirm SCA3 as the most prevalent cause of dominant ataxia worldwide, with other loci demonstrating greater variability (Figures 1.1, 1.2 and 1.3).

Figure 1.1 appears to demonstrate a clear difference between Asian and European series. However, closer inspection of individual study frequencies highlights a wide variability, even within individual countries (Figures 1.2 and 1.3). Indeed, the number of series from Japan potentially skews the aggregated Asian results in favour of Japanese populations (Table 3.5, page 59). Despite such restrictions, there appear to be systematic differences between series. For instance, in most Asian families the most important SCA mutations are SCA3 (32.5% range 5.1–48.2%), SCA6 (13.6% range 0–25.5%) and DRPLA (11.2% range 0–20.5%) with SCA2 relatively infrequent (6% range 0–36.8%). SCA3 is also common in Europe (18% range 0–84.2%) along with SCA2 (20.2% range 2–47.4%) but SCA6 and DRPLA are much less important (7.7% range 1.1–22.1 and 0.4% range 0–1.4% respectively). SCA2 is most important in Indian populations (28.4% range 25.6–44.4%). The proportion of families without a confirmed molecular diagnosis is also highly variable (12.2–86.4%).[37,72] Undiagnosed familial ataxia is more common in European (58.4%, range 11.5–86.4%) compared to Asian (28.4%, range 5.3–61.5%) series.

In addition, SCA mutations account for only 1.7–18.5% of sporadic idiopathic cases in reported series.[103,120] Additional diagnostic possibilities in sporadic disease include FA and FXTAS. FA accounted for 8.1, 3.2 and 1.7% of sporadic
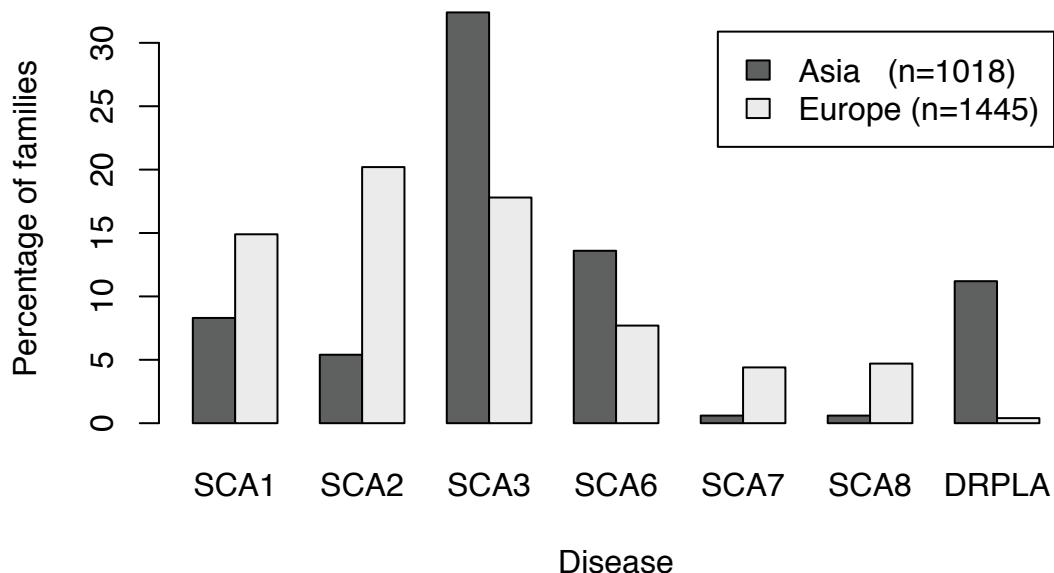
Figure 1.1: Aggregated data showing ethnic differences in SCA subtype frequency among families with ADCA. Data from Table 3.5.

ataxia in German, English and Spanish series respectively.[72,103,120] The significance of FXTAS in chronic progressive LOCA is unclear, but it is suggested that it may account for 3.6–4.2% of sporadic ataxia in male patients over the age of 50 years.[12,147]

The explanation for the widely variable distribution of disease causing expansions remains unclear. In some cases, there is a clear founder effect, such as that seen for SCA3 in Portuguese populations,[123] but it is also important to consider whether such variability reflects genuine differences in the risk of disease arising in a population. Repeat length polymorphism in unaffected control populations is variable and dependent on the population under study, and as such, may offer an explanation for the differences in pathogenic repeat expansion frequency. High-normal repeats in the background indigenous population may act as a reservoir for novel expansions and if so, an association might exist between
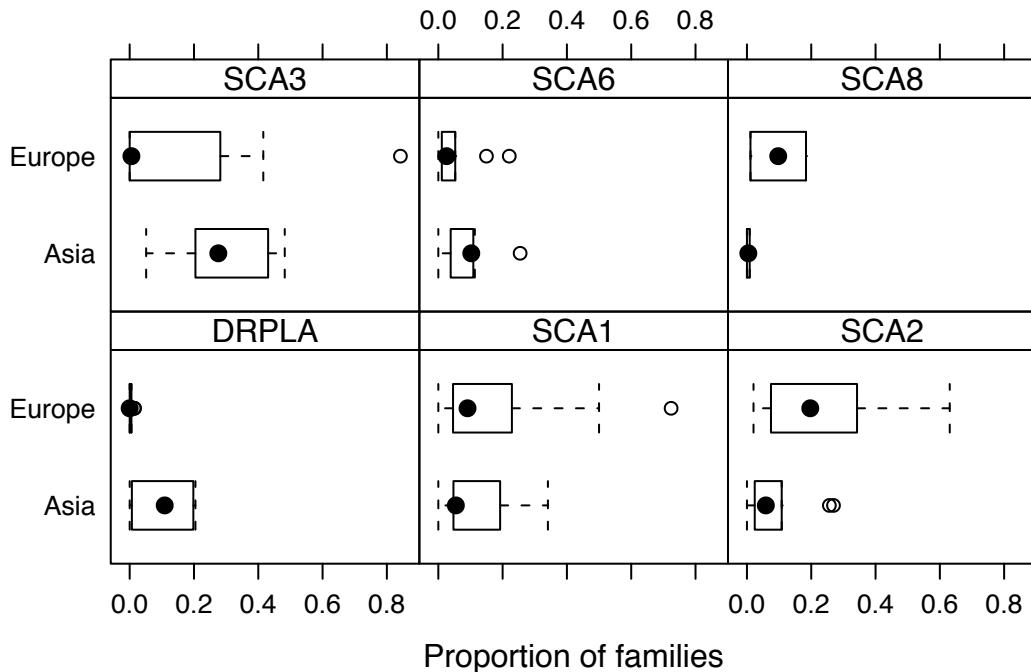
Figure 1.2: Wide variability in SCA subtype frequency among families with ADCA, grouped by region. Data from Table 3.5.

the distribution of high-normal repeats and disease prevalence within that population.[137] There have been similar studies demonstrating such an association in Huntington's disease and myotonic dystrophy,[60,128] but there are conflicting data regarding dominant ataxia and no equivalent data from the United Kingdom (UK).[62,109,137] However, study of LOCA is further complicated by ascertainment bias in which patients are commonly recruited from highly selected clinic-based cohorts. In such studies, hereditary ataxias and those with more severe disease tend to be over-represented compared to population-based or national studies and such systematic bias may account for the widely observed variability in prevalence of different inherited disorders.

The systematic genetic investigation of patients with LOCA from South Wales are described in Chapter 3.
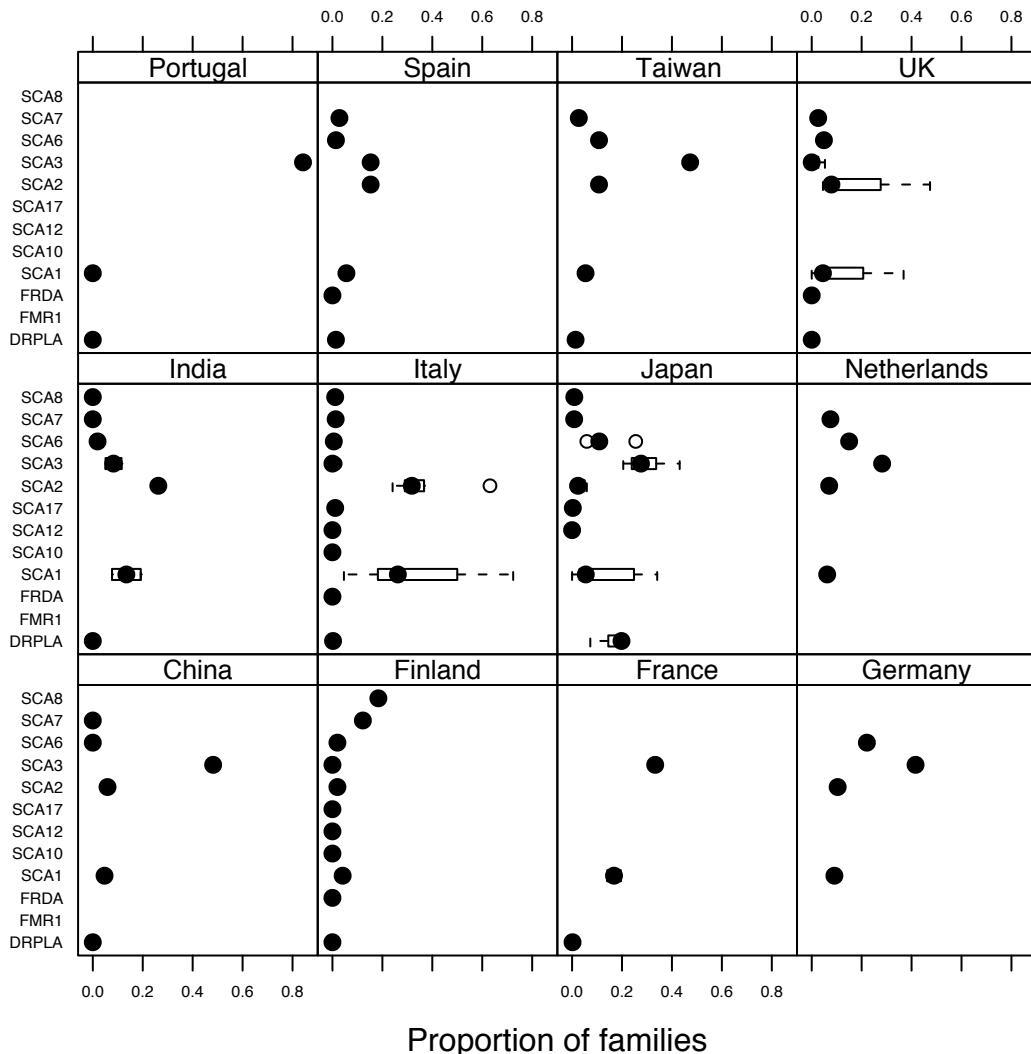
Figure 1.3: Variability in SCA subtype frequency among families with ADCA, grouped by country. Data from Table 3.5. Boxplots are shown for countries in which there have been multiple surveys.

1.3 Sporadic ataxia

Chronic progressive LOCA may result from a wide spectrum of overlapping heterogeneous inherited and sporadic clinical disorders. Such overlap has led to historical difficulties with clinical characterisation and classification[50,51] and while

the nosology of inherited ataxias has been transformed by advances in molecular genetics,[24,27] the classification of sporadic disease remains problematic resulting in difficulties for both researchers and clinicians. Indeed, while hereditary ataxias are well-described in the literature, the investigation and study of sporadic disease is traditionally neglected and likely under-reported.[48]

The term "idiopathic" LOCA was first used by Harding in 1981[48] to describe patients with sporadic adult-onset cerebellar ataxia of unknown aetiology specifically excluding those patients with a symptomatic cause, such as chronic alcoholism, remote malignancy or vitamin deficiency (Table 9.1). However, patients with LOCA are clinically, radiologically and pathologically heterogeneous[1,65] and longitudinal follow-up may subsequently identify a previously neglected symptomatic cause, or confirm evolving clinical features suggesting an alternative neurodegenerative diagnosis, such as MSA. The evolution of clinical symptoms and signs with time commonly results in difficulties for both clinical practice and research studies. It is estimated that up to a quarter of patients presenting with sporadic cerebellar ataxia will subsequently develop parkinsonism or autonomic failure compatible with a diagnosis of MSA within five years of disease onset, and such transition carries a poor prognosis.[35] The clinical features and natural history of patients with LOCA from South Wales are described in Chapter 7.

It is unclear whether there are specific genetic susceptibility risk factors for the development of apparently idiopathic sporadic cerebellar ataxia, and we have undertaken a case-control study to examine repeat length polymorphism comparing affected patients and controls (Chapter 4).

1.3.1 Multiple system atrophy

MSA, previously known as striatonigral degeneration, olivopontocerebellar atrophy and Shy-Drager syndrome, is a synucleinopathy characterised by autonomic failure, parkinsonism, cerebellar ataxia and pyramidal signs in any combination.[163] Despite the widely variable clinical features, two main clinical presentations are described.[162] Most commonly (80%) patients present with predominantly extrapyramidal features ("MSA-P") while the remainder present with cerebellar ataxia ("MSA-C"). However, previous literature has predominantly focused

Features / criteria
Autonomic features
1. Orthostatic hypotension ($\geq$ 20mmHg systolic, $\geq$ 10mmHg diastolic)
2. Urinary incontinence or incomplete bladder emptying
Autonomic criterion
Orthostatic fall in blood pressure ($\geq$ 30mmHg systolic or $\geq$ 15mmHg diastolic) or urinary incontinence (accompanied by erectile dysfunction in men)
Parkinsonian features
1. Bradykinesia
2. Rigidity
3. Postural instability
4. Tremor (postural or resting)
Parkinsonian criterion
Bradykinesia plus at least one of items 2–4
Cerebellar features
1. Gait ataxia
2. Ataxic dysarthria
3. Limb ataxia
4. Sustained gaze-evoked nystagmus
Cerebellar criterion
Gait ataxia plus at least one of items 2–4

Diagnostic categories
Possible MSA
one criterion *plus* two features from separate other domains (when criterion is parkinsonism, a poor levodopa response qualifies as one feature)
Probable MSA
criterion for autonomic failure *plus* poorly levodopa responsive parkinsonism *or* cerebellar dysfunction
Definite MSA
pathologically confirmed by the presence of a high density of glial cytoplasmic inclusions in association with a combination of degenerative changes in the nigrostriatal and olivopontocerebellar pathways.

Table 1.2: Diagnostic features, criterion and categories for MSA. Reproduced and adapted from Gilman, 1999.[36]

on patients with MSA-P, and indeed, usually included patients in the later stages of disease. Such studies have suggested that 29–33% of patients with LOCA and 8% of patients with parkinsonism will eventually develop MSA.[1,35,163] The diagnostic features, criterion and categories are shown in Table 1.2.

1.4 Measurement of ataxia severity

The ICARS was published in 1997 with the long-term goal of supporting double-blind controlled trials for treatments of ataxia.[144] Since that time there have been several studies investigating a range of fundamental psychometric properties of ICARS in a variety of ataxia disorders which have demonstrated high intra- and inter-rata reliability together with adequate internal consistency.[16,23,113,114,133,140] ICARS consists of four subscales (posture and gait disturbance, score 0–34; kinetic functioning, score 0–52; speech disturbance, score 0–8 and oculomotor function, score 0–6) which together make a total score of 100 points. However, several investigators have questioned this division suggesting that subscale totals do not fulfil essential psychometric criteria invalidating the use and reporting of these totals.[16,113] In addition, there are limited data measuring the ability of ICARS to assess change, despite its use in a number of interventional trials,[8,82,102] with only two reports investigating ICARS in natural history studies of Friedreich's ataxia.[30,107]

Chapter 8 details our investigation of ICARS with an evaluation of fundamental psychometric properties including correlates to detailed clinical characteristics and indicators of disease progression and disability together with an analysis of the responsiveness of the ICARS to detect clinically important change.

1.5 Study objectives

The principal aims of this study are

- Perform a population-based epidemiological survey of South East Wales to create a contemporary centralised ataxia register (Chapter 2).

- Systematically investigate patients with sporadic and familial disease for known expansions to determine the relative importance of these disorders in this well-defined geographical region (Chapter 3).

- Examine repeat length polymorphism in the background unaffected Welsh population to investigate the significance of high-normal repeats on prevalence of disease-range expanded repeats (Chapter 3).

- Determine whether high-normal repeats are a risk factor for familial or sporadic ataxia in South Wales (Chapter 4).

- To detail the clinical and genetic characteristics of DRPLA in South Wales (Chapter 5) together with a review of other non-Asian cases series (Chapter 6).

- To document the clinical characteristics of LOCA in South Wales, examine natural history and prognostic indicators (Chapter 7).

- Investigate appropriate measures of ataxia severity, examining the psychometric properties of ICARS (Chapter 8).

- Formulation of a rational diagnostic strategy (Chapter 9).

- Identify areas of further study (Chapter 10)

Materials and methods

2.1 Introduction

Wales is one of the four countries that make up the United Kingdom (UK) with a population of 2,965,900 people representing 4.9% of the total UK population (`http://www.statistics.gov.uk/`, 2006). As part of national health service (NHS) structural reforms in 2003, the five Welsh Health Authorities were abolished and replaced with 22 local health boards (LHBs). Bro-Taf Health Authority was replaced with four LHBs (Cardiff, Vale of Glamorgan, Rhondda Cynon Taff, and Methyr Tydfil), Gwent with five (Blaenau Gwent, Newport, Monmouthshire, Caerphilly and Torfaen), Dyfed Powys with four (Pembrokeshire, Ceredigion, Carmarthenshire and Powys), Bro Morgannwg with three (Neath Port Talbot, Swansea, Bridgend) and North Wales with six (Gwynedd, Conwy, Anglesey, Wrexham, Flintshire, and Denbighshire) (Figure 2.1) The geographical boundaries of these NHS organisational units formed the population-base for the study of patients with cerebellar ataxia during the study period (1999-2007).

2.2 Case ascertainment

Patients with cerebellar ataxia were identified using a number of ascertainment sources, including: local general practitioners (GPs), departmental databases in the Department of Neurology and Institute of Medical Genetics, liaison with and personal notifications from regional consultant neurologists over the study period, self-referral via other family members or response to an advertisement in the Ataxia UK newsletter (`http://www.ataxia.org.uk`) and regional NHS administrative databases searching for a diagnosis of "ataxia" according to the 9th and 10th editions of the International classification of diseases (ICD). In addition clinicians who had requested any form of spinocerebellar ataxia (SCA) testing were identified from a laboratory-based genetic database to prompt consideration of referral to a dedicated central clinic. Ascertainment methods are detailed in Section 2.2.2.

To facilitate the calculation of accurate population-based prevalence estimates, a detailed and systematic survey was performed in South East Wales — the region spanning Bro-taf and Gwent health authority boundaries. This detailed survey in-

ANG	Anglesey
BLG	Blaenau Gwent
BRG	Bridgend
CAE	Caerphilly
CAR	Carmarthenshire
CDF	Cardiff
CER	Ceredigion
CNY	Conwy
DEB	Denbighshire
GWY	Gwynedd
FLT	Flintshire
MON	Monmouthshire
MER	Merthyr Tydfil
NEW	Newport
NPT	Neath Port Talbot
PEM	Pembrokeshire
POW	Powys
RCT	Rhondda Cynon Taff
SWA	Swansea
TOR	Torfaen
VOG	Vale of Glamorgan
WRX	Wrexham
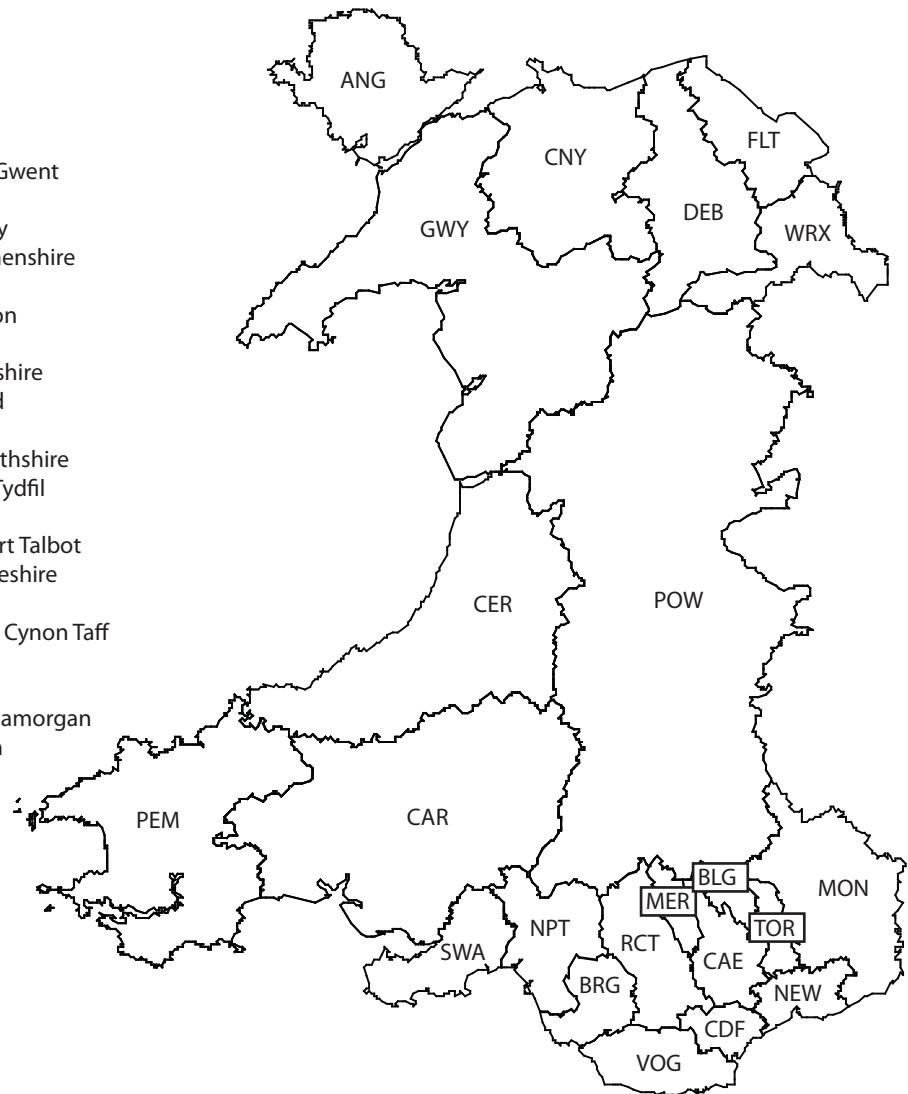
Figure 2.1: Wales and its constituent 22 local health boards.

cluded using all the listed ascertainment sources, including contacting all general practitioners and performing ICD searches using health authority data. The population identified as part of this phase of ascertainment is used as a denominator for epidemiological analysis if those patients were alive and resident within this region on 1st January 2007. There were 78 patients identified as part of a previous epidemiological survey between 2001–3 in the Bro-taf region.[86] To maximise case ascertainment, additional patients were recruited from outside the South East Wales region. While there was no systematic survey of general practitioners and clinicians from outside South East Wales, patients were referred by neurologists, identified from a laboratory-based genetic database or self-referred. Patient selection is defined in more detail in Section 2.2.4.

2.2.1 Study compliance

The study was performed in compliance with the guidelines of the Declaration of Helsinki in the Tokyo version of 2004,[166] the European ICH Guideline for Good Clinical Practice (1997), the Medical Research Council (MRC, UK) Operational and Ethical Guidelines of human tissue and biological samples for use in research[80] and the General Medical Council (GMC, UK) Guidelines in Research: roles and responsibilities of doctors (2000). Project protocols and documentation were reviewed and agreed by a local research and ethics committee (LREC).

2.2.2 Ascertainment sources

We have performed regular systematic recruitment of patients from a wide variety of sources since 1999 creating a contemporary centralised ataxia register (Figure 2.2). As of March 2009, the register contains 671 records but not all of these represent unique and affected patients. For instance, patients who indicated that they did not wish to know the results of diagnostic tests had two records created; one for demographic information and one for clinical and laboratory data. In these circumstances there is a one-way link from the record with patient-identifiable information to the clinical and laboratory record with no straightforward method of tracing results back to a named patient. Such a one-way mechanism prevents an
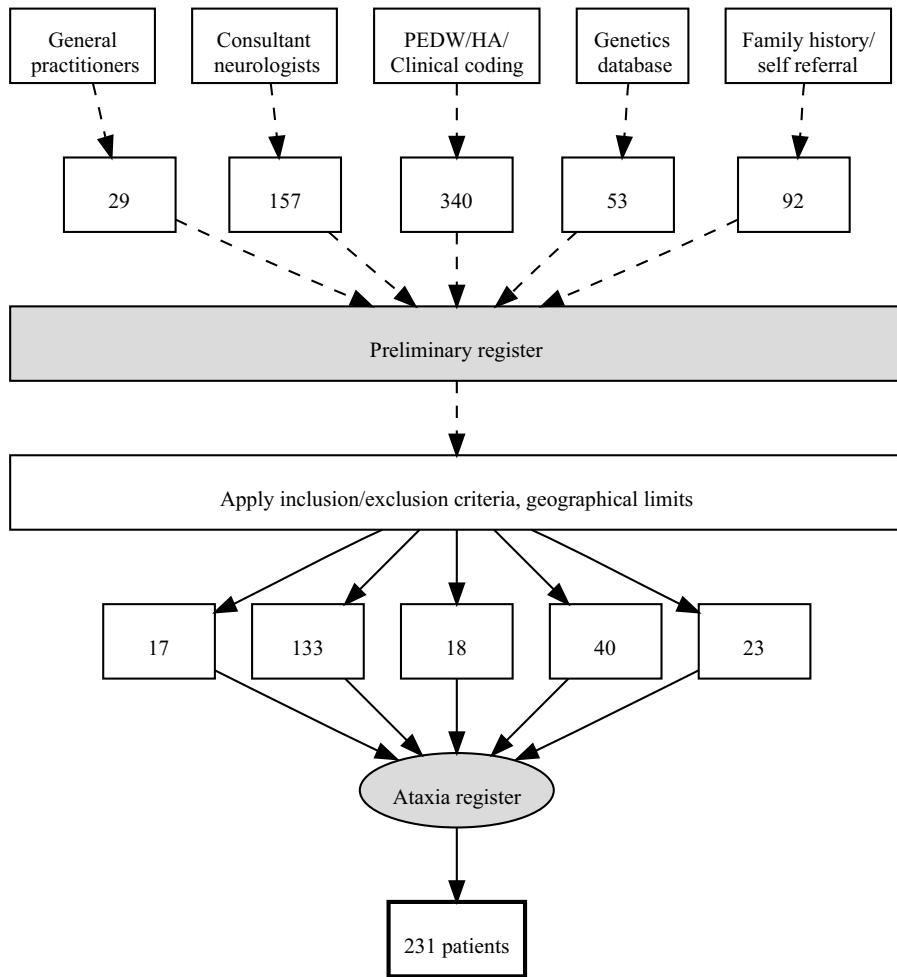
Figure 2.2: Schematic overview of case ascertainment for patients with chronic progressive cerebellar ataxia

inadvertent release of unwanted clinical and laboratory investigations (see Chapter 2.2.6) to those patients who do not wish to know (Chapter 2.3.5) relieving the need to manually double-check consent during every event and minimising inadvertent operator error.

A detailed breakdown of case ascertainment is shown in Table 2.1 together with patient location in Figure 2.3.

	No. patients	Referral source(s)					
		GP	Neurologist	Family / self	Geneticist	HA / PEDW	Unknown[†]
Diagnosis							
DRPLA	13	0	5	7	2	0	0
Dominant LOCA	26	0	10	14	1	2	2
EOCA	2	0	1	1	0	0	0
FRDA	4	1	2	0	0	0	1
FXTAS	1	0	1	0	0	0	0
Familial LOCA	25	1	12	2	4	2	5
SCA-11	1	0	1	0	0	0	0
SCA-6	10	0	3	3	5	0	0
SCA-8	2	1	0	1	0	0	0
Sporadic LOCA	156	14	101	1	28	14	6
Other							
Excluded or not applicable	431	12	21	63	13	51	273

Table 2.1: Breakdown of referral sources and ataxia diagnosis. Each patient may be referred from multiple sources. † referral data unavailable or incomplete.

2.2.3 Ascertainment procedure

A provisional ataxia register was generated using department databases. A contemporary list of GPs was obtained from the respective local health boards together with contact details for each practice manager. A cover letter and patient information leaflet was sent to each practice manager, together with individual and personalised letters to each clinician asking for their help with patient recruitment. In all cases, patients already known to the project were listed when appropriate. All GPs within the region were contacted to verify the details of such cases where available and to request notification of any suspected cases within their practice populations. A patient information leaflet was provided and their permission was sought to approach patients under their care. Up to three reminders, including telephone calls and emails, were used for GPs who did not respond. Using such systematic and repeated contacts resulted in a response rate of 78% from local GPs.

In conjunction with the Institute of Medical Genetics, a letter was sent to all clinicians who had requested SCA mutation analysis for a patient. A list of the clinician's patients was attached to the letter and the clinician asked to notify the research team of any patients who were candidates for inclusion and were willing to take part in the study. It was expected that a significant proportion of patients who had undergone SCA mutation analysis were candidates for inclusion. In addition, if there were consultant neurologists who had not requested SCA mutation analysis, a letter was sent asking them to notify the research team of any patients who were willing to take part in the study.

Clinicians were subsequently contacted by post, telephone or secure email to verify the details of reported cases, and permission sought to get further information about the patients notified. Specifically, the referring clinician was asked to determine whether, i) the patient was suitable for research and met required inclusion criteria (Section 2.2.4) and, ii) the patient was happy to be contacted for research purposes.
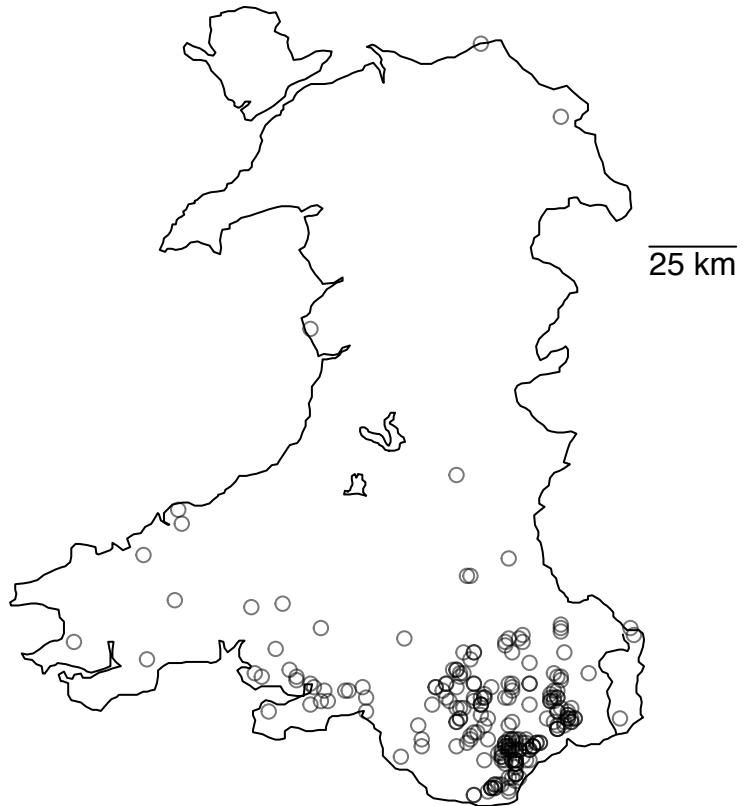
Figure 2.3: Geographical location of all patients notified to ataxia register.
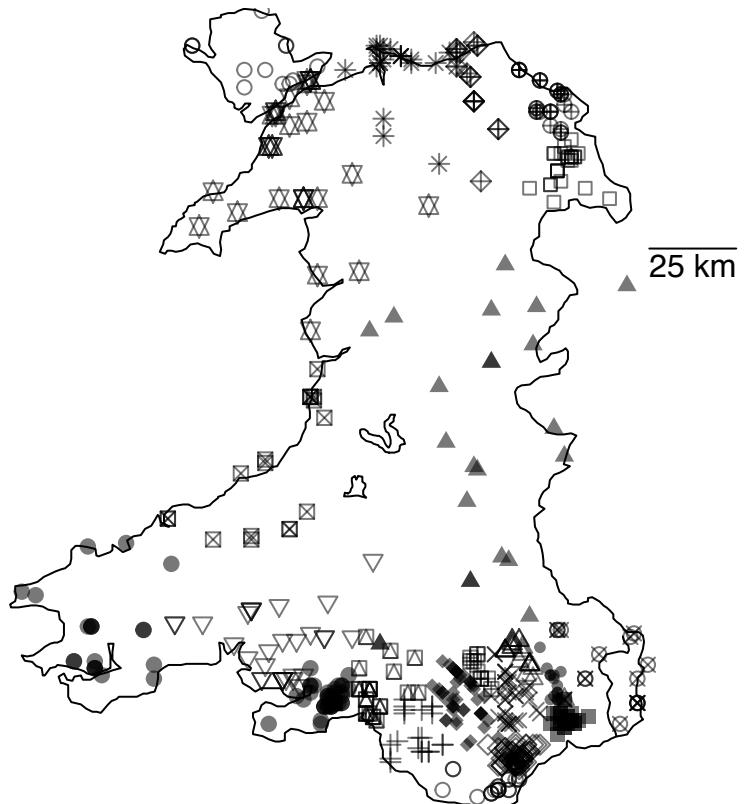
Figure 2.4: General practices in Wales. Different symbols reflect practices in different local health boards.

2.2.4   Inclusion and exclusion criteria

The inclusion criteria were: patients with chronic progressive cerebellar ataxia, no identified symptomatic cause, disease duration of greater than one year and age at onset of 18 or over. Patients were also excluded if ataxia was only a minor feature or if a symptomatic cause was subsequently identified. After obtaining informed consent, patients underwent a systematic clinical evaluation together with detailed review of contemporary medical notes where possible. A standardised data collection protocol was used to document clinical and investigative results and data were stored in a dedicated database in accordance with the Data Protection Act, 1998.

2.2.5   Confirmation of cases

Following confirmation from the clinician that the patient was aware of the study, a letter was sent to the patient and, if necessary, supplemented by a telephone call. Up to three attempts were made to contact a patient who did not respond. Informed consent was then obtained after further explanation and discussion about the project.

2.2.6   Patient information and informed consent

We explained the nature of the study, its purpose and associated procedures, the expected duration and the potential benefits and risks of participation to each patient prior to clinical evaluation. Patients were provided with a patient information leaflet (Appendix B.3) and given an opportunity to ask questions. Specifically, patients were informed about the voluntary nature of the participation, the right to withdraw from the study at any time without any disadvantage and without having to provide reasons for his or her decision.

Following this informative discussion, patients were asked to sign a statement of informed consent for participation into the study and for medical illustration (Appendix B.2). The signed statement of informed consent was subsequently filed in the patient's research records. If a patient was not capable of providing a signature, a verbal statement of consent was allowed in the presence of a witness.

2.3 Data collection

2.3.1 Clinical evaluation

Clinical information was primarily obtained by direct history taking, or if not possible, from medical records and family members. Details of previous investigations were confirmed from contemporary electronic and paper records when available. Patients with a confirmed ataxic syndrome underwent more detailed assessments including clinical studies, measurements of ataxia and activities of daily living (ADL).

A detailed standardised data collection booklet was created to collect structured data including patient demography, primary and incidental diagnoses, investigation results, clinical history and examination (Chapter 7.2.2 and Appendices B.4 and B.5). In addition, several standardised data collection tools were used including an assessment of ataxia severity (International Cooperative Ataxia Rating Scale (ICARS), Appendix B.6), activities of daily living (Barthel ADL, Appendix B.7) and quality of life indicators (SF-36, Appendix B.8 and FAIS, Appendix B.9).

2.3.2 DNA and serum collection

When possible, 20-30ml of blood was taken in EDTA and Li-heparin anticoagulant-treated tubes to allow subsequent extraction and storage of DNA and serum for later mutation analysis. A DNA bank was established in conjunction with the Institute of Medical Genetics, University Hospital of Wales, Cardiff who undertook DNA extraction and subsequent storage. A serum bank was also created for future studies.

2.3.3 Longitudinal assessment

A subset of patients were re-assessed prospectively to allow the estimation of disease progression and facilitate clinical re-evaluation. Patients who had not been seen for more than two years were sent new invitation letters. In addition to the usual systematic clinical evaluation, patients under longitudinal follow-up were

sent quality of life questionnaires and transition questions (see Chapter 8 and Appendix B.10) to assess patient reported change in function.

2.3.4 Data quality

Detailed demographic information was recorded for every patient together with common NHS identifiers. The NHS number is a unique patient identifier for use within and between NHS organisations. It can be used with the NHS strategic tracing service (NSTS)[1] and the NHS administrative register (NHSAR)[2]. The NSTS holds key administrative information including: NHS number, name, date of birth, sex, date of death (where applicable) and details of all GP-registered patients, GP details and practice addresses. The NHSAR provides similar functionality for patients within Wales.

2.3.5 Project management and data entry

Two separate databases were designed to support research administration and to support data analysis respectively. The former database was created using Filemaker to support:

- Identification and contact with ascertainment sources (NHS-data)
- Creation of a master patient index (MPI).
- Patient recruitment information
  - Current and historical demographic information
  - NHS identifiers, including NHS number, GP and individual hospital identifiers (Figure 2.6).
  - Ascertainment sources
- Patient clinical information
  - Family references (Figure 2.5).
  - Diagnostic and medication histories
  - All clinical data, including use of standardised tools as outlined in Section 2.3.1 (Figure 2.7).

---

[1]http://www.nhsia.nhs.uk/nsts/pages/default.asp

[2]http://www.wales.nhs.uk/sites3/page.cfm?orgid=166&pid=4267

- Supporting investigators
    - Managing appointments and investigator scheduling
    - To-do lists
    - Keeping track of notifications from GPs and other clinicians (including identifying non-responders)
    - Facilitating correspondence (automatic generation of appointment letters, visit reports and notifications)
    - Printing investigator booklets labelled with patient identifiers
    - Printing travel directions for patient appointments

The database schema of the working Filemaker database is shown in Figure 2.8.

Confidentiality

The design and implementation of study methodology was performed in strict accordance with previously issued guidance on good practice within clinical research (see page 22). There are several scenarios in which maintaining confidentiality during clinical research may be problematic, especially since patients could request the results of any diagnostic tests. Steps were taken to develop robust methods to ensure good practice at all times during the research process. Where possible, automated safeguards were introduced at the planning and design stages avoiding the need for manual checking and possibility of investigator error.

Case ascertainment was performed using a number of sources (Section 2.2.2) including laboratory and central NHS databases. In all notifications, the GP or nominated hospital consultant were asked to inform the patient that there was an ongoing research opportunity, and seek their consent for inclusion. Such measures avoided contact with a patient for research purposes without their explicit consent. In addition, once a patient indicated they did not wish to take part, their record was flagged resulting in their information being obscured from day to day database use. Unless an explicit request was made, basic recruitment information was not deleted to avoid subsequent identification of that patient via an alternative ascertainment source resulting in an unwanted second contact.

As part of the process of consent (Section 2.2.6), patients are asked whether
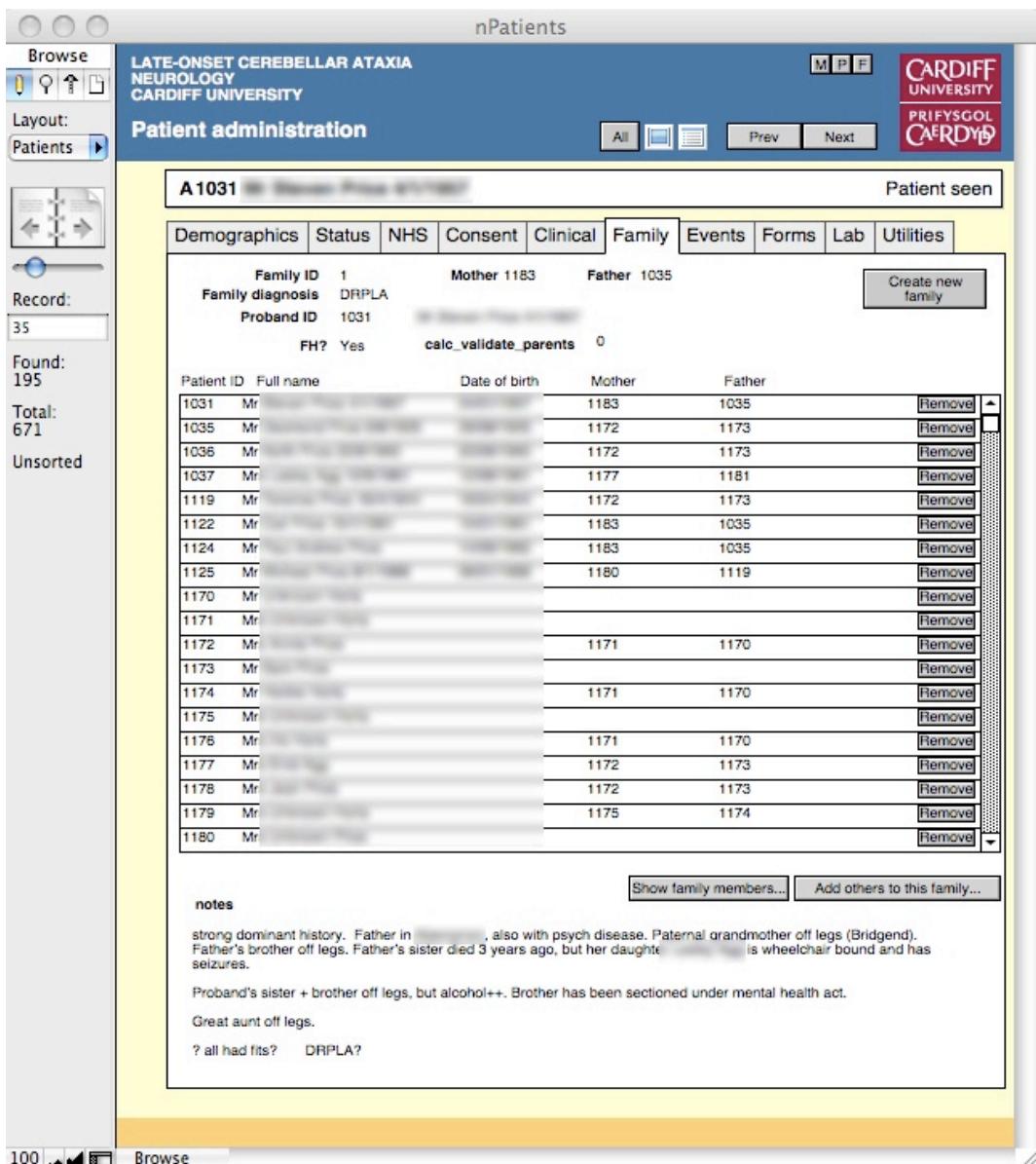
Figure 2.5: Editing family information in ataxia database.
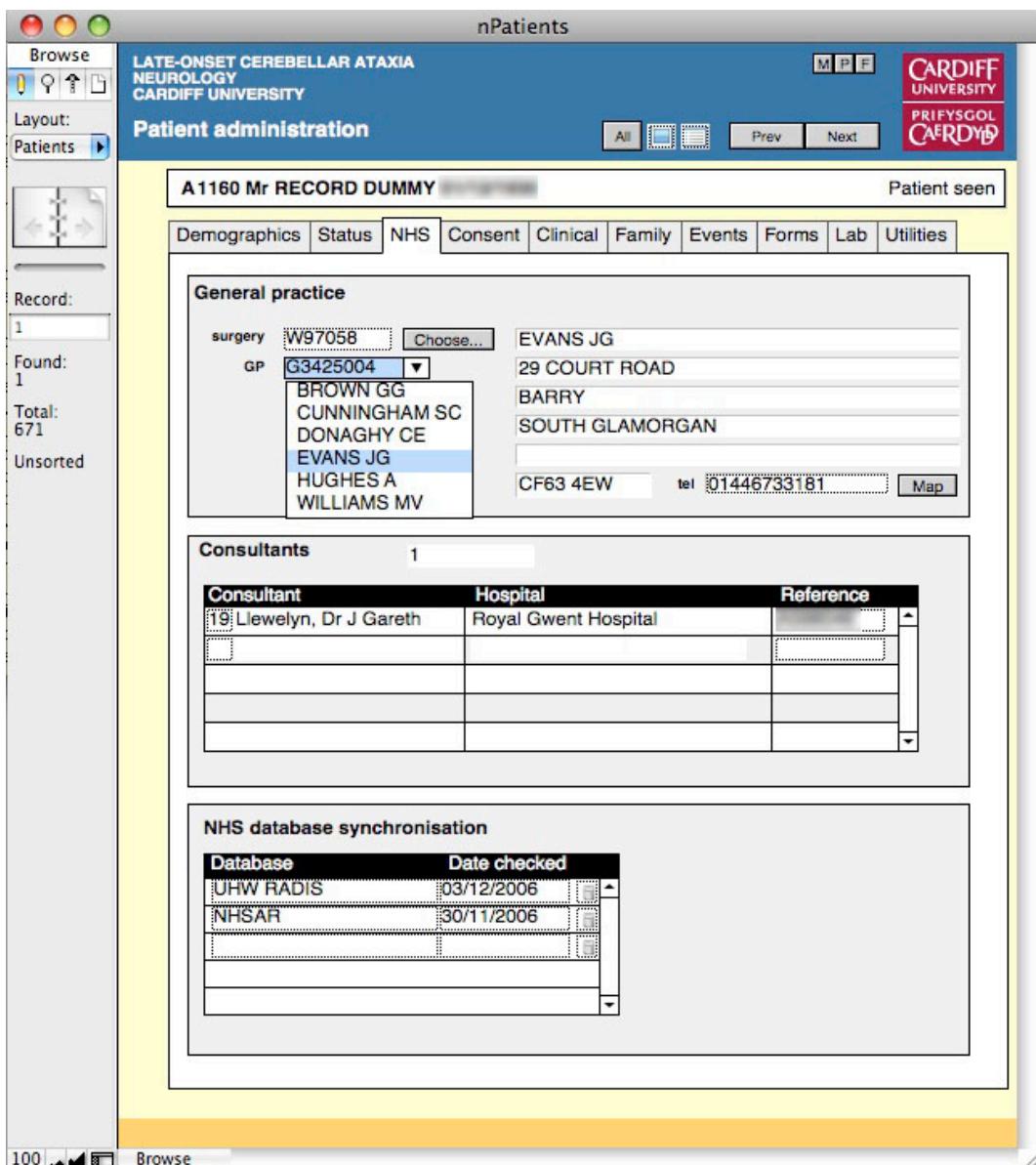
Figure 2.6: Editing NHS data for a patient record and choosing current general practitioner.

Figure 2.7: Booking appointments and entering clinical data (ICARS) for a patient visit.
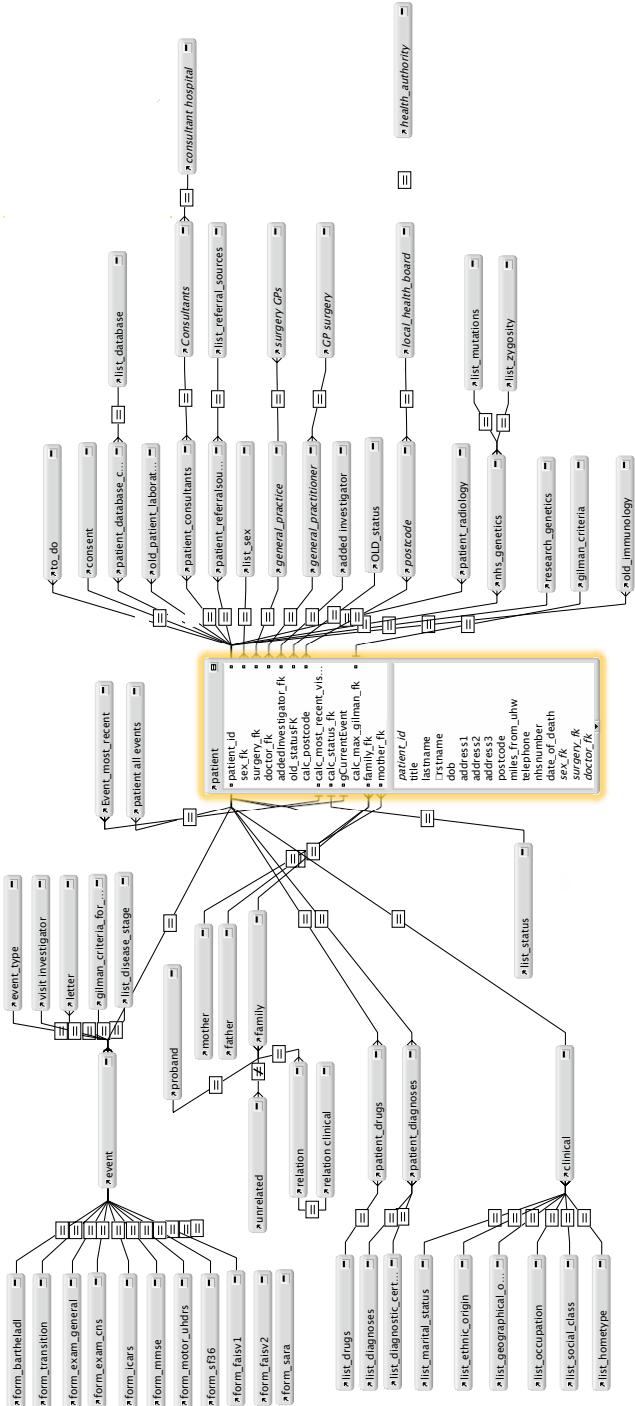
Figure 2.8: Graphical representation of Filemaker database schema.
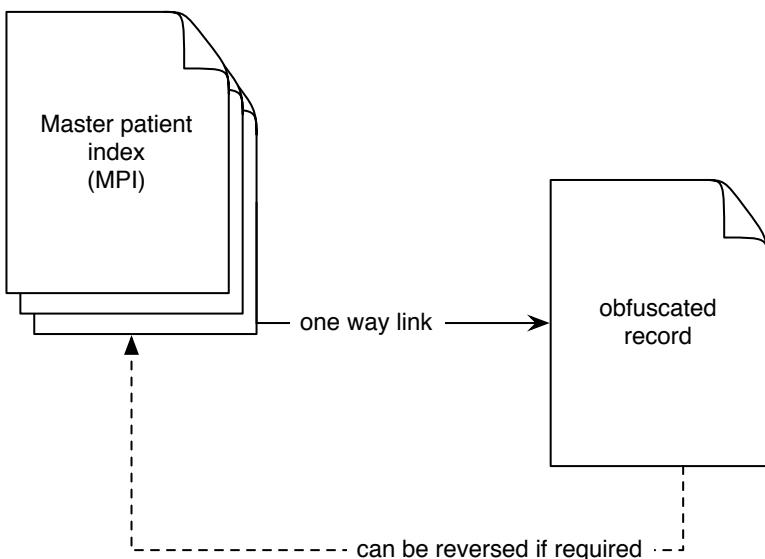
Figure 2.9: Obfuscation of clinical and laboratory data within database.

they wanted to be informed of research results. In cases in which patients declined this opportunity, two separate database records were created with a secure one-way link using relational database technology to obfuscate demographic information and prevent accidental notification. The first record contains the patient identifiable information as usual, but does not contain any clinical or laboratory data and is flagged as excluded ("dummy record"). This record contains a one-way link to another database record containing clinical and laboratory data (Figure 2.9) In cases in which patients subsequently change their mind, or a life-threatening result is found, an emergency (administrator-only) safety protocol is available to find original information for any record. In the event of a positive laboratory investigation in a patient wishing to know results of diagnostic tests, further tests were performed in an NHS laboratory with subsequent referral to clinical neurological and genetic services as required.

2.4 Laboratory analysis

DNA was extracted from peripheral blood leucocytes by standard methods. Repeat length analysis was performed using standard methods as detailed in Chap-

ters 3.2.3 and 4.2.3 by technicians at the Institute of Medical Genetics together with Dr. Elisa Majounie and Dr. Nigel Williams, Department of Psychological Medicine, Cardiff University.

Control patients

Control samples were ascertained from consecutive consenting blood donors at the National Blood Transfusion Service who had been born in Wales and whose grandparents were Welsh. 306 Caucasian controls were recruited in this way from South Wales as part of a schizophrenia case-control study (NM Williams, unpublished data).

2.5 Data management and analysis

While data were entered in Filemaker for day-to-day project management, all patient-identifiable information was removed with the remaining anonymous data routinely exported into PostgreSQL for subsequent analysis on University or personal computers. Such export was automated using custom-written Filemaker scripts generating dynamic structured query language (SQL) to update data held in PostgreSQL.

Once in PostgreSQL, standard SQL could be used to define arbitrarily complex queries (Listing 2.1) This query performs a SQL "outer join" linking seven different tables and lists all ICARS assessments including core clinical information such as disease stage, investigator, Barthel ADL score and disease duration at time of assessment.

To simplify analysis, SQL clinical queries were defined for each relevant clinical category (for example, demographic information, examination findings, history, transition questions, mini-mental result etc.), and these could be combined for analysis in code. The example in Listing 2.2 fetches relevant clinical information including demographic information ("pt"), family history ("family"), most recent ICARS results ("icars") and diagnostic categories ("diag") and then creates a graphical plot based on the data. The code for `ataxia.query()` is shown in Listing 2.3 which performs the equivalent of a relational database outer join using

```
select patient_id ,
q1_walking , q2_gait , q3_standing , q4_feet_spread , q5_body_sway_eyes_open ,
    q6_body_sway_eyes_closed , q7_sitting_quality ,
q8_knee_shin_dysmetria_right , q8_knee_shin_dysmetria_left ,
    q9_knee_shin_tremor_left , q9_knee_shin_tremor_right ,
q10_finger_nose_dysmetria_right , q10_finger_nose_dysmetria_left ,
    q11_finger_nose_tremor_right , q11_finger_nose_tremor_left ,
q12_finger_finger_right , q12_finger_finger_left , q13_dysdiadochokinesis_right ,
    q13_dysdiadochokinesis_left ,
q14_archimedes , q15_speech_fluency , q16_speech_clarity , q17_nystagmus , q18_pursuit
    , q19_saccade ,
calc_posture_gait as ic_posture_gait , calc_kinetic as ic_kinetic , calc_dysarthria
    as ic_dysarthria , calc_oculomotor as ic_oculomotor ,
icars_total as ic_total ,
calc_duration_at_visit as duration ,
form_bartheladl . calc_total as barthel_total ,
case when calc_disease_stage_fk=0 then '0'
when calc_disease_stage_fk=1 then 'I'
when calc_disease_stage_fk=2 then 'II'
when calc_disease_stage_fk=3 then 'III'
when calc_disease_stage_fk=4 then 'IV'
else '' end as disease_stage ,
initials as investigator
from
form_icars
left join event on ( form_icars . event_fk = event . event_id )
left join clinical on ( event . patient_fk = clinical . patient_fk )
left join patient on ( event . patient_fk = patient . patient_id )
left join list_sex on ( patient . sex_fk = list_sex . sex_id )
left join investigator on ( investigator_fk = investigator_id )
left join form_bartheladl on ( form_bartheladl . event_fk = event . event_id )
where excluded=0
```

Listing 2.1: Example SQL querying ICARS data together with clinically relevant data

```
icars ← ataxia.query(c(sql.cl$pt, sql.cl$family, sql.cl$icars, sql.cl$diag))
nf ← layout(rbind(c(1,2)), widths=c(3,1))
par(mar=c(5,5,1,1))
plot(ic.total ~ duration, data=icars,
                main='', xlab='Disease duration',
                ylab='Total ICARS score')
# and add marginal boxplot
par(mar=c(5,0,1,1))                    # bottom, left, top, right
boxplot(ic.total ~ disease.stage, data=icars, yaxt='n', notch=T, xlab='Stage')
```

Listing 2.2: Example R code fetching data and generating a plot of ICARS score vs. disease duration with patients grouped by ataxia diagnosis. This code generates Figure 7.2

consecutive SQL statements from within R.

In addition, these queries were designed to be dynamic, generating tables and graphs from live-research data. As such, missing data, mistakes in data entry and other data quality problems were quickly identified. Such dynamic analysis and reporting resulted in analyses, papers (and a thesis) that readily update when new data are made available. Should a single patient be added, then every patient count, graph and statistical analysis will update to include their new data.

2.5.1 Geographical profiling

All patients were categorised geographically based on their home address. The inclusion of a national UK-wide postcode data set mapped to NHS-organisational boundaries resulted in an automatic process that did not require manual intervention. A single database table was created listing all UK postcodes to their respective LHB or primary care trusts. Such primary care organisational units were mapped to regional administrative units ("health authorities") using SQL inner joins. As such, all postcodes were immediately validated and mapped to the relevant NHS administrative organisations.

2.5.2 Algorithmic clinical phenotyping

Research projects have traditionally focused on sequential and fundamentally iterative processes: planning, implementation, data gathering, analysis and writing-up. However, integration of data gathering and continual analysis throughout a project lifecycle results in several key advantages. Analysis, especially if per-

```
ataxia.query ← function (sql, merge.by = "patient.id")
{
    l = length(sql)
    if (l == 0)
        stop("Invalid query")
    if (l == 1) {
        r = sqlQuery(channel, sql, na.strings = "", errors = FALSE)
        err = odbcGetErrMsg(channel)
        if (length(err)) {
            stop(err)
        }
        names(r) ← make.names(names(r), allow_ = FALSE, unique = TRUE)
        return(r)
    }
    else {
        if (is.na(merge.by))
            stop("No merge column specified.")
        m = ataxia.query(sql[1])
        num.rows = nrow(m)
        sql = sql[2:1]
        for (q in sql) {
            n = ataxia.query(q)
            m = merge(m, n, all = T, by = merge.by)
            if (nrow(m) > num.rows)
                warning(paste("Possible duplicate rows: ", nrow(m),
                    " rather than", num.rows, " for ", merge.by,
                    "\n", sep = ""))
        }
        return(m)
    }
}
```

Listing 2.3: Database access combining data for analysis (R code)

formed automatically and dynamically, can identify missing or invalid data. In addition, using algorithmically generated, clinically useful data at runtime provides an opportunity to support clinical practice. For instance, for each and every patient contact, custom and specialist code (Listing 2.4) applies published criterion for a diagnosis of multiple system atrophy (MSA),[36] highlighting cases in which there is missing or insufficient clinical data, and providing immediate feedback after data entry. Such clinically valuable yet automatic algorithmic derivations reduce the need for repeated, error-prone and frequently laborious manual calculations. In addition, such calculations can be used to algorithmically generate clinical correspondence. For instance, it was straightforward to automatically create visit reports informing patients' GPs of their involvement in research.

2.6 Statistical methodology

All analysis was performed using "R: A Language and Environment for Statistical Computing".[104] Details of individual analyses are described separately in individual chapters and are not reproduced unnecessarily here. For hypothesis tests, including likelihood tests used in statistical modelling, $P \leq 0.05$ was considered statistically significant. Statistical modelling, including multivariate linear, logistic (generalised linear) and linear mixed-modelling, were performed using saturated models incorporating clinically relevant covariates together with variables identified at univariate analysis. Manual step-down procedures were used using likelihood tests, standardised information criterion (such as Akaike's) and analysis of diagnostic plots with tests of modelling assumptions performed before arriving at a final model. Where possible, results of modelling are shown with 95% confidence intervals.

```
Let ([
current_age = calc_age_at_visit;
insufficient_data =  not  (calc_exists_ExamCNS and calc_exists_MMSE and patient::
    calc_exists_Clinical) or form_exam_cns::calc_completed=0;
excluded = If ( clinical::calc_age_first_ataxic_symptom < 30 ; 1 ; 0 ) or
    patient::calc_has_family_history or form_mmse::calc_total < 26;
post_hypotension = If ( IsEmpty ( form_exam_cns::postural_hypotension ) ;
  If ( (form_exam_cns::lying_bp_systolic −30)>form_exam_cns::standing_bp_systolic
        ;  1;
  If ( (form_exam_cns::lying_bp_diastolic −15)>form_exam_cns::standing_bp_
      diastolic ; 1 ;0)) ;
form_exam_cns::postural_hypotension )
                                                             ;
urinary_incontinence = If ( IsEmpty(clinical::urinary_incontinence__age_onset)
    and clinical::urinary_incontinence=1 ; 1 ;
  If (clinical::urinary_incontinence__age_onset  > 0 and current_age  >=
      clinical::urinary_incontinence__age_onset; 1;0));
erectile_dysfunction = If (IsEmpty(clinical::erectile_dysfunction__age_onset) and
     clinical::erectile_dysfunction=1; 1 ;
  If ( clinical::erectile_dysfunction__age_onset  > 0 and current_age  >=
      clinical::erectile_dysfunction__age_onset ; 1;0));
urinary_catheter    = If (IsEmpty(clinical::urinary_indwelling_catheter__age_
    onset) and clinical::urinary_indwelling_catheter=1; 1 ;
  If (clinical::urinary_indwelling_catheter__age_onset > 0 and current_age  >=
      clinical::urinary_indwelling_catheter__age_onset;1;0));
autonomic_failure   = post_hypotension  or urinary_incontinence or urinary_
    catheter;
parkinsonism = form_exam_cns::L08_bradykinesia   and (form_exam_cns::L04_tone_
    rigid or form_exam_cns::L06_tremor_resting or form_exam_cns::L07_tremor_
    postural);
parkinsonism_any = form_exam_cns::L08_bradykinesia   or form_exam_cns::L04_tone_
    rigid or form_exam_cns::L06_tremor_resting or form_exam_cns::L07_tremor_
    postural;
cerebellar  = form_exam_cns::g01_ataxia_gait and (form_exam_cns::g05_dysarthria
    or form_exam_cns::L16_finger_nose or        form_exam_cns::em08_eyes_
    nystagmus_gaze_evoked);
cerebellar_any = form_exam_cns::g01_ataxia_gait or form_exam_cns::g05_dysarthria
    or form_exam_cns::L16_finger_nose or form_exam_cns::em08_eyes_nystagmus_gaze_
    evoked;
ext_plantars = If ( form_exam_cns::reflex_plantar_right=2 or form_exam_cns::
    reflex_plantar_left=2 ; 1 ; 0 );
hyperreflexia = If (Max(form_exam_cns::reflex_knee_right;form_exam_cns::reflex_
    knee_left;form_exam_cns::reflex_ankle_right;form_exam_cns::reflex_ankle_left)
    >= 3;1;0)
]; Case (       excluded ; 2; // not MSA
  insufficient_data ; 1;  // insufficient data
  autonomic_failure and (parkinsonism or cerebellar) ; 4;  // Probable MSA
  autonomic_failure and (parkinsonism_any or cerebellar_any) ; 3;  // Possible
     MSA;
  parkinsonism and (autonomic_failure or cerebellar_any) ; 3; // Possible MSA
  cerebellar and (autonomic_failure or parkinsonism_any) ; 3; // Possible MSA
  2)    // not MSA
)
```

Listing 2.4: Algorithmic derivation of per-event Gilman MSA status (Filemaker script code)

The genetic aetiology of chronic progressive cerebellar ataxia: a population-based study

3.1 Introduction

As outlined in Chapter 1, genetic testing is now routinely available for many of the spinocerebellar ataxia (SCA) mutations. However, these disorders frequently have overlapping clinical features resulting in considerable practical diagnostic difficulties for clinicians and, despite extensive investigation, many families and a majority of sporadic patients remain undiagnosed. In addition, the explanation for the widely variable distribution of disease causing expansions remains unclear. It is suggested that high-normal repeats in the background indigenous population may act as a reservoir for novel expansions and if so, an association might exist between the distribution of high-normal repeats and disease prevalence within that population.[137]

To determine the relative importance of different genetic aetiologies of ataxia in Wales (UK), we have recruited, assessed and investigated a predominantly population-based sample of patients with chronic progressive late-onset cerebellar ataxia (LOCA). To inform a rational diagnostic strategy we have evaluated the significance of SCA1, SCA2, SCA3, SCA6, SCA7, SCA8, SCA10, SCA12, SCA17, dentatorubral pallidoluysian atrophy (DRPLA), Friedreich's ataxia (FA) and fragile-X associated tremor ataxia syndrome (FXTAS). In addition we have investigated repeat length polymorphism in unaffected control chromosomes to determine the molecular origins of ethnic and geographical variation in disease prevalence and to allow comparison with other populations.

3.2 Methods

3.2.1 Case ascertainment

South East Wales is a well-defined geographical region of the UK with a population of 1,265,000 of whom 997,087 are aged 18 or over (`http://www.statistics.gov.uk/`). There are 232 general practices responsible for patients locally with well-defined referral pathways to secondary and tertiary neurological services in Cardiff and Newport and historically low levels of migration. Patients with chronic progressive LOCA have been identified since 1999 with regular sys-

tematic searches of multiple sources to create a contemporary centralised ataxia register held at the regional neurology unit in Cardiff. Ascertainment sources have included: local general practitioners, departmental databases in the Department of Neurology and Institute of Medical Genetics, liaison with and personal notifications from regional consultant neurologists over the study period, self-referral via other family members or response to an advertisement in the Ataxia UK newsletter (`http://www.ataxia.org.uk`) and regional NHS administrative databases searching for a diagnosis of "ataxia" according to the 9th and 10th editions of the International classification of diseases (ICD). In addition clinicians who had requested any form of SCA testing were identified from a laboratory-based genetic database to prompt consideration of referral to a dedicated central clinic.

The inclusion criteria were: patients with chronic progressive cerebellar ataxia, no identified symptomatic cause, disease duration of greater than one year and age at onset of 18 or over. In all cases general practitioners or nominated hospital clinicians were asked to confirm diagnosis and inform patients of the research project. Patients were also excluded if ataxia was only a minor feature or if a symptomatic cause was subsequently identified. After obtaining informed consent, patients underwent a systematic clinical evaluation together with detailed review of contemporary medical notes where possible. A standardised data collection protocol was used to document clinical and investigative results and data were stored in a dedicated database in accordance with the Data Protection Act, 1998.

All markers were originally genotyped in a collection of 306 Caucasian blood donor control individuals recruited from South Wales (Chapter 2.4).

The project was approved by the relevant local ethics committee and NHS research and development office.

3.2.2   Statistical methodology

All analysis was performed using "R: A Language and Environment for Statistical Computing".[104] Crude prevalence and confidence intervals were determined by a Poisson exact method. Analysis of differences in the frequency of large normal alleles and distribution of SCA subtypes were performed using the Fisher exact test and the χ^2 test with Yates' correction.

3.2.3 Genetic analysis

DNA was extracted from peripheral blood leucocytes by standard methods. Repeat length analysis was performed using standard methods: Polymerase chain reaction (PCR) for amplification of the trinucleotide and pentanucleotide repeats was performed in a total volume of 12μl (5mM dNTPs, 0.3U Taq, 2.5pmol/μl HEX or FAM labelled forward primer, 2.5pmol/μl reverse primer, 4ng/μl DNA, with or without DMSO). The cycling conditions were optimised for each gene at: 1 cycle at $95°$C for 15 minutes, 35 cycles at $94°$C for 20 seconds, $54 - 65°$C for 30 seconds, $72°$C for 1.5 minutes and a final extension at $72°$C for 10 minutes. A volume of 2μL of diluted PCR product (1/10 to 1/20) was loaded on an ABI 3100 Sequencer (Applied Biosystems) and electrophoresed for 1 hour for fluorescent detection using a MapMarker1000 Rox internal size standard (BioVentures Inc.). Large repeats in FRDA, SCA7 and SCA8 were investigated using a TP-PCR which features a gene-specific forward primer and a repeat-specific reverse primer.[18] The PCR reaction was conducted in a 10μL reaction with 60ng DNA, under the following cycling conditions: 1 cycle at $95°$C for 15 minutes, 35 cycles at $94°$C for 1 minute, $55°$C for 1 minute, $72°$C for 3 minutes and a final extension at $72°$C for 10 minutes. The PCR products were analysed as described above.

3.3 Results

3.3.1 Genetic aetiology of ataxia

We identified 401 patients with a reported history of cerebellar ataxia between 1999 and 2007 in South East Wales. Applying inclusion and exclusion criteria as described above resulted in a subset of 178 with chronic progressive LOCA with no identified aetiology as a denominator population for study. There were 55 (26 male, 29 female) familial cases segregating in 38 kindreds and 123 (79 male, 44 female) sporadic patients. Ascertainment source was variable with considerable overlap: 107 from local neurologists and departmental databases, 36 from geneticists and a genetic laboratory database, 13 from general practitioners and 11 in response to advertising or via other family members. Mean prevalent age

(1st January 2007) was 62 (range 29–88) years for sporadic patients and 56 (range 21–86) years for familial patients. The overall minimum prevalence of LOCA was estimated as 11.33 per 100,000 (95% CI 9.55–13.34).

Pathological range expansions were identified in 11/38 (28.9%) of families and in 5/123 (4.1%) of sporadic patients (Tables 3.1 and 3.2). There were 6 families with SCA6 (6/38, 15.8%), 4 families with DRPLA (4/38, 10.5%) and 1 family with SCA8 (1/38, 2.6%). The proband of one member of a SCA6 family also had a pathological range expansion at the SCA8 locus (93 repeats). We did not demonstrate pathological range expansions at any locus in 27/38 (71.1%) families. FA accounted for 3/123 (2.4%) of patients with sporadic ataxia, and of 3/40 (7.5%) of those with an age at onset below 40. Apart from an adult age of onset, two patients with FA otherwise had a characteristic phenotype. However one patient with FA had chronic progressive LOCA with age at onset of 20, no evidence of skeletal deformities and a diagnosis made when aged 61 during this study. FA was not identified in patients with an age at onset above 40 or in patients with a family history. One sporadic patient (1/123, 0.8%) was found to have an expanded SCA6 allele. No disease-range expansions were found at the SCA1, SCA2, SCA3, SCA7, SCA10, SCA12 or SCA17 loci. The most important factor predicting identification of a defined molecular diagnosis was a positive family history (P <0.0001).

	UK (%)			Other (%)				
	This study	Other UK [37,42,72]	Combined UK	Finland [62]	Portugal [122]	France / USA [137]	Japan [77,90,94,137,159]	India [3,37,109]
Disorder								
SCA1	0.0	10.1	6.8	4.1	0.0	15.3	8.6	12.2
SCA2	0.0	16.5	11.1	2.0		14.1	3.1	28.4
SCA3	0.0	1.3	0.9	0.0	84.2	29.9	31.4	12.2
SCA6	15.8	5.0	9.2	2.0		5.1	16.2	1.5
SCA7	0.0	2.6	1.3	12.2			0.4	0.0
SCA8	2.6		2.6	18.4			0.9	0.0
SCA10	0.0		0.0	0.0				
SCA12	0.0		0.0	0.0			0.0	
SCA17	0.0		0.0	0.0			0.3	
FRDA	0.0	0.0	0.0	0.0				
DRPLA	10.5	0.0	6.7	0.0	0.0	0.0	13.9	0.0
FMR1	0.0		0.0					
Totals								
Positive diagnosis	28.9	32.9	31.6	38.8	84.2	64.4	73.7	54.1
Unexplained	71.1	67.1	68.4	61.2	15.8	35.6	26.3	45.9
No. families	38	79	117	49	38	177	794	74

Table 3.1: Genetic aetiology of familial LOCA in Wales together with aggregated data from other series.

	UK (%)			Other (%)		
	This study	Other [72]	Combined	Finland [62]	Japan [77]	India [3]
Disorder						
SCA1	0.0	0.8	0.4	0.0	0.2	3.2
SCA2	0.0	4.0	2.0	0.0	0.3	9.7
SCA3	0.0	0.8	0.4	0.0	4.2	3.2
SCA6	0.8	4.8	2.8	0.0	4.5	0.0
SCA7	0.0		0.0	0.6	0.0	
SCA8	0.0		0.0	5.5		
SCA10	0.0		0.0	0.0		
SCA12	0.0		0.0	0.0	0.0	
SCA17	0.0		0.0	0.6	0.0	
FRDA	2.4	3.2	2.8	0.0		
DRPLA	0.0	1.6	0.8	0.0	2.0	
FMR1	0.8		0.8			
Totals						
Positive diagnosis	4.1	15.3	9.7	6.7	11.2	16.1
Unexplained	95.9	84.7	90.3	93.3	88.8	83.9
No. patients	123	124	247	165	598	31

Table 3.2: Genetic aetiology of sporadic LOCA in Wales together with aggregated data from other series.

We identified one woman aged 88 with a Fragile-X allele in the pre-mutation range (57 repeats) with no relevant family history. She had developed slowly progressive gait difficulty with a tendency to stumble and fall aged 55, coinciding with complaints of a marked asymmetric predominantly left sided tremor associated with progressive clumsiness of the upper limbs. She was found to have a moderate gait ataxia but was able to walk without support with difficulties turning, limb ataxia with prominent intention and postural tremor and dysdiadochokinesis but no extra-pyramidal features. There was no cognitive impairment (MMSE 30/30), dysarthria or nystagmus evident. MRI brain demonstrated moderate generalised cerebral atrophy with scattered non-specific hyper-intense lesions in the deep white matter and sub-cortical regions and evidence of an old right sided cerebellar infarction. There was no evidence of middle cerebellar peduncle or brainstem white matter lesions. The combination of these findings is compatible with a diagnosis of "possible FXTAS" according to published criterion[44] and it therefore represents 1/123 (0.8%) of sporadic disease or 1/91 (1.1%) of those over 50.

The identification of 7 patients with SCA6 (6 familial cases and 1 sporadic) suggests a crude minimum prevalence in South Wales in 2007 of 0.55 per 100,000 (95% CI 0.22–1.14). Estimated prevalence of SCA8 and "possible FXTAS" in South Wales are 0.08 per 100,000 (95% CI 0–0.44) each.

3.3.2 Repeat length polymorphism

Repeat length polymorphism was examined in chromosomes from 307 control individuals (Figure 3.1). SCA8, SCA3 and DRPLA demonstrated most variability (23, 22 and 17 alleles identified respectively) and SCA2 and SCA7 the most conserved (9 and 6 alleles) (Table 3.3).

Six control patients (2%) had repeats at the SCA8 locus in the pathogenic range with allele lengths of 72, 74, 80, 81, 93 and 97 repeats. All were asymptomatic with no relevant family history at time of recruitment as controls (aged 71, 52, 57, 62, 66 and 38 respectively). No pathogenic range alleles were identified at other loci in the control population.
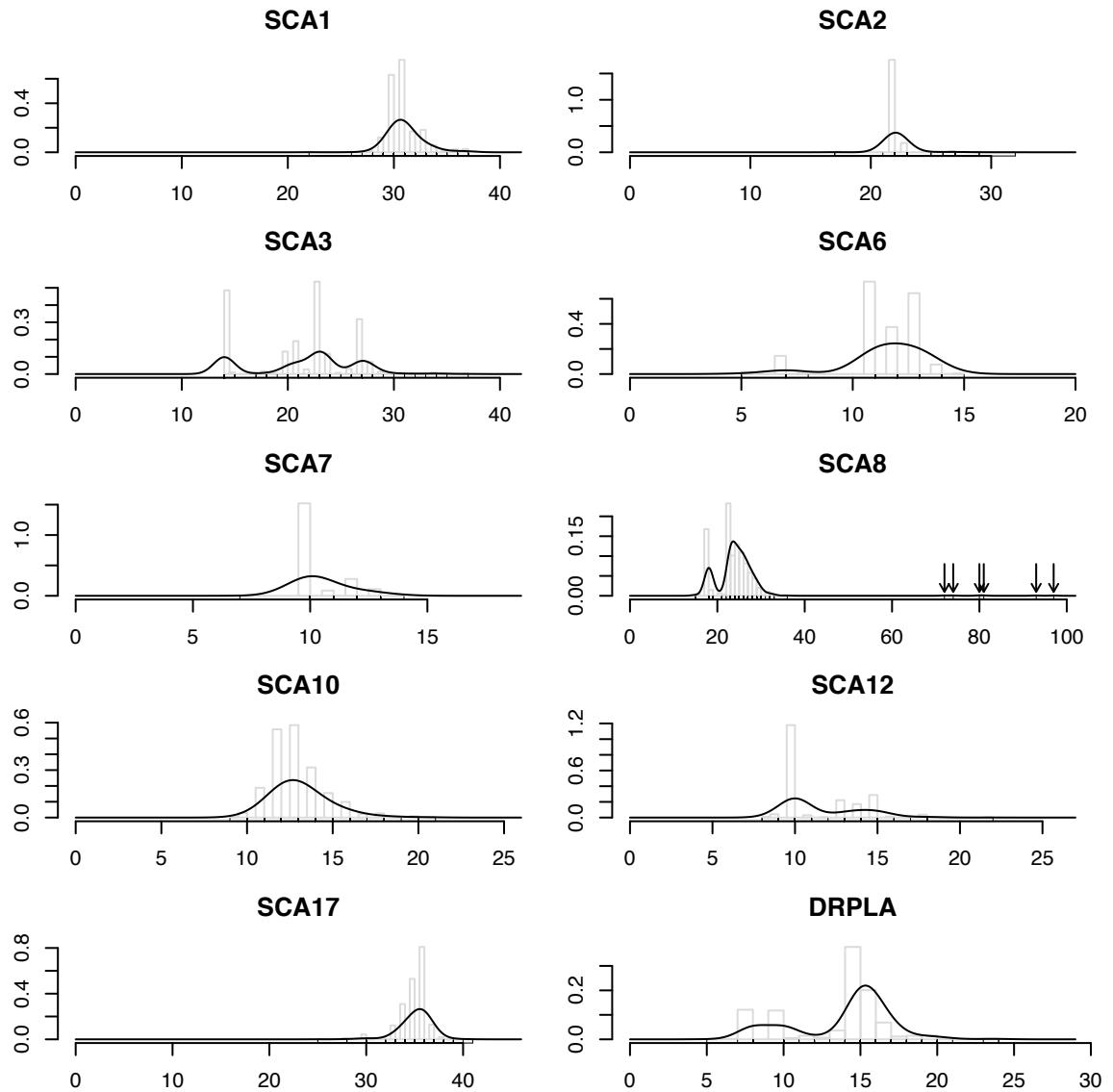
Figure 3.1: Distribution of normal alleles at SCA and DRPLA loci. Arrows indicate pathogenic range alleles at SCA8 locus.

	Median	Range	Variance	No. alleles
DRPLA	15	5–24	10.1	17
SCA1	31	22–37	2.4	13
SCA10	13	9–21	2.6	13
SCA12	10	8–22	5.2	12
SCA17	35	25–41	2.3	13
SCA2	22	17–32	0.9	9
SCA3	23	14–37	24.7	22
SCA6	12	5–15	2.9	8
SCA7	10	7–14	0.9	6
SCA8	24	15–97	47.6	23

Table 3.3: Distribution of alleles at SCA and DRPLA loci in control population.

3.3.3 High-normal repeats

The frequencies of high-normal length alleles in the control population at the SCA1,2,3,6 and DRPLA loci are shown in Table 3.4 with equivalent studies identified from the literature to allow detailed comparison with other populations.To facilitate comparison we have employed cut-offs from other published series corresponding to 5–10% of the upper tail of the distribution. High-normal allele frequency was significantly different to that from Japanese populations at all loci tested but this difference was variable and determined by the locus studied. High-normal alleles at SCA1 and SCA2 are more frequent in Wales than Japan but this relationship is reversed for SCA3, SCA6 and DRPLA ($P < 0.0001$ for each). Differences between Wales, Finland, the combined French and American series and India are less striking and more difficult to interpret.

	Wales	Finland[62]		Portugal[123]		France/USA[137]		Japan[137]		India[109]	
DRPLA											
> 17	0.05	0.04		0.06		0.10	*	0.24	***	0.11	**
> 18	0.04	0.02				0.06		0.13	***	0.07	*
> 19	0.02	0.01	*			0.03		0.10	***		
SCA1											
> 31	0.24	0.22				0.16	**	0.04	***	0.12	***
> 32	0.15	0.12				0.04	***	0.01	***		
> 33	0.06			0.11	*						
SCA2											
> 22	0.11	0.07	*	0.13		0.12		0.01	***	0.06	*
> 23	0.03	0.04		0.04		0.03		0.01		0.02	
> 24	0.03	0.03				0.03		0.00	**		
SCA3											
> 27	0.06	0.10	*	0.07		0.09		0.21	***	0.07	
> 28	0.03	0.02		0.02		0.04		0.11	***	0.03	
SCA6											
> 13	0.04	0.02		0.02		0.04		0.20	***	0.02	
> 14	0.00	0.00				0.00		0.08	***	0.00	

Table 3.4: Frequencies of high-normal alleles in control populations with results of comparison to Welsh data ($*: P < 0.05$, $**: P < 0.01$, $***: P < 0.001$).

3.4 Discussion

There have been few population-based studies of genetic ataxia as most have examined clinic-based cohorts or have performed retrospective analysis of patients referred for laboratory testing. We have performed a detailed and systematic study of chronic progressive LOCA in a well-defined geographical region of the UK and included analysis of all currently known repeat expansion mutations in this heterogeneous and complex group of patients.

In Wales, SCA6, DRPLA and SCA8 are the most important genetic diagnoses in familial ataxia, with no families identified with expanded alleles at the SCA1, SCA2, SCA3, SCA7, SCA10, SCA12, or SCA17 loci. Based on previous work, we had expected to find SCA1, SCA2 and SCA6 and assumed SCA10, SCA12, SCA17 and DRPLA to be rare or absent in the UK population. The identification of SCA6 in Wales is compatible with previous UK reports.[42,72] Whilst the presence of DRPLA was unexpected, it is not without precedent. 8 families from the UK have been reported in the literature to date comprising 29 individuals with the majority being isolated case series or reports, but two unrelated patients were identified as part of a laboratory based audit of generic SCA requests in sporadic ataxia.[72] These families with DRPLA may have a common founder, but subsequent analysis has demonstrated a unique haplotype in one of the four families suggesting that they do not share an immediate common ancestor with the other three families (Chapter 5). We identified two affected individuals from two families with expanded SCA8 alleles one of whom also had an expanded allele at the SCA6 locus. We have been unable to study other individuals from these families and so it remains unclear whether SCA8 expansions co-segregate with disease. However, expanded SCA8 alleles were also identified in six (2%) control patients and the median age of control patients at time of ascertainment was 59.5 years suggesting that these expansions are non-pathogenic or poorly penetrant. Expanded alleles in control populations have been identified in the literature previously[131,167] and it is suggested that penetrance of the expanded allele is variable and dependent on repeat length and other, as yet unknown factors[58]. The identification of unaffected individuals with repeat expansion in this study provides further evidence of the variable penetrance of expanded repeats at the SCA8 locus

and highlights the uncertain role of SCA8 in diagnostic and predictive testing in ataxia.

Data regarding sporadic LOCA in Wales are broadly similar to previous UK reports with most cases being unexplained and SCA6 and FA identified as the most important pathogenic mutations.[72] FA accounted for 2.4% (95% CI 0.6–7.3%) of sporadic ataxia in our series compared to 0.7% (95% CI 0–5%) for SCA6 emphasising the importance of screening for FA even in those patients without the characteristic phenotype, especially in those with an onset below the age of 40. The identification of one lady with "possible FXTAS" suggests that it may account for 0.7% (95% CI 0–5%) of sporadic LOCA, compatible with previous series.[12,147] Our 95% upper confidence limit for the proportion of sporadic LOCA caused by expansions at other loci is 3.6%.

The marked reported variability in relative prevalence of SCA subtypes is highlighted in Chapter 1.2.2 and Tables 3.1 and 3.2 in dominant and sporadic disease respectively (and shown in more detail in Tables 3.5 and 3.6). Even single studies investigating families in different regions of the same country have demonstrated significant differences in SCA subtype frequency.[32] Most SCA prevalence studies examine clinic, population or laboratory-based cohorts and each is subject to a number of confounding factors that may explain at least some of the observed variation. Population and laboratory-based studies usually result in a greater proportion of unexplained cases when compared to clinic-based cohorts, in whom large, previously documented families commonly reside. Such clinic-based samples are often from tertiary referral centres that review highly selected families from a wide geographical region making inferences regarding geographical variability more difficult. Studies of laboratory requests are retrospective and subject to considerable ascertainment bias often with insufficient or inaccurate clinical information, and marked variability in referral criteria dependent on referring clinician. Population-based samples, similar to this study in Wales, focus on one geographical region and will therefore be sensitive to founder effects and usually have more limited sample sizes as a result of the practical limitations in systematically reviewing and investigating large cohorts.

Despite these restrictions, several clear patterns emerge from the highly variable data in the literature. While SCA3 appears the most common disorder in

dominant families worldwide, the significance of SCA3 is much more variable between European series than Asian series. For example SCA3 is very common in Portugal, but was not described in series from Finland and the United Kingdom. Frequencies in Asian series appear more consistent except for India where results are more similar to those from European series, so that SCA2 is much more common in India than other Asian series. In Japan, SCA6 and DRPLA are the most frequent diagnoses after SCA3 but even this is variable depending on the region of Japan studied. SCA6 is generally rare in European series, but appears consistently in series from the UK and Germany. DRPLA is uncommon in European series ($< 2\%$) but is a significant cause of LOCA in most Japanese series. SCA1 and SCA2 are more variable in both Asian and European series and so make comparison more difficult.

Comparison of the prevalence of SCA10, SCA12 and SCA17 is also problematic as there have been fewer systematic surveys. SCA10 and SCA12 have only been described in Mexican and Indian populations respectively and it seems likely that their origin in these defined groups is due to a common founder in these populations. SCA17 is commonly considered in the differential diagnosis of Huntington's disease (HD) since it is characterised by cerebellar ataxia associated with prominent extra-cerebellar features including dementia, chorea and dystonia. Previous work in the UK and Italy has estimated SCA17 as the cause of 2/192 (1%) and 2/225 (0.9%) of families with unexplained ataxia respectively.[11,22]

The widespread variability in the relative importance of different repeat expansion disorders in LOCA remains poorly understood. In some cases, there is a clear founder effect but in others, differences in disease frequency may simply reflect ascertainment bias and local clinical awareness. Founder effects are the probable cause of the unique distribution of SCAs identified in Wales. However it is unclear whether founder effects can explain all observed geographic variation. It has previously been suggested that new expansion may occur from high-normal alleles and lead to an association between the prevalence of high-normal alleles and disease prevalence.[137] Certainly trinucleotide repeat disorders are characterised by meiotic repeat length instability that is proportional to the repeat length giving rise to anticipation at meiosis from affected parent to child. It is therefore conceivable that such a process may result in *de novo* expansion from high-normal

range repeats in association with, as yet unknown, additional factors. A multistep model has been proposed for many loci in which there is first a mutational bias towards larger alleles at a locus leading to expanded, more unstable alleles resulting in disease-range expansions in distant offspring.[128,169] Indeed, expansion from large normal alleles have been described in sporadic HD,[88] but in this disorder there is overlap between repeat lengths of normal individuals and affected patients (unaffected: 8–39, affected: > 36) suggesting variable penetrance dependent on repeat length.[56,101,108] Alleles in HD are defined as normal (< 26 repeats), mutable or intermediate alleles (27–35 repeats, do not cause disease but may be unstable at meiosis and lead to sporadic disease), reduced penetrant alleles (36–39 repeats) and fully penetrant alleles (> 39 repeats). Intermediate or mutable alleles are also described in other trinucleotide disorders, including FA (22–120 repeats),[29] myotonic dystrophy (20–30 repeats),[60] Fragile-X (41–60 repeats)[85] and SCA7 (28–35 repeats).[130] The longest SCA7 allele found in our control population was 14 repeats. The risk of expansion from mutable alleles in HD is estimated at 2–10%, with expansion determined by sequence interruptions, flanking haplotype, sex of the transmitting parent, sperm mosaicism and other, as yet unknown factors.[17,40] Although intermediate length alleles have not yet been described in other SCA disorders, a common haplotype has been identified in DR-PLA segregating with both high-normal alleles and expanded alleles in the disease range suggesting a common founder for both and supporting the hypothesis of *de novo* expansion from high-normal alleles.[169]

Our data demonstrate a significant difference between Welsh and Japanese control chromosomes at all loci (Table 3.4). High-normal repeats are more common at the SCA3, SCA6 and DRPLA loci in Japan and this correlates with their greater importance in Japan compared to Wales and other UK series. However, the data would also predict SCA1 and SCA2 to be more important in Wales than Japan, and we failed to identify any families with expanded alleles at these loci although previous studies from the UK and Japan have demonstrated a difference in the relative importance of SCA2: 16.5% in UK compared to 3.1% in Japan.[37,42,72,77,90,94,137,159] Therefore, when the Japanese and UK populations are compared, there does appear to be an association between prevalence of high-normal repeats and prevalence of SCA2, SCA3, SCA6 and DRPLA. However,

no such association is evident for SCA1 in which prevalence figures are broadly similar despite a marked difference in high-normal repeat length prevalence.

Examination of Caucasian and Indian series identifies only minor differences in high-normal frequency, often at one cut-off only, and the significance of these differences is uncertain as many are not statistically significant when a Bonferroni correction is applied to account for multiple testing. In some cases, the pattern appears to correlate with disease prevalence, such as DRPLA in Wales and Finland, but in other cases no such association exists suggesting no definite conclusions can be drawn regarding these differences.

The relative contributions of new mutation formation and founder effects to disease prevalence in familial ataxia is uncertain. In Caucasian series, there is no clear association between high-normal repeat frequency and disease prevalence and the variation seen among these studies may be primarily due to founder effects. However, Japanese high-normal repeat frequencies are significantly different to that from other series and the pattern of this relationship reflects the relative importance of these disorders in Japanese series. Further exploration of the origins of repeat expansion disorders in human populations will require detailed analysis of disease allele haplotypes together with investigation of meiotic instability in intermediate length alleles.

	n	SCA1	SCA2	SCA3	SCA6	SCA7	SCA8	DRPLA
Asia								
China[139]	85	4.7	5.9	48.2	0.0	0.0		0.0
India[3]	26	19.2	26.9	11.5	3.8			
India[109]	39	7.7	25.6	5.1	0.0	0.0	0.0	0.0
Japan[77]	330	5.5	2.4	27.6	25.5	0.0		7.3
Japan[90]	44	34.1	0.0	20.5	11.4			20.5
Japan[94]	117	24.8	0.9	23.9	10.3	1.7	0.9	14.5
Japan[137]	202	3.0	5.0	43.1	10.9			19.8
Japan[159]	101	0.0	5.9	33.7	5.9			19.8
Taiwan[126]	74	5.4	10.8	47.3	10.8	2.7		1.4
Europe								
Finland[62]	49	4.1	2.0	0.0	2.0	12.2	18.4	0.0
France[6]	416							0.2
France[26]	71	14.1						
France[28]	87	19.5		33.3				
Germany[117]	77	9.1	10.4	41.6	22.1			
Italy[11]	183	26.2	29.0	1.1	1.1	1.1	1.1	0.5
Italy[32]	29	72.4	24.1	0.0	0.0	3.4		0.0
Italy[32]	22	18.2	31.8	0.0	0.0	0.0		0.0
Italy[32]	65	4.6	63.1	0.0	3.1	1.5		1.5
Italy[37]	30	50.0	36.7	0.0				
Netherlands[146]	227	6.2	7.0	28.2	15.0	7.5		
Portugal[122]	38	0.0		84.2				0.0
Spain[103]	72	5.6	15.3	15.3	1.4	2.8		1.4
UK[37]	19	36.8	47.4	5.3				
UK[42]	38	0.0	7.9	0.0	5.3	2.6		
UK[72]	22	4.5	4.5	0.0	4.5			0.0
Other								
Australia[132]	88	18.2	6.8	13.6	19.3	2.3		0.0
France / USA[137]	177	15.3	14.1	29.9	5.1			0.0
Multiple[122]	67	4.5		55.2				1.5
Multiple[122]	29	10.3		17.2				3.4
Portugal / Brazil[123]	106	0.0	2.8	63.2	0.9	0.9	1.9	1.9
USA[34]	47	6.4	12.8	23.4				0.0
USA[83]	178	5.6	15.2	20.8	15.2	4.5		

Table 3.5: Dominant ataxia - worldwide SCA prevalence studies: % of patients with a defined genetic diagnosis.

	n	SCA1	SCA2	SCA3	SCA6	SCA7	SCA8	DRPLA
Asia								
India[3]	31	3.2	9.7	3.2	0.0			
Japan[77]	598	0.2	0.3	4.2	4.5	0.0		2.0
Taiwan[126]	49	0.0	0.0	0.0	4.1	0.0		0.0
Europe								
Finland[62]	165	0.0	0.0	0.0	0.0	0.6	5.5	0.0
France[6]	393							0.3
Germany[120]	124	0.0	0.8	0.0	7.3	0.0	2.4	
Spain[103]	60	0.0	0.0	0.0	0.0	0.0		0.0
UK[72]	124	0.8	4.0	0.8	4.8			1.6
Other								
USA[83]	134	0.0	1.5	0.7	1.5	0.7		

Table 3.6: Sporadic ataxia - worldwide SCA prevalence studies: % of patients with a defined genetic diagnosis.

Case control analysis of repeat expansion length in ataxia

4.1 Introduction

While the majority of patients with sporadic ataxia do not have an identified genetic cause (Chapters 1.2 and 3 and Muzaimi et al.[86]) it is unclear whether there are specific genetic risk factors associated with the development of late-onset cerebellar ataxia (LOCA). Given the phenotypic similarity between familial and sporadic disease (Chapter 7) it is conceivable that polymorphisms in the familial ataxia genes could be risk factors for the development of sporadic ataxia. Alternatively, patients with sporadic ataxia may reflect a population of patients with high-normal repeats below the traditional pathogenic range and that their disease reflects variable penetrance.

To examine the role of repeat expansion lengths in sporadic ataxia, we have undertaken a case-control study comparing normal controls with patients with sporadic ataxia in whom pathogenic mutations have been excluded.

4.2 Methods

4.2.1 Patients

Patients were recruited as outlined in Chapter 2 (page 19) and Section 3.2 (page 44) with controls recruited from consecutive consenting Welsh blood donors (Chapter 2.4). Patients were excluded if a pathogenic range repeat expansion was identified.

4.2.2 Statistical methodology

We performed four comparisons: i) all ataxia cases vs. controls, ii) sporadic ataxia vs. controls, iii) sporadic ataxia cases without features suggesting a diagnosis of multiple system atrophy (MSA) vs. controls, iv) sporadic patients with MSA vs. controls.

Possible differences between affected and unaffected patients were assessed using two non-parametric tests: the Kolmogorov-Smirnov 2-sample test and the Mann-Whitney U (Wilcoxon paired) test. In addition, we compared frequencies of

high-normal repeats between patient groups using cut-offs from previously published reports and those used in Chapter 3.[62,109,123,137]

Traditional association analyses have used univariate contingency tests such as Pearson χ^2 and Fisher's exact test to analyse marker frequencies in affected and control patients. However, such analyses are problematic when there is marked polymorphism as high numbers of allelic variants results in sparse contingency tables, invalid sampling distributions and reduced power to distinguish differences between affected and control patients.[121] The usual approach is to collapse adjacent rows of a contingency table by grouping those alleles with low numbers of counts. We have used a CLUMP analysis to perform repeated contingency tests to generate four statistics: T1: a straightforward χ^2 test, T2: χ^2 test with rare alleles grouped together to prevent small expected cell counts, T3: comparison of one allele against the others grouped together and T4: all possible 2x2 tables comparing any combination of alleles against the rest.[121] Rather than making a Bonferroni correction to account for multiple testing, Monte-Carlo methods are used to generate probability statistics.

In addition, since the *a priori* hypothesis is that larger repeat lengths may be found in ataxic patients, we have used an additional custom clumping technique to generate sequential 2x2 contingency tables from allele counts. This algorithm takes advantage of the fact that while spinocerebellar ataxia (SCA) loci can be highly polymorphic, alleles reflect triplet repeat length. Therefore it becomes possible to generate a number of 2x2 tables for each locus, grouping allele frequencies at sequentially higher cut-offs, to determine the cut-off that maximises differences between groups. Such a mechanism makes more sense than the T3 model above for triplet repeats. For instance, we are less interested in whether patients with ataxia are more likely to have 8 repeats than 9 repeats or 7 repeats, but that there are overall more (or less) repeats. We then use Monte-Carlo methods to generate an appropriate probability statistic and additionally generate a statistic from an asymptotic distribution with a Bonferroni correction. This latter method is considered a conservative approach. Our sample size had over 90% power to demonstrate significant differences between repeat length distributions between controls and affecteds.

```
clump.allele ←
function (repeats, group)
{
    start ← min(repeats, na.rm = T)
    end ← max(repeats, na.rm = T)
    r ← data.frame(cut = (start + 1):(end − 1), p.value = NA,
        statistic = NA)
    for (i in r$cut) {
        res ← clump.dochi(repeats, i, group)
        r[r$cut == i, "p.value"] = res$p.value
        r[r$cut == i, "statistic"] = res$statistic
    }
    return(r)
}
clump.dochi ←
function (repeats, i, group)
{
    breaks = c(min(repeats, na.rm = T) − 1, i, max(repeats, na.rm = T) +
        1)
    tab ← table(cut(repeats, breaks = breaks), group)
    res ← chisq.test(tab, simulate.p.value = T)
}
do.clump ←
function (g1, g2, FUN = return)
{
    repeats ← c(g1, g2)
    group ← c(rep("g1", length(g1)), rep("g2", length(g2)))
    FUN(clump.allele(repeats, group))
}
best.clump.p ←
function (g1, g2)
{
    do.clump(g1, g2, FUN = function(r) {
        r[which.min(r$p.value), "p.value"]
    })
}
```

Listing 4.1: Sequential clumping algorithm for comparing allele frequencies (R code)

	Number	Percentage	Mean age (range)
Sporadic ataxia			
Men	79	64.2%	61 (29–86)
Women	44	35.8%	63 (33–88)
All	123	100%	62 (29–88)
Familial ataxia			
Men	26	47.3%	57 (23–83)
Women	29	52.7%	54 (21–86)
All	55	100%	56 (21–86)
Control population			
Men	225	73.3%	51 (25–75)
Women	82	26.7%	51 (27–74)
All	307	100%	51 (25–75)

Table 4.1: Demographics of the sporadic, familial and control patients.

4.2.3   Genetic methodology

Genomic DNA was isolated from peripheral blood using standard methods. Detailed genetic methodology is described in Section 3.2.3 and the published version of this chapter (see Majounie, 2007[75]).

All markers were originally genotyped in a collection of 306 Caucasian blood donor control individuals recruited from South Wales as part of a schizophrenia case-control study (NM Williams, unpublished data — see Chapter 2.4).

4.3   Results

We identified 178 with chronic progressive LOCA with no identified aetiology as a denominator population for study. There were 55 (26 male, 29 female) familial cases segregating in 38 kindreds and 123 (79 male, 44 female) sporadic patients (Table 4.1). Mean age at onset was 48 (range 10–78) and the mean age in 2007 was 60 (range 21–88).

As explained in Section 3.3.2 (and Table 3.3 on page 52), the number of alleles at each locus is highly variable with some loci conserved (SCA2 and SCA7) and some demonstrating wide variability (DRPLA and SCA3). The overall allelic distribution was similar between cases and controls (Figure 4.1) with repeat length distributions highly skewed and non-normally distributed (Figures 3.1 and 4.3).

Results of a detailed comparison of allele frequency for all possible repeat lengths is shown in Table 4.2. Non-parametric comparison between patient groups did not demonstrate any significant difference for most loci. Mann-Whitney test suggested possible differences between SCA7 alleles in controls and sporadic MSA patients, SCA10 in controls vs. familial cases and SCA17 in controls vs. familial cases. The results of a modified CLUMP analysis are shown in Table 4.3. In all cases, further examination of any positive results demonstrates no biologically significant difference; for example differences at the SCA7 locus are due to some control patients having higher numbers of repeats than affected patients (Figure 4.4). In addition, a comparison of the frequency of high-normal repeats for each locus between controls and affected patients is shown in Table 4.4 demonstrating no significant difference between controls and affected patients of any clinical category.
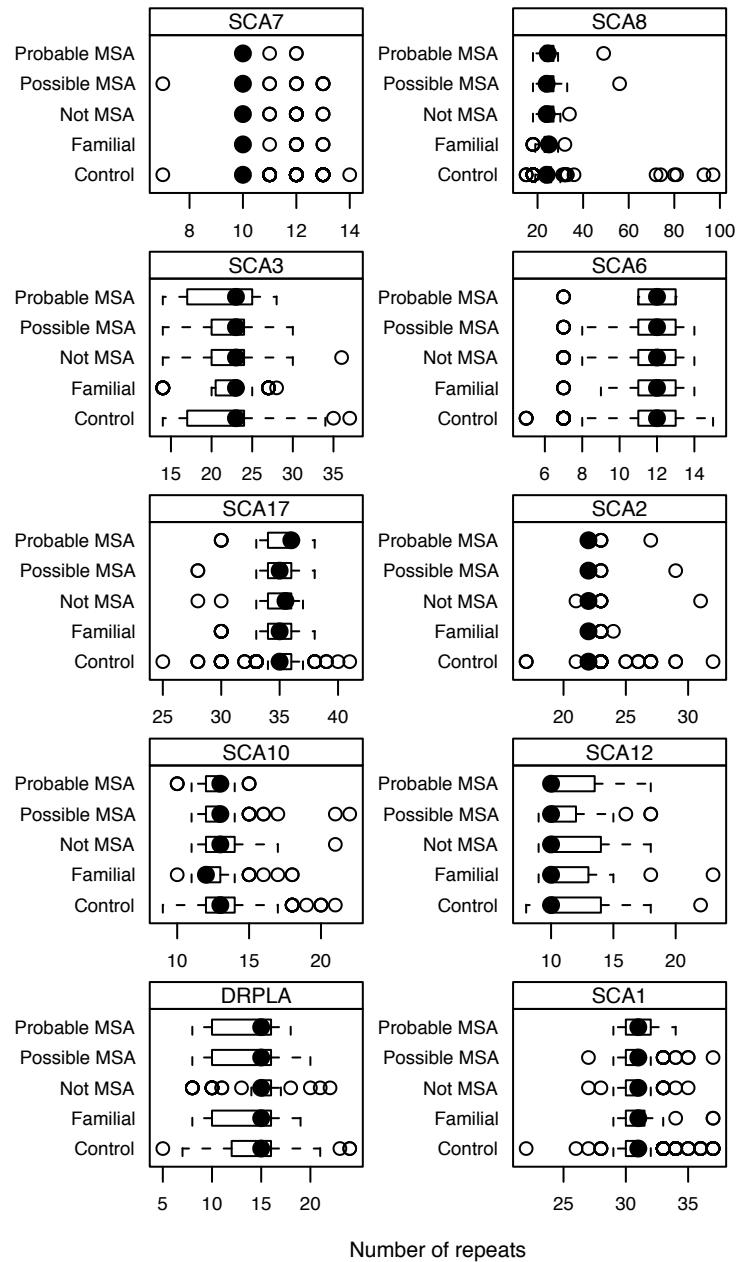
Figure 4.1: Comparison of allele distributions between ataxic and control patients. An alternative representation is shown in Figure 4.2.
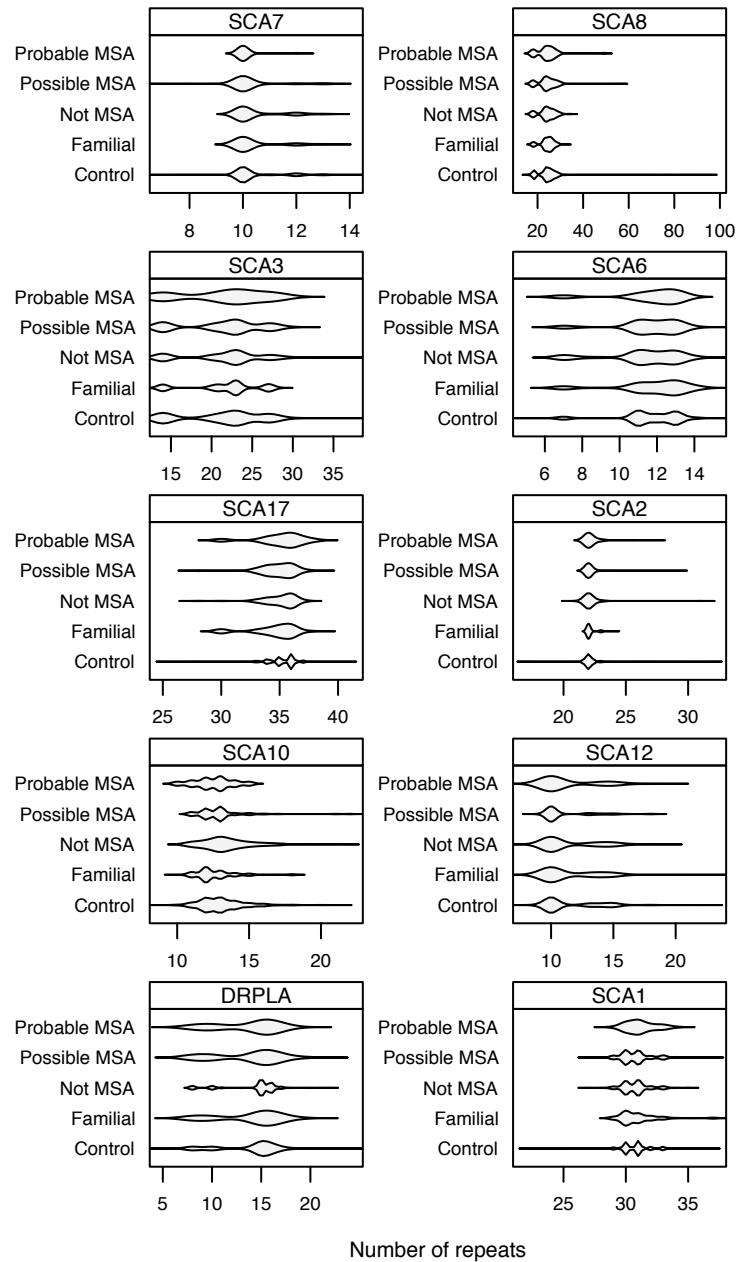
Figure 4.2: Comparison of allele distributions between ataxic and control patients. This is an alternative ("violin-plot") version of Figure 4.1.
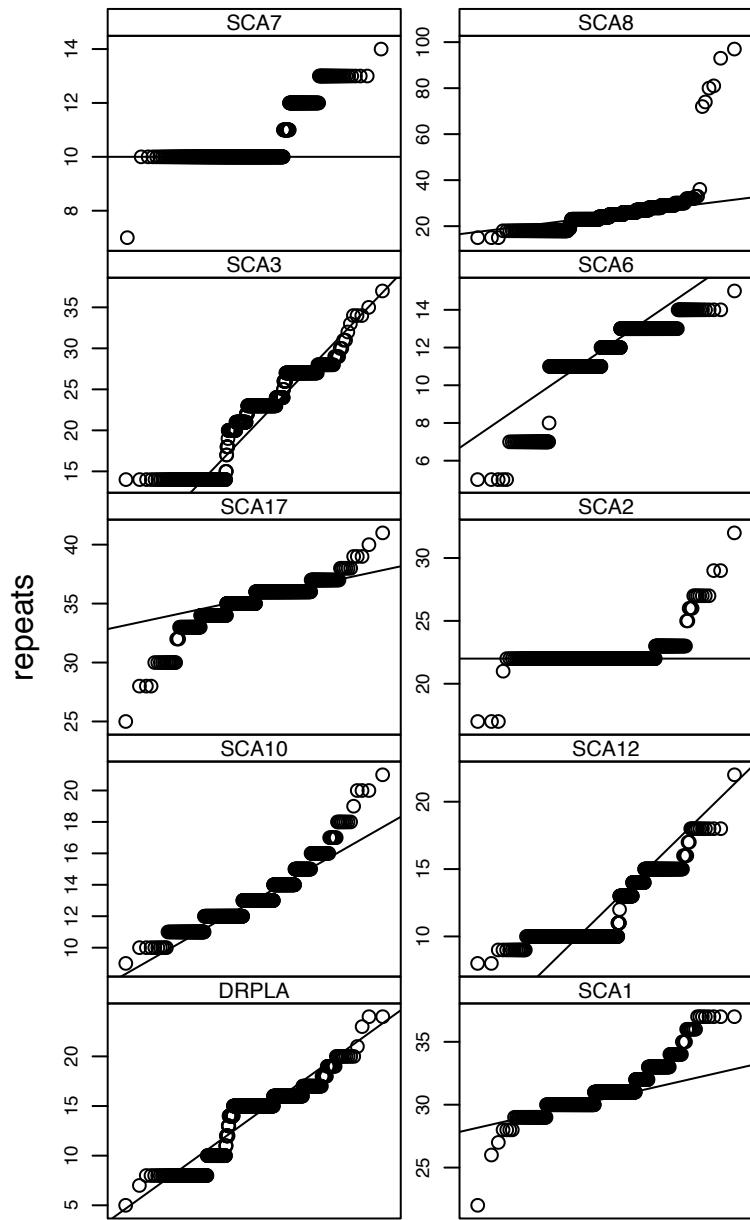
Figure 4.3: Q-Q plots in control samples to show non-normality with considerably skewed distributions. These plots compare the distribution of allele lengths (circles) with a normal distribution (line).

	Sporadic			Familial
	All	MSA	Not MSA	
DRPLA				
ks	1	0.9	1	0.9
wx	0.7	0.7	0.6	0.8
clump	0.5	0.3	0.5	0.1
SCA1				
ks	1	1	1	0.6
wx	0.6	0.3	0.4	0.3
clump	0.2	0.4	0.3	0.1
SCA2				
ks	1	1	1	1
wx	0.3	0.6	0.1	0.5
clump	0.3	0.8	0.1	0.4
SCA3				
ks	0.9	1	0.9	0.7
wx	0.6	0.8	0.6	0.9
clump	0.3	0.3	0.3	0.1
SCA6				
ks	0.9	0.5	1	0.7
wx	0.6	0.4	0.4	0.1
clump	0.1	0.1	0.1	0.1
SCA7				
ks	0.7	0.4	1	1
wx	0.1	<0.05	0.3	0.4
clump	0.1	<0.05	0.3	0.5
SCA8				
ks	1	1	1	0.7
wx	0.4	0.9	0.4	0.3
clump	0.2	0.3	0.3	0.1
SCA10				
ks	1	0.8	1	0.1
wx	0.6	0.1	0.9	<0.05
clump	0.1	<0.05	<0.05	<0.01
SCA12				
ks	0.4	0.8	0.6	1
wx	0.2	0.5	0.2	0.8
clump	0.1	0.2	0.1	0.1
SCA17				
ks	1	0.8	1	0.5
wx	0.5	0.5	0.3	<0.05
clump	0.3	<0.05	0.2	<0.01

Table 4.2: Results comparing control genotypes to patients with sporadic disease, MSA, Not MSA and familial disease respectively. Figures represent p-values. (ks=Kolgorov-Smirnov, wx = Wilcoxon rank sum, clump = result of modified CLUMP algorithm).

DRPLA sporadic			SCA7 MSA			SCA10 familial,			SCA17 MSA			SCA17 familial		
Cut-off	P	χ^2	Cut-off	P	χ^2	Cut-off	P	χ^2	Cut-off	P	χ^2	Cut-off	P	χ^2
6	1.0	0.37	8	1	0.07	10	1	0.00	26	1	0.06	26	1	0.11
7	0.6	0.75	9	1	0.07	11	0.3	1.19	27	1	0.06	27	1	0.11
8	0.7	0.16	10	<0.05	4.57	12	<0.01	7.19	28	1	0.24	28	1	0.42
9	0.9	0.05	11	<0.05	4.32	13	0.1	2.70	29	1	0.24	29	1	0.42
10	0.9	0.06	12	0.3	2.13	14	0.5	0.54	30	0.1	3.46	30	<0.01	15.22
11	0.7	0.24	13	1	0.07	15	0.7	0.31	31	0.1	3.46	31	<0.001	15.22
12	0.8	0.09				16	0.7	0.34	32	0.1	2.51	32	<0.01	12.30
13	0.7	0.25				17	0.7	0.25	33	0.8	0.12	33	<0.01	7.42
14	0.9	0.04				18	1	0.53	34	0.9	0.16	34	0.1	2.76
15	0.5	0.59				19	1	0.42	35	0.7	0.23	35	0.2	2.15
16	0.7	0.14				20	1	0.11	36	<0.05	5.30	36	0.4	1.00
17	0.6	0.34							37	0.2	2.41	37	1	0.02
18	0.5	0.63							38	1	0.30	38	1	0.53
19	0.8	0.23							39	1	0.12	39	1	0.21
20	1.0	0.12							40	1	0.06	40	1	0.11
21	1.0	0.01												
22	0.6	1.12												
23	0.6	0.75												

Table 4.3: Example result of iterative modified CLUMP algorithm with sequential cuts together with p-values and χ^2 statistics. Data from control patients is compared to each category specified.

Cut off	Control	Sporadic			Familial
		All	MSA	Not MSA	
DRPLA					
> 16	0.12	0.13 (ns)	0.11 (ns)	0.13 (ns)	0.19 (ns)
> 17	0.05	0.04 (ns)	0.03 (ns)	0.04 (ns)	0.03 (ns)
> 18	0.04	0.03 (ns)	0.00 (ns)	0.03 (ns)	0.03 (ns)
> 19	0.02	0.02 (ns)	0.00 (ns)	0.02 (ns)	0.00 (ns)
> 20	0.01	0.01 (ns)	0.00 (ns)	0.01 (ns)	0.00 (ns)
> 21	0.00	0.00 (ns)	0.00 (ns)	0.01 (ns)	0.00 (ns)
SCA1					
> 30	0.61	0.60 (ns)	0.69 (ns)	0.58 (ns)	0.52 (ns)
> 31	0.24	0.23 (ns)	0.31 (ns)	0.22 (ns)	0.25 (ns)
> 32	0.15	0.14 (ns)	0.17 (ns)	0.13 (ns)	0.12 (ns)
> 33	0.06	0.04 (ns)	0.03 (ns)	0.05 (ns)	0.05 (ns)
> 34	0.03	0.03 (ns)	0.00 (ns)	0.03 (ns)	0.03 (ns)
SCA12					
> 15	0.03	0.03 (ns)	0.03 (ns)	0.03 (ns)	0.03 (ns)
SCA17					
> 38	0.01	0.00 (ns)	0.00 (ns)	0.00 (ns)	0.00 (ns)
> 39	0.00	0.00 (ns)	0.00 (ns)	0.00 (ns)	0.00 (ns)
SCA2					
> 22	0.11	0.08 (ns)	0.14 (ns)	0.07 (ns)	0.14 (ns)
> 23	0.03	0.02 (ns)	0.03 (ns)	0.02 (ns)	0.02 (ns)
> 24	0.03	0.01 (ns)	0.03 (ns)	0.01 (ns)	0.00 (ns)
SCA3					
> 27	0.06	0.08 (ns)	0.11 (ns)	0.07 (ns)	0.02 (ns)
> 28	0.03	0.03 (ns)	0.00 (ns)	0.03 (ns)	0.00 (ns)
> 29	0.02	0.01 (ns)	0.00 (ns)	0.02 (ns)	0.00 (ns)
> 30	0.02	0.00 (ns)	0.00 (ns)	0.01 (ns)	0.00 (ns)
> 31	0.01	0.00 (ns)	0.00 (ns)	0.01 (ns)	0.00 (ns)
SCA6					
> 13	0.04	0.03 (ns)	0.00 (ns)	0.03 (ns)	0.09 (ns)
> 14	0.00	0.00 (ns)	0.00 (ns)	0.00 (ns)	0.00 (ns)
SCA7					
> 14	0.00	0.00 (ns)	0.00 (ns)	0.00 (ns)	0.00 (ns)
SCA8					
> 27	0.15	0.15 (ns)	0.12 (ns)	0.15 (ns)	0.11 (ns)
> 28	0.09	0.11 (ns)	0.12 (ns)	0.11 (ns)	0.06 (ns)

Table 4.4: Frequency of large normal alleles at different loci in controls compared to affected patients with results of χ^2-squared tests (ns=not significant).
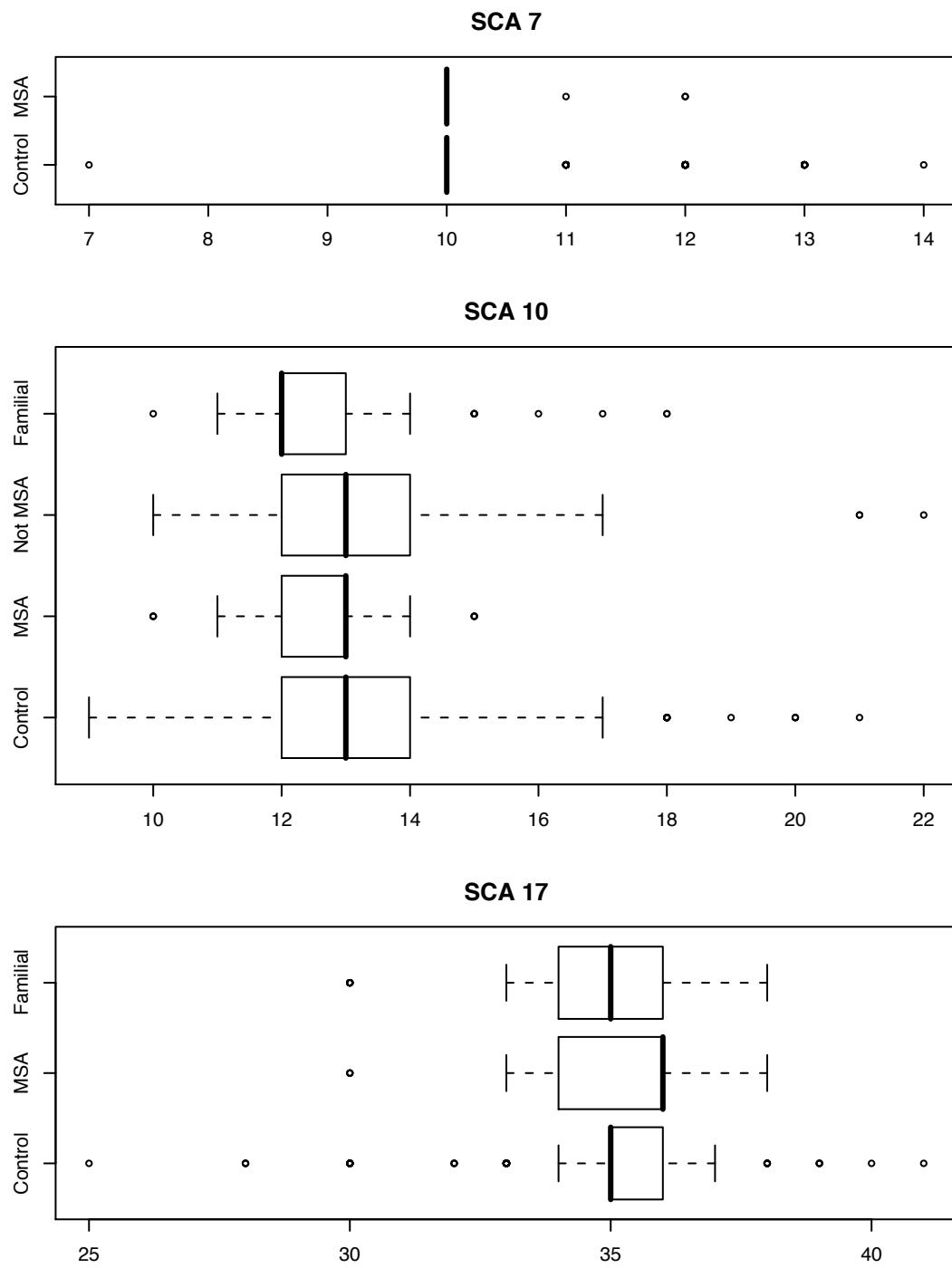
Figure 4.4: Comparison of control allele frequencies with affected patients. These charts graphically investigate possible differences suggested in Table 4.2

4.4   Discussion

This study is the first to investigate non-Mendelian risk in chronic LOCA. We have used a robust population-based approach to minimise case ascertainment bias and have included study of 306 Caucasian control patients recruited from the same geographical region. We did not demonstrate any important difference between repeat expansion length distributions between control and affected patients suggesting that repeat length is not a susceptibility risk factor for the development of ataxia.

We highlighted the difficulties involved in testing for SCA8 expansions in Chapter 3 and therefore recommend caution in testing and interpretation at this locus, especially for pre-symptomatic testing and counselling.

Our study has failed to demonstrate an association between large normal repeats and the development of ataxia, however the frequency of sporadic ataxia warrants ongoing research into the clinic-pathological basis of ataxia and its genetic background.

DRPLA in South Wales

5.1 Introduction

Dentatorubral pallidoluysian atrophy (DRPLA) is a rare, autosomal dominant, clinically heterogeneous neurodegenerative disorder characterised clinically by a variable combination of progressive dementia, ataxia, chorea, myoclonus, epilepsy and psychiatric disturbance and pathologically by combined degeneration of dentatorubral and pallidoluysian systems. As outlined in Chapter 1.2.1, it is considered to be found "almost exclusively among the Japanese".[145]

We describe the clinical features of seventeen patients in four Caucasian families from South Wales with DRPLA and report the crude prevalence within this well-defined geographical region of the United Kingdom (UK). To determine the origins of DRPLA within this region, we have searched for evidence of a common founder and assessed repeat length polymorphism in both affected patients and 306 controls.

5.2 Methods

5.2.1 Case ascertainment

Patients with DRPLA were identified using a systematic search of local departmental databases, local ataxia and Huntington's disease (HD) registers, a laboratory-based genetic database, and liaison with local neurologists and geneticists.

A standardised protocol was used to collect detailed clinical and family data, together with examination findings and details of previous investigations. For each affected family member a detailed clinical evaluation was undertaken in conjunction with an informant history and review of contemporary medical records. Age at onset was defined as age at which first clinical symptoms were first noticed and presenting feature as one of myoclonus, epilepsy, choreoathetosis, ataxia, mental retardation or psychiatric disturbance. Clinical features associated with the subsequent disease course and age at death where relevant were also noted. Psychiatric disturbance was defined as severe depression or psychosis requiring specialist psychiatric care or admission to a psychiatric hospital for treatment. A prior history

of substance misuse or mild depression was noted but not characterised as a presenting feature.

Control patients were recruited from consecutive consenting Welsh blood donors as outlined in Chapter 2.4.

The project was approved by the relevant local ethics committee and NHS research and development office and information was stored in accordance with the Data Protection Act 1998.

5.2.2 Genetic analysis

DNA was extracted from peripheral blood leucocytes by standard methods. Polymerase chain reaction (PCR) amplification and analyses of the CAG repeat were performed as previously described.[67] Microsatellite analysis was performed using three markers located 800kb (F8VWF) and 110kb (D12S1623) upstream and 3.3Mb (D12S77) downstream of the ATN1 gene and were analysed using FAM- or HEX- labelled primers on the ABI3100 DNA sequencer. Single nucleotide polymorphism (SNP) analysis of the ATN1 gene was achieved using a SNaPshot reaction with three markers: rs34199021 and rs2071075 (previously described as the A-B system)[76] and rs2071076 (Figure 5.1). Direct sequencing of two intronic regions (intron 4 and intron 6) of the ATN1 gene was also carried out to determine the genotype in known SNPs and identify additional SNPs (ABI BigDye Terminator V3.0).

Repeat length polymorphism was investigated in 306 unrelated Caucasian blood donor control individuals (224 males, 82 females, mean age 53, range 27–77) originally recruited from South Wales as part of a schizophrenia case-control study (NM Williams, unpublished data).

5.2.3 Statistical analysis

All analysis was performed using "R: A Language and Environment for Statistical Computing".[104] Crude prevalence and confidence intervals were determined by a Poisson exact method. Analysis of the differences in the frequency of large normal alleles were performed using the Fisher exact test and the χ^2 test with Yates' correction.[104]

5.3 Results

We identified a total of 17 patients with DRPLA (10 male, 7 female) segregating in 4 kindreds (Table 5.1) in South Wales providing an estimated minimum crude prevalence of 0.71 per 100,000 (95% CI 0.33–1.35). There was considerable overlap in ascertainment source but the most important were the ataxia registry (seven individuals in three families), the HD clinic (two individuals in two families), consultant neurologists (five individuals in four families) and the laboratory-based genetics database (two individuals in two families). DRPLA was not identified in 359 schizophrenia patients. The ataxia registry which represented the largest source of case ascertainment contained 401 patients with cerebellar ataxia recruited between 1999 and 2007. DRPLA was the underlying defined genetic aetiology in 11.4% of families with dominant ataxia (22.8% of familial cases) but was not an identified cause of sporadic ataxia.

Mean age at onset was 37 (range 20–46). Common presenting features included epilepsy (5/17), cerebellar ataxia (3/17), psychiatric disturbance (3/17), dementia (3/17) and chorea (1/17) but patients then usually developed a variable combination of other additional features including dementia (mild or moderate in 9/17, severe in 2/17), ataxia (9/17), epilepsy (9/17) and chorea (6/17). Two middle-aged patients were pre-symptomatic at the time of evaluation.

Patient	Age	Sex	Onset	Ataxia	Dementia	Psychiatric	Epilepsy	Chorea	Extrapyramidal	Repeats
Family A										
II-1	†	F		++	+		+			
II-3	†	M		(++)			+			
III-6‡	†	F			+			+		
III-3	55	M	40		+		(+)		+	8/51
III-2	71	M	42	+	++	+	(+)			8/54
IV-16	45	F	31	+	+		(+)			17/59
IV-1	49	M	45	(++)	+		+			15/56
IV-3	45	M	35	+		+				17/55
Family B										
III-1	49	M	46				+	(++)		8/60
II-1	82†	M			+					
II-6‡	39†	M			+			+		
III-11	44†	F	34	(+)	(+)		(++)	+		11/66
Family C										
II-1	†	F			++	+		++		
III-1	62†	M	29	++	+	(++)				?/61
Family D										
II-2	43	M	20	+	+		(++)	+		15/61
II-5		F	Pre-symptomatic							
II-8		F	Pre-symptomatic							

Table 5.1: Clinical features of DRPLA in South Wales. Boldface indicates proband. ++ and + represent major and minor clinical features respectively. Presenting features highlighted with parentheses. † signifies deceased patients and age of death. ‡ indicates patients with limited informant history thought to have HD.

The median repeat length was 59 (range 51–66) on the affected allele and 15 (range 8–17) on the unaffected allele. Within the four families there were only two documented meiotic events with full clinico-genetic data available and both were paternal transmissions with an increase of 2 and 5 repeats respectively.

Haplotype analysis identified a 4Mb common haplotype spanning the DRPLA locus from F8VWF to D12S77 in family A (Figure 5.1) with the haplotype inferred from multiple family members. The genotypes in a single affected member of family B were consistent with a shared haplotype spanning the 4Mb region. In a single affected member of family D, the disease haplotype differed from the three other families by marker D12S77 located 3.3Mb from the gene, but the genotypes were consistent with a smaller shared haplotype spanning 1.5Mb. Further refinement of the haplotype was made by identification of rare intronic SNPs lying in the DRPLA gene. A unique allele was identified approximately 800bp from the CAG repeat (rs12426246) that segregated with DRPLA in family C but was not present in the other families. The recombination rate for this region is estimated as 3.0 cM/Mb (UCSC database `http://genome.ucsc.edu/`), suggesting this family is unlikely to share a recent common ancestor with the other three families.

The gene was highly polymorphic in control individuals with repeat length ranging from 5 to 24. A bimodal distribution was noted with two main peaks at 8–10 and 15 repeats (median). Fourteen individuals (4.6%) had repeat lengths of more than 19 (see Figure 5.2). This demonstrates a statistically significant lower proportion of "high-normal" repeats (> 19) in the Welsh background population compared to Japanese populations (7.4%, $P < 0.001$ and 10%, $P< 0.05$) but a significantly higher proportion than that observed in North American (0%, $P< 0.05$)[13] and Finnish Caucasian series ($< 0.1\%$, $P< 0.001$).[62] However, there was no statistical difference between our background population and a combined French and North American Caucasian series (3.0%, P=0.6).[138]
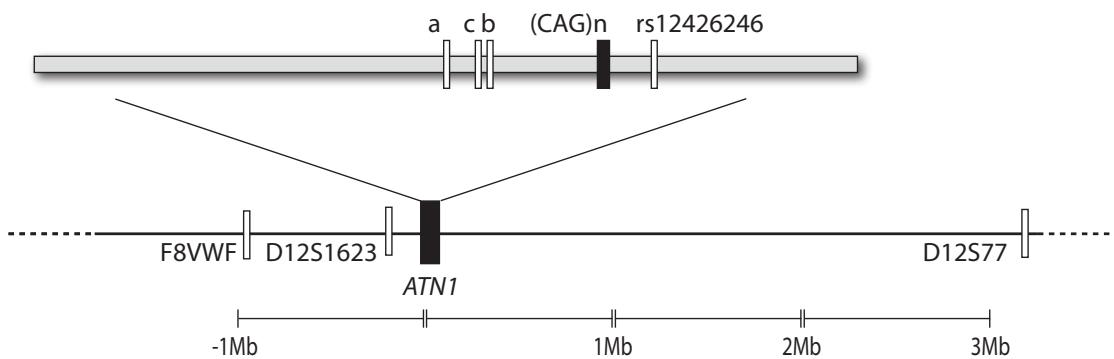
Figure 5.1: Schematic representation of microsatellite markers and SNPs on the 4Mb region spanning *ATN1*. Microsatellite markers are: F8VWF, D12S1623 and D12S77. $(CAG)_n$: region of CAG repeats in the *ATN1* gene. a,b,c: SNP assay using rs34199021, rs2071075 and rs2071076 respectively. The haplotype for the largest family spans from F8VWF to D12S77 ($\sim$ 4Mb).

5.3.1 Case reports

The pedigrees are shown in Figure 5.3.

Family A

Patient A-IV:1 (Male, aged 49 years). Presented with a pure cerebellar gait disorder aged 45, but within four years, he had developed epilepsy, personality change, cognitive difficulties and chorea. Clinical examination revealed mild dysarthria, a prominent gait ataxia with considerable staggering and difficulties with half-turn, limb ataxia and chorea. Deep tendon reflexes were pathologically brisk in the lower limbs. Cognitive testing revealed mild dyscalculia and motor sequencing impairment, MMSE 28/30.

Patient A-III:1 (Male, aged 71 years). Developed epilepsy aged 42 and at the same time had severe depression, a history of multiple overdoses and required psychiatric inpatient care. He developed progressive ataxia, dementia and chorea at 50; he required a wheelchair aged 60 but was not investigated until the diagnosis of his son in 2006. At that time, he was disorientated, disinhibited with prominent memory difficulties associated with mild dysarthria, prominent gait and limb ataxia, marked chorea and truncal dystonia. MMSE 16/30.
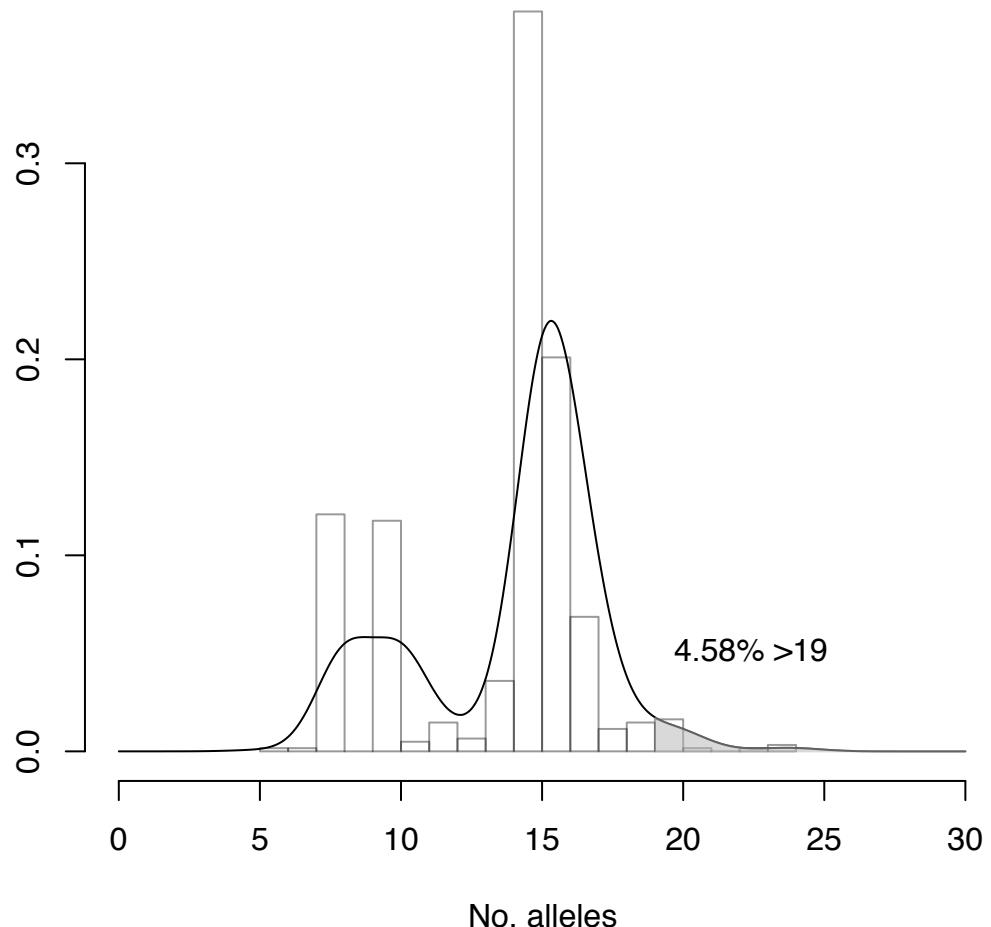
Figure 5.2: Distribution of DRPLA repeat lengths in control population (n=306 patients, 612 chromosomes). 4.58% (14) have repeat lengths more than 19.
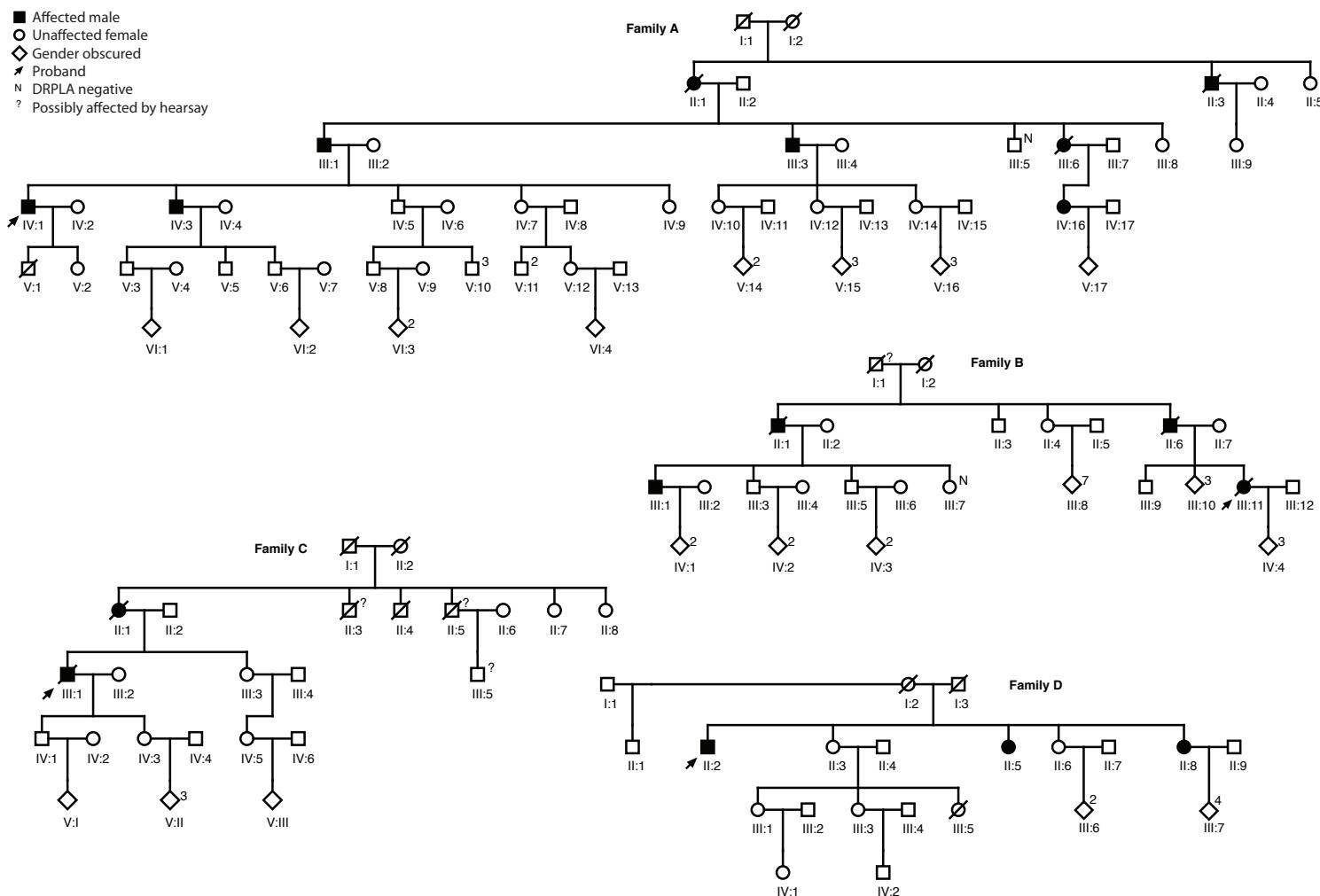
Figure 5.3: DRPLA family pedigrees

Family B

Patient B-III:11 (Female, age at death 44 years). At the age of 34 she developed recurrent generalised tonic-clonic seizures associated with myoclonus with impaired balance and memory. On examination, she was noted to have cognitive impairment, an ataxic gait and abnormal posturing. Within five years, she was unable to stand independently and had a spastic quadraparesis.

Family C

Patient C-III:1 (Male, age at death 62 years) presented with what was thought to be primary psychiatric disease aged 29 and was admitted for inpatient psychiatric care. Over twenty years he developed progressive gait ataxia, increasing behavioural problems and chorea. When examined aged 57, there was marked perserveration, dysarthria, gait ataxia, jerky ocular pursuit movements, and slow saccades initiated with head movement. There was no history of epilepsy.

Family D

Patient D-II:2 (Male, aged 43 years) presented with epilepsy aged 20. Progressive gait ataxia from age of 25 but within 15 years he was wheelchair bound and totally dependent, with prominent spontaneous action and stimulus sensitive myoclonus in association with dysarthria, dysphagia and he required a percutaneous endoscopic gastrostomy aged 41.

5.4 Discussion

The families and case histories described emphasise the broad clinical heterogeneity of DRPLA and suggest that it should be considered in the differential diagnosis of a wide spectrum of neurological disease especially if there is an autosomal dominant family history of dementia or movement disorders. DRPLA has previously been considered rare in the Europe and the United States but our data confirm DRPLA as an important genetic cause of late-onset cerebellar ataxia in Caucasian patients and is at odds with previous assumptions that it is found

"almost exclusively among the Japanese".[145] DRPLA was the underlying genetic aetiology cause of 11.4% of families with dominant ataxia in South Wales compared to 0.4% in previously reported European series.[6,11,32,62,72,103,122] We would therefore suspect that DRPLA is more common in the UK than previously thought and likely to be under-reported. Pedigree analysis of the four families identified in South Wales implicates 76 individuals at risk of developing DRPLA within this region and adult and paediatric neurologists should be alert to its clinical heterogeneity.

The cause of the wide variability in importance of DRPLA is unclear. While much variability may reflect a combination of ascertainment bias, under-reporting and founder effects, it is suggested that the rate of *de novo* expansion may vary between ethnic groups. Indeed it is reported that the proportion of high-normal repeats within the background indigenous population may correlate with disease prevalence and that high-normal repeats may act as a reservoir for new expansion.[137] The reported wide variability in prevalence of trinucleotide repeat (TNR) disorders may simply reflect ascertainment bias and under-reporting but there are a number of other factors that may contribute including genuine population-based differences. The latter may be related to a common founder of expanded alleles within specific populations, but it has also been suggested that the rate of *de novo* expansion may vary between ethnic groups. It is suggested that population-wide distribution of TNRs at a specific locus may correlate with disease prevalence within a given population and that expansions may arise on chromosomes bearing a high-normal range of triplet repeats.[13,137] The proportion of high-normal repeats within the background indigenous population may therefore determine disease prevalence. Indeed, repeat length polymorphism of *atrophin-1* in the unaffected Japanese population is significantly greater than in Caucasians and African-Americans correlating with the higher prevalence of DRPLA. Our data partially support this hypothesis demonstrating a significantly lower proportion of "high-normal" repeats (> 19) in the Welsh background population compared to Japanese populations but higher than Caucasian series from North America and Finland.

Three patients from South Wales had a preceding history of major psychiatric disease prompting the hypothesis that DRPLA may account for some cases of

major psychiatric illness. However, DRPLA was not found in 359 schizophrenia patients tested locally (unpublished data) and therefore DRPLA does not appear to be an important cause of psychosis in South Wales. However, psychiatric illness was common within our families and further study is required to document and classify psychiatric phenotypes in DRPLA since we are unaware of any detailed previous work in this field.

Our data suggest that a founder effect accounts for some, but not all of the high prevalence of DRPLA in Wales — three families have genotypes at the DRPLA locus which are consistent with a common founder haplotype although the detailed pedigree data available from multiple family members has not led to a plausible link. We have demonstrated a distinct haplotype segregating within one family not present within the other families suggesting the expansion in at least one family did not arise from a recent common ancestor. While there are no data regarding haplotype analysis between reported families from the literature, families are often widely geographically isolated. Such isolation, in conjunction with proven anticipation, a clear relationship between age at onset and repeat length and a plausible association between prevalence of disease and background prevalence of high-normal repeats would all support a hypothesis of spontaneous mutation as a contributory factor in the prevalence of DRPLA.

Non-Asian DRPLA: A systematic review of the literature

6.1 Introduction

As outlined in Chapters 1.2.1 and 5, dentatorubral pallidoluysian atrophy (DR-PLA) is an autosomal dominant neurodegenerative disorder considered found "almost exclusively among the Japanese".[145] DRPLA is caused by a $(CAG)_n$ expansion in *atrophin-1* (ATN-1) on chromosome 12p13.31 resulting in a polyglutamine tract thought to lead to a toxic gain of function.[67,138,170] The CAG tract is highly polymorphic with a normal length of up to 35 repeats and is expanded to over 49 repeats in affected patients.[67,169] A number of other genetic characteristics have also been reported in both affected Japanese populations and mouse models including somatic mosaicism and age-dependent inter-generational instability particularly on paternal transmission resulting in anticipation.[59,111] Recent reports have suggested that disease phenotype observed in polyglutamine disorders may be modified by ethnic background.[41] However, because of the relative rarity of DRPLA in Caucasian populations, it is unclear whether the clinical features, correlation between repeat length and phenotype and intergenerational repeat stability are similar to that observed in the more commonly reported Japanese populations.

We have performed a systematic review of published cases of non-Asian DR-PLA with a particular emphasis on the clinical and genetic phenomenology.

6.2 Methods

6.2.1 Case identification

A series of non-Asian DRPLA cases were identified from the literature to investigate genotype-phenotype correlations in these populations. We performed a systematic search of multiple electronic databases including Medline and Embase and review of reference lists from published reviews and original research on DRPLA using the search terms DRPLA, Haw River syndrome (HRS) and reviewed published literature on the prevalence of other trinucleotide repeat (TNR) disorders including the autosomal dominant cerebellar ataxia (ADCA) and Huntington's disease (HD). Inclusion criteria included non-Asian cases reported with
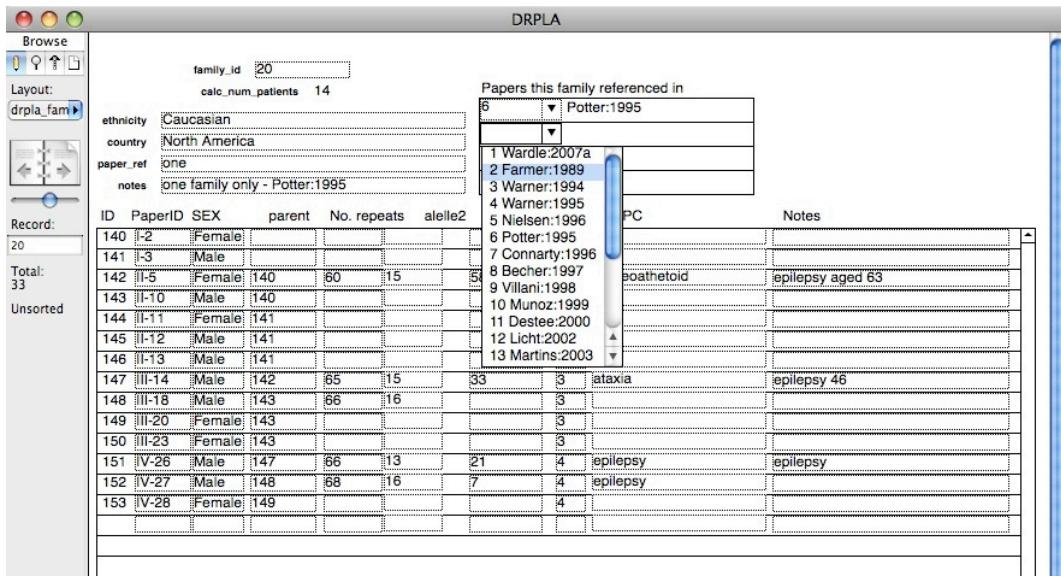
Figure 6.1: Recording reported patients and families with DRPLA.

a molecularly confirmed diagnosis in at least one family member. Many papers included reports of relatives affected by hearsay and these were included in the total counts when related to a patient with molecularly proven DRPLA. Families or individuals reported in more than one paper were identified and excluded where possible. All data were stored in a custom relational database with each reported patient linked to the relevant family and citation(s) (Figure 6.1).

6.2.2 Statistical analysis

All analysis was performed using "R: A Language and Environment for Statistical Computing".[104] We used linear regression to model the relationship between repeat length and age at onset, with or without logarithmic transformation, together with analysis of model diagnostics and standardised information criterion. Multivariate logistic regression together with simpler univariate methods (Kruskal-Wallis one-way analysis of variance) were used to analyse the factors associated with presenting complaint. Mann-Whitney U (Wilcoxon rank sum test) and Student's t-test were used to compare paternal and maternal transmission.

6.3 Results

6.3.1 Identified patients

A systematic literature search identified 183 individuals (90 male, 73 female and 20 unknown) in 27 families (Table 6.1 and Figure 6.2. The level of clinical information provided was variable although it was possible to ascertain age at onset in 78 patients, presenting features in 66 patients (30 epilepsy, 21 ataxia, 11 choreoathetoid and 4 psychiatric) and genotype data in 66 patients. Mean age at onset was 31 (range 1–67) with 19 patients aged below 20, 31 aged between 20 and 40, and 28 aged 40 or over. Data on age and cause of death were very limited but mean age of death was 46 (16–68) years (n=10).

6.3.2 Repeat length and age at onset and age at death

A highly significant correlation was identified between repeat length and age at onset (Figure 6.3). Repeat length accounted for 62% of observed variation in age at onset, with a Pearson correlation coefficient of -0.79 (P< 0.0001, 95% CI -0.88 to -0.66). Step-down linear modelling including polynomial and logarithmic terms as covariates confirmed that these did not significantly improve the predictive power of the final, more simple, model. Logarithmic transformation of age at onset is intuitive biologically and does not result in predictions of negative ages of onset, but regression diagnostics on our limited data set suggested the linear model was better than the exponential model (Figures 6.7 and 6.8). Assessment of the significance of the length of the unaffected allele, gender, ethnicity and country of origin did not improve the model's explanatory power. A similar relationship was observed between age at death and number of repeats, although there were limited data available (n=8) with a linear model combining repeat length and gender accounting for 83.5% of observed variation in age at death.

Year	Country	Patients	Reference(s)
African-American			
1989	North America	39	[31]
1997	North America	7	[5]
2002	North America	7	[73]
Caucasian			
1994	United Kingdom	4	[155–157]
1995	Malta	11	[157]
1995	United Kingdom	4	[157]
1995	United Kingdom	5	[157]
1995	Holland	19	[92,93]
1995	North America	14	[100]
1996	United Kingdom	5	[19,72]
1997	North America	6	[5]
1997	United Kingdom	2	[5]
1997	United Kingdom	2	[5]
1997	United Kingdom	1	[72]
1998	Italy	3	[148]
1999	Spain	12	[87]
2000	France	4	[25]
2000	United Kingdom	6	[20]
2003	Portugal	4	[76]
2003	Portugal	2	[76]
2003	Portugal	2	[76]
2003	Portugal	2	[76]
2005	Australia	3	[149]
2007 †	United Kingdom	8	[152]
2007 †	United Kingdom	5	[152]
2007 †	United Kingdom	2	[152]
2007 †	United Kingdom	4	[152]

Table 6.1: Reports of 183 non-Asian patients segregating in 27 families with DRPLA. †signifies families described in Chapter 5
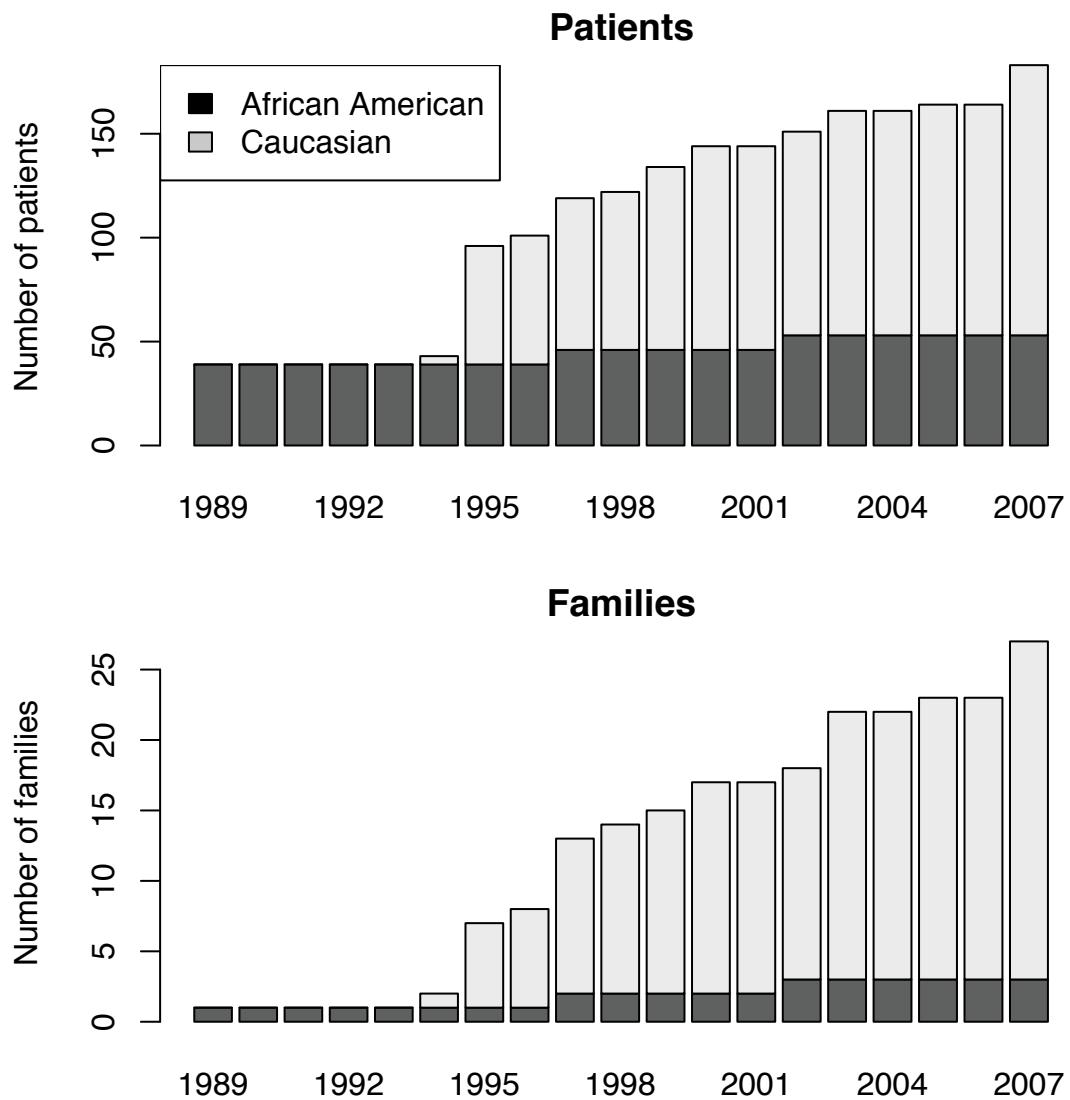
Patients

Families

Figure 6.2: Cumulative total of patients and families reported in literature from non-Asian series between 1989 and present day.
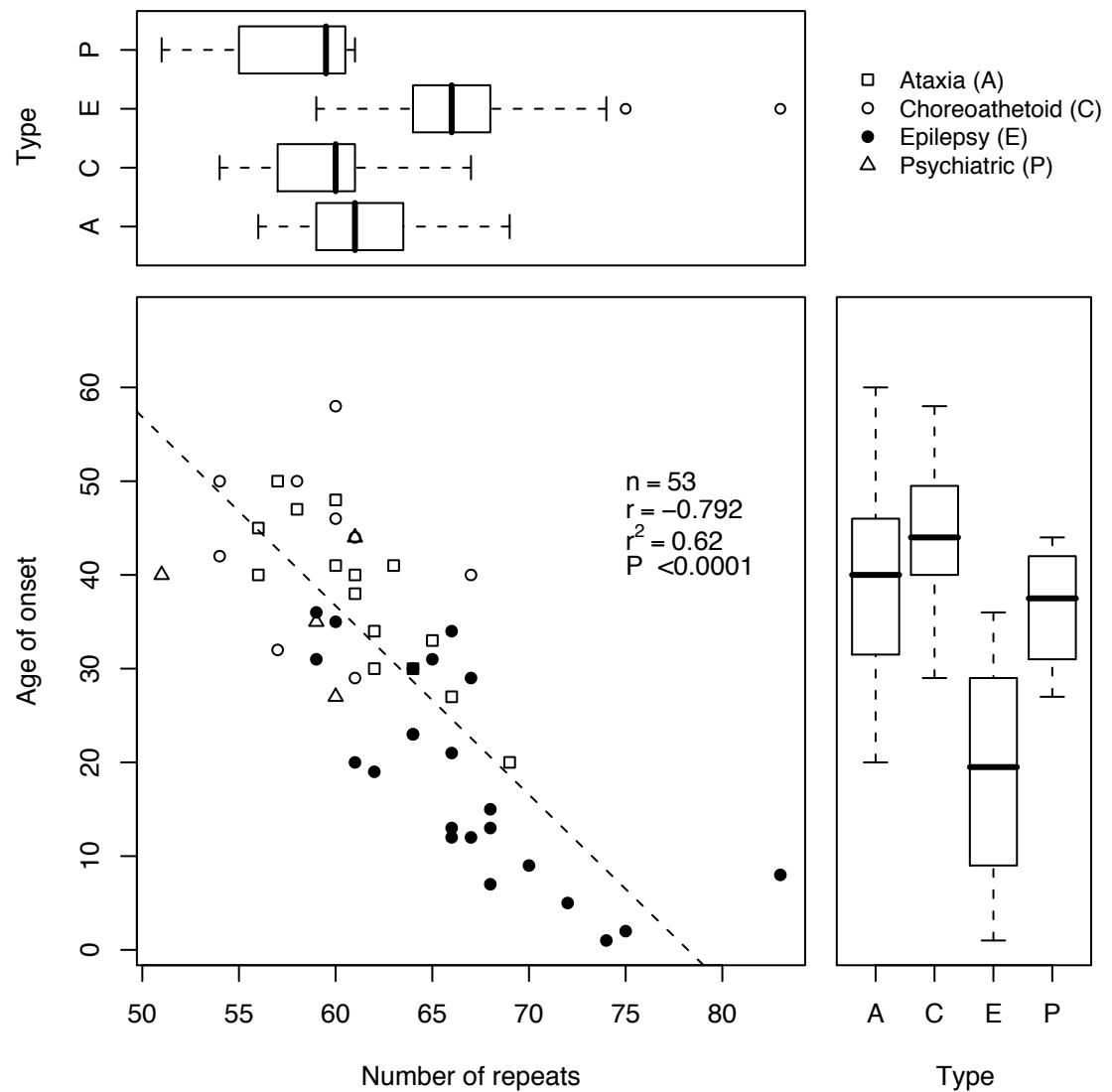
Figure 6.3: Relationship between age at onset, repeat length and mode of presentation. Regression diagnostics shown in Figure 6.4. A version of this figure with confidence and prediction limits is shown in Figure 6.6.
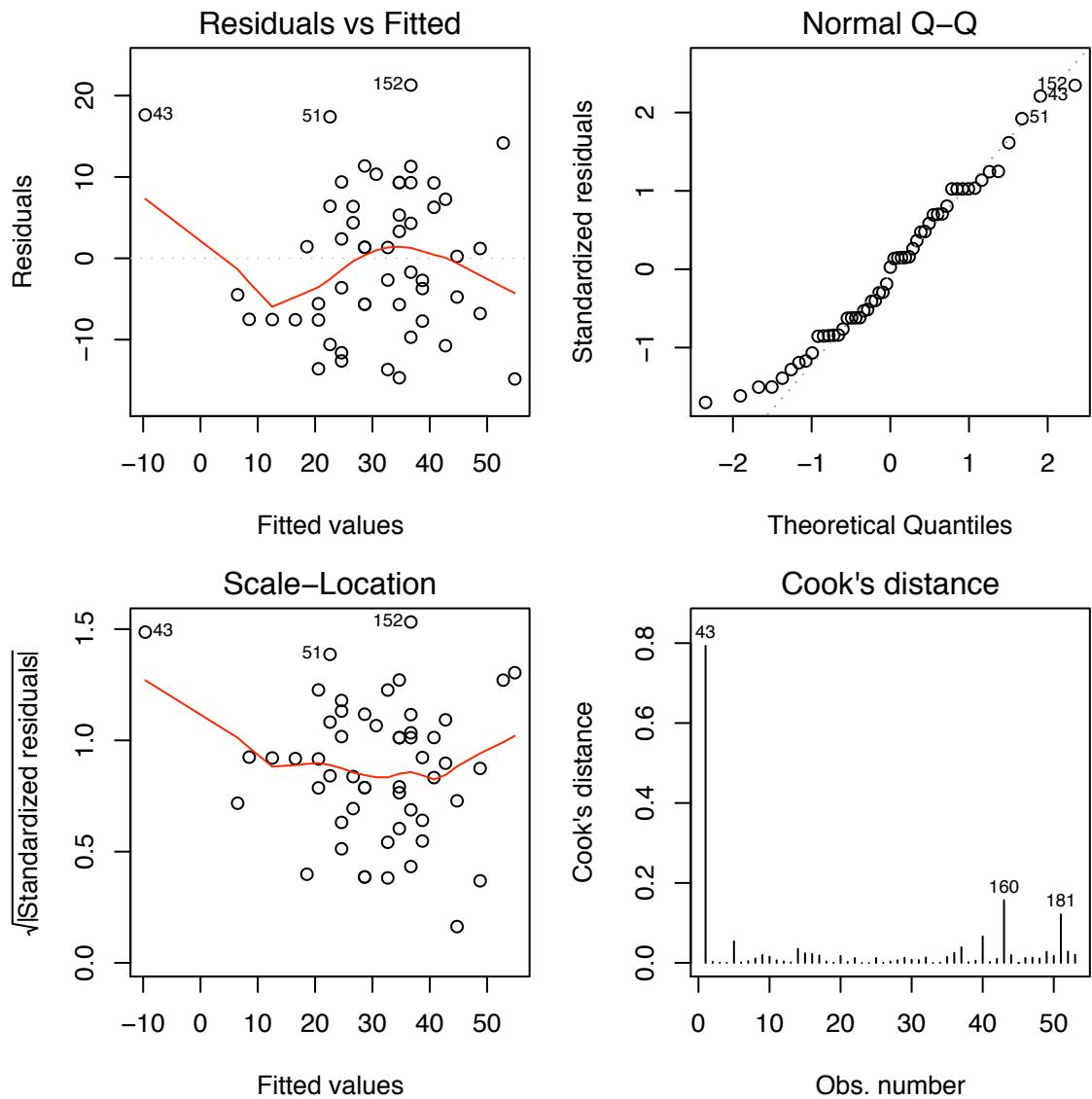
Figure 6.4: Regression diagnostics for relationship between age at onset and repeat length as shown in Figure 6.3
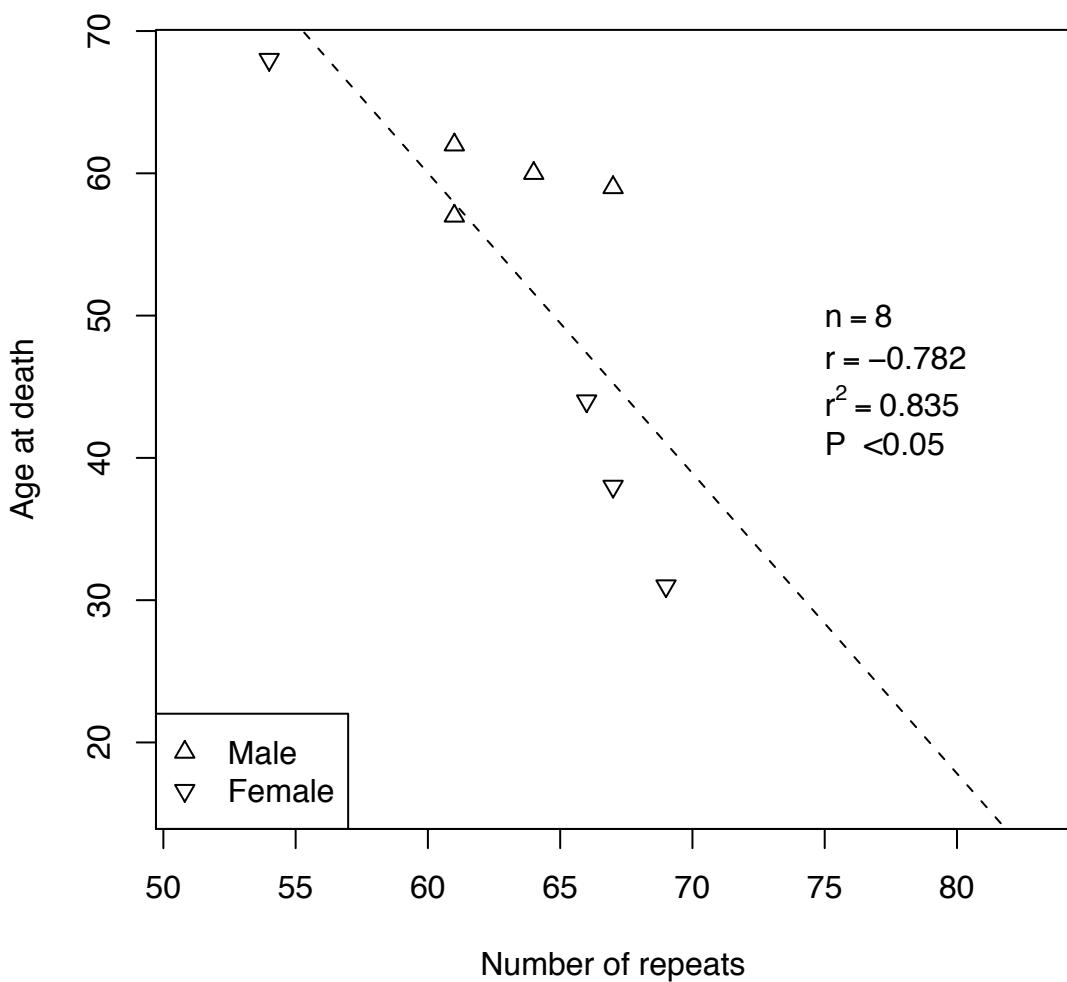
Figure 6.5: Relationship between age at death and number of repeats.
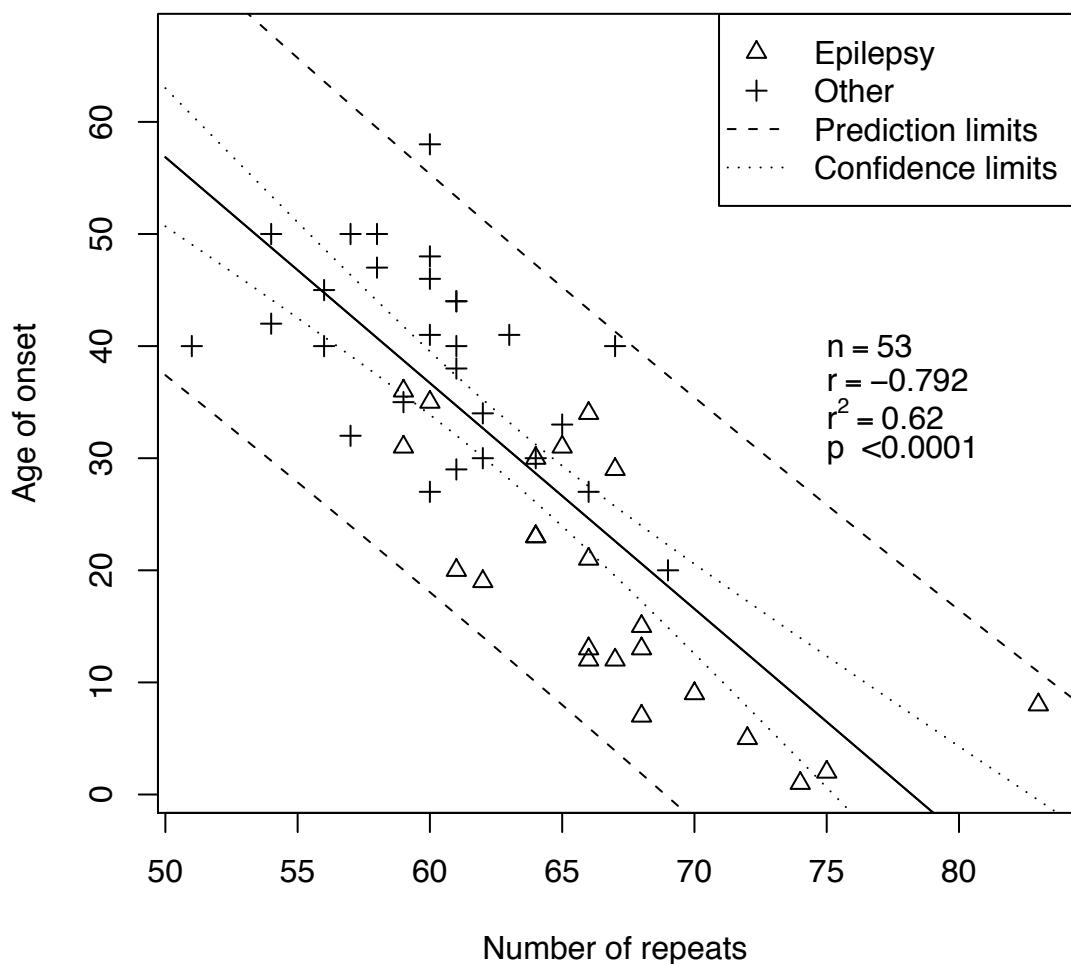
Figure 6.6: Relationship between age at onset and repeat length (with prediction and confidence limits).
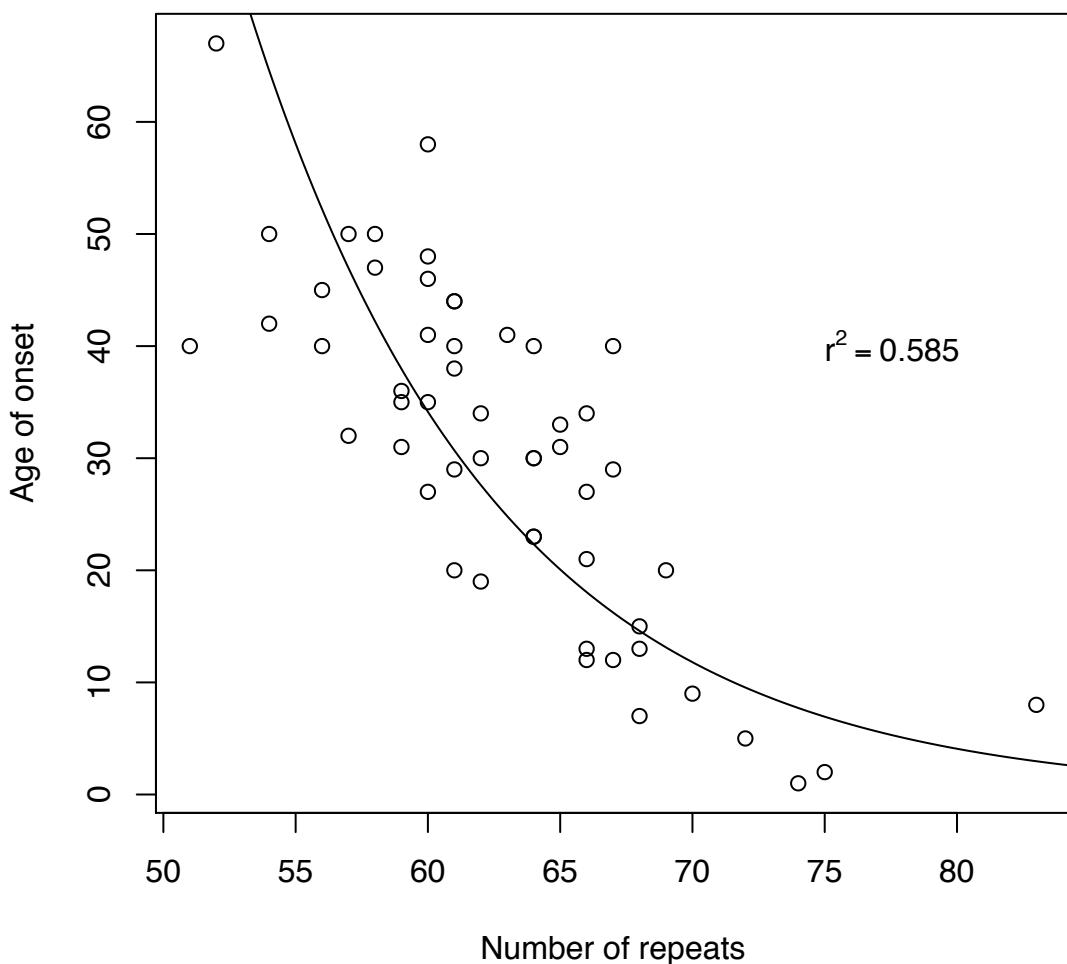
Figure 6.7: Relationship between age at onset and repeat length. Logarithmic transformation. Diagnostic plots shown in Figure 6.8
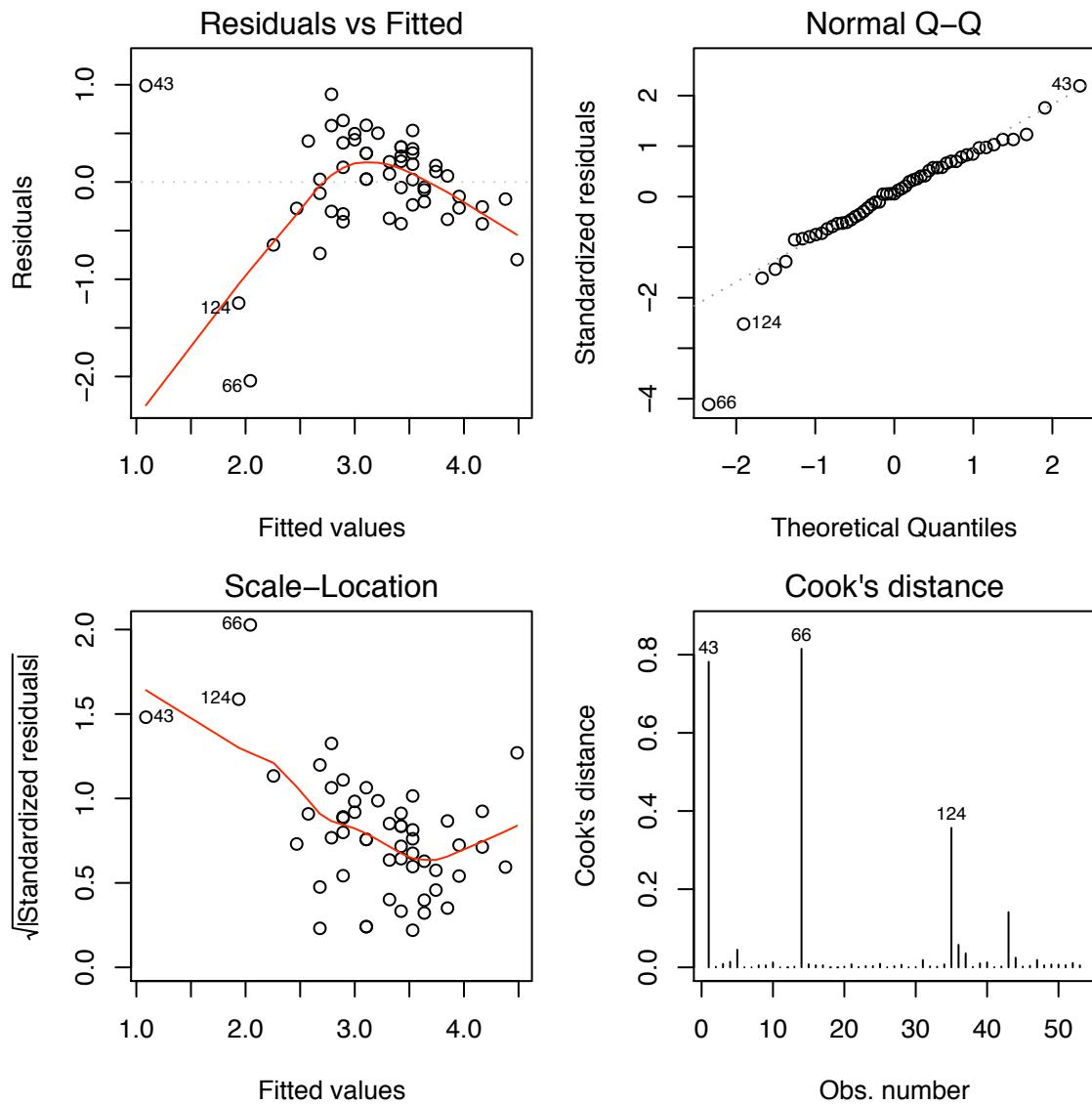
Figure 6.8: Regression diagnostic plots for logarithmic model shown in Figure 6.7

6.3.3 Number of repeats and presenting complaint

In addition, a highly significant relationship between repeat length and main presenting complaint was identified (Kruskal-Wallis $P < 0.001$, Table 6.2 and Figure 6.10). This collective analysis of available data suggests that progressive myoclonic epilepsy is the main presenting feature in those below the age of twenty and that older patients tend to present with a variable combination of ataxia, dementia, chorea and psychiatric disturbance although may later develop epilepsy (Figures 6.11 and 6.12).

6.3.4 Genetic anticipation

There is evidence of marked anticipation in DRPLA. A crude analysis of repeat length and generation within families demonstrates that repeat length increases at each generation (Figure 6.13). We identified 92 meiotic events although not all had complete genotype or phenotype data to facilitate a more detailed analysis. There was a median inter-generational reduction in age at onset of 19 (-20 to 47, n=40) years per generation, with a corresponding increase of 5 (-1 to 23, n=26) repeats per generation. We were able to analyse 21 meiotic events for paternal transmission and 5 meiotic events for maternal transmission. The median intergenerational expansion for both paternal and maternal transmission was five repeats (paternal range 0 to 23, n=21, maternal range -1 to 7, n=5) and we did not find a statistically significant difference between these groups (P=0.2). However, the two largest intergenerational increases in repeat length and age at onset were paternal (from 60 to 83 repeats and from 60 to 74 repeats) and the only contraction in repeat length was maternal in origin (from 56 to 55 repeats). There was no observed relationship between change in repeat length at meiosis and absolute parental repeat length (Figure 6.16). The intergenerational change in repeat length and age at onset are shown in Figures 6.14 and 6.15.
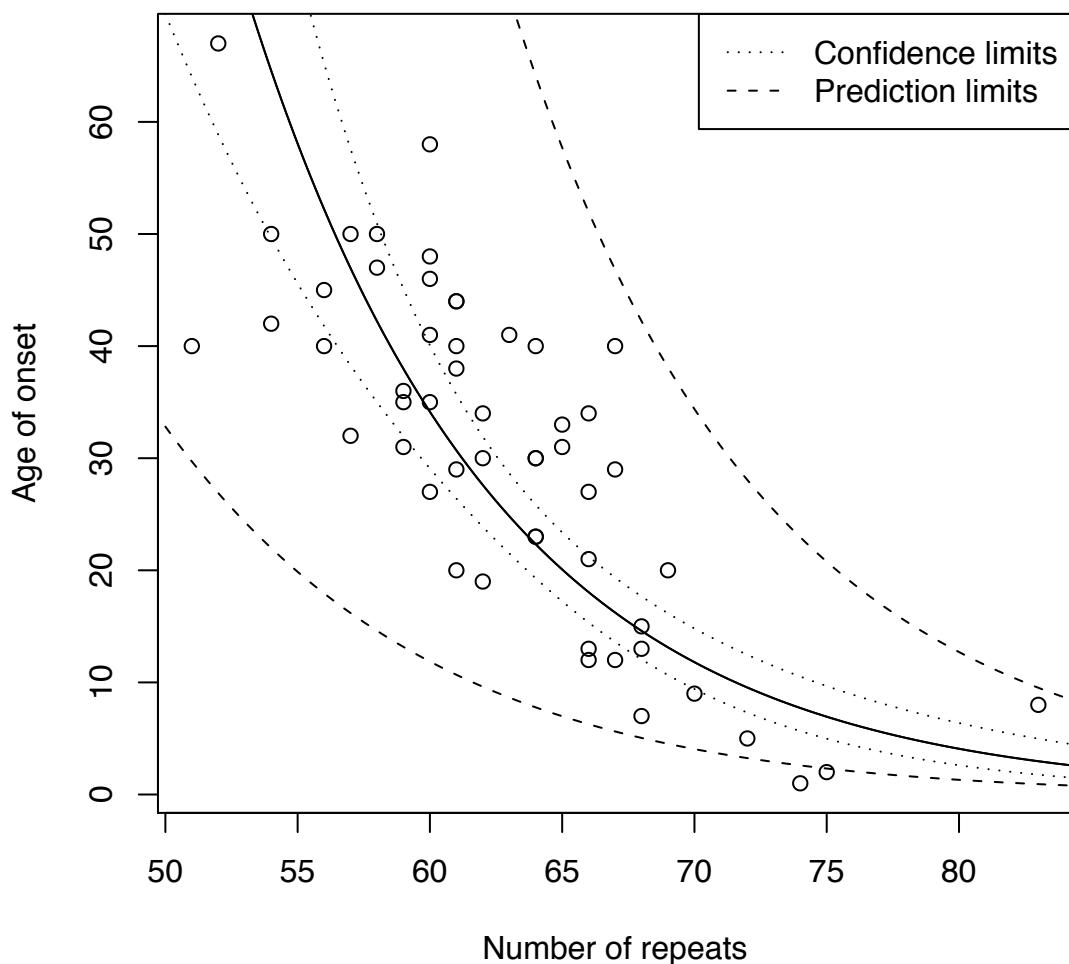
Figure 6.9: Relationship between age at onset and repeat length with prediction and confidence limits shown. Logarithmic transformation. Diagnostic plots shown in Figure 6.8
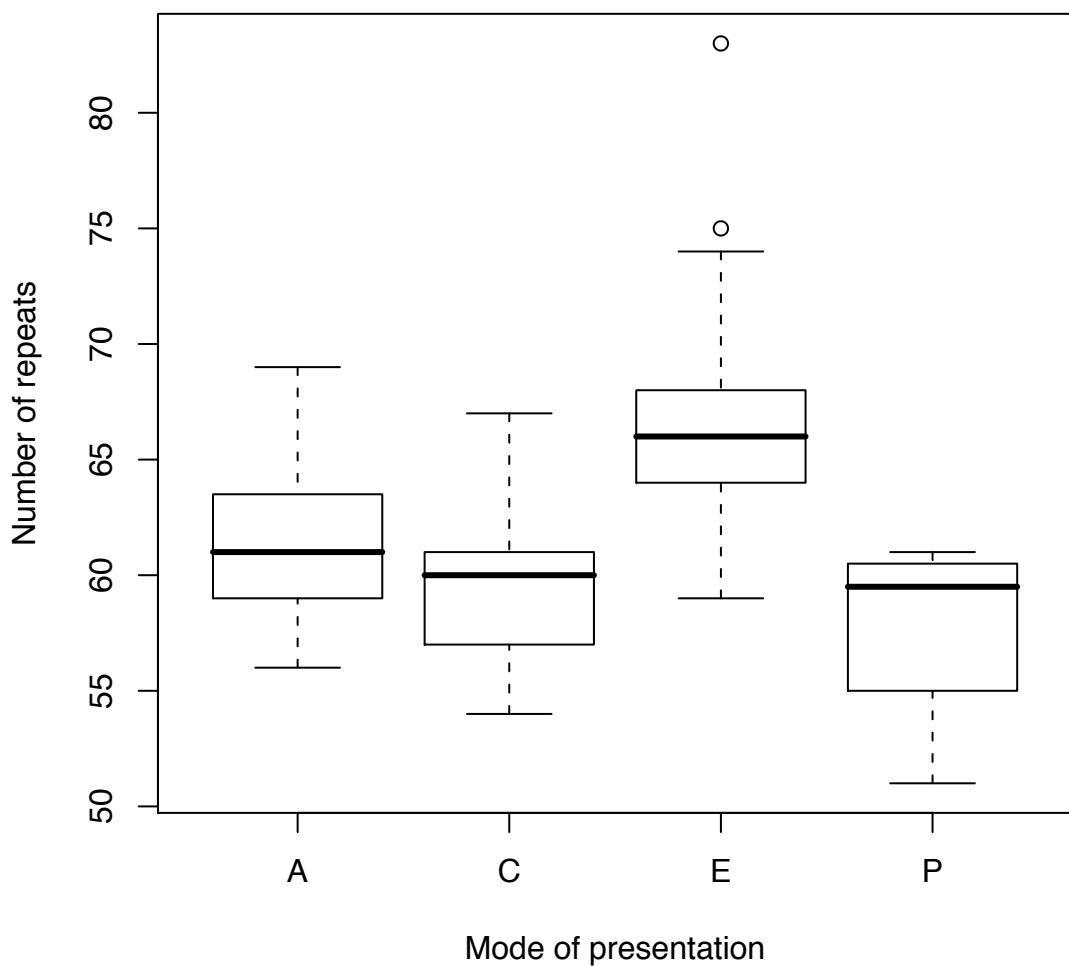
Figure 6.10: Mode of presentation and number of repeats. Kruskal-Wallis $P < 0.001$. A: ataxia, C: choreoathetoid, E: epilepsy, P: psychiatric.
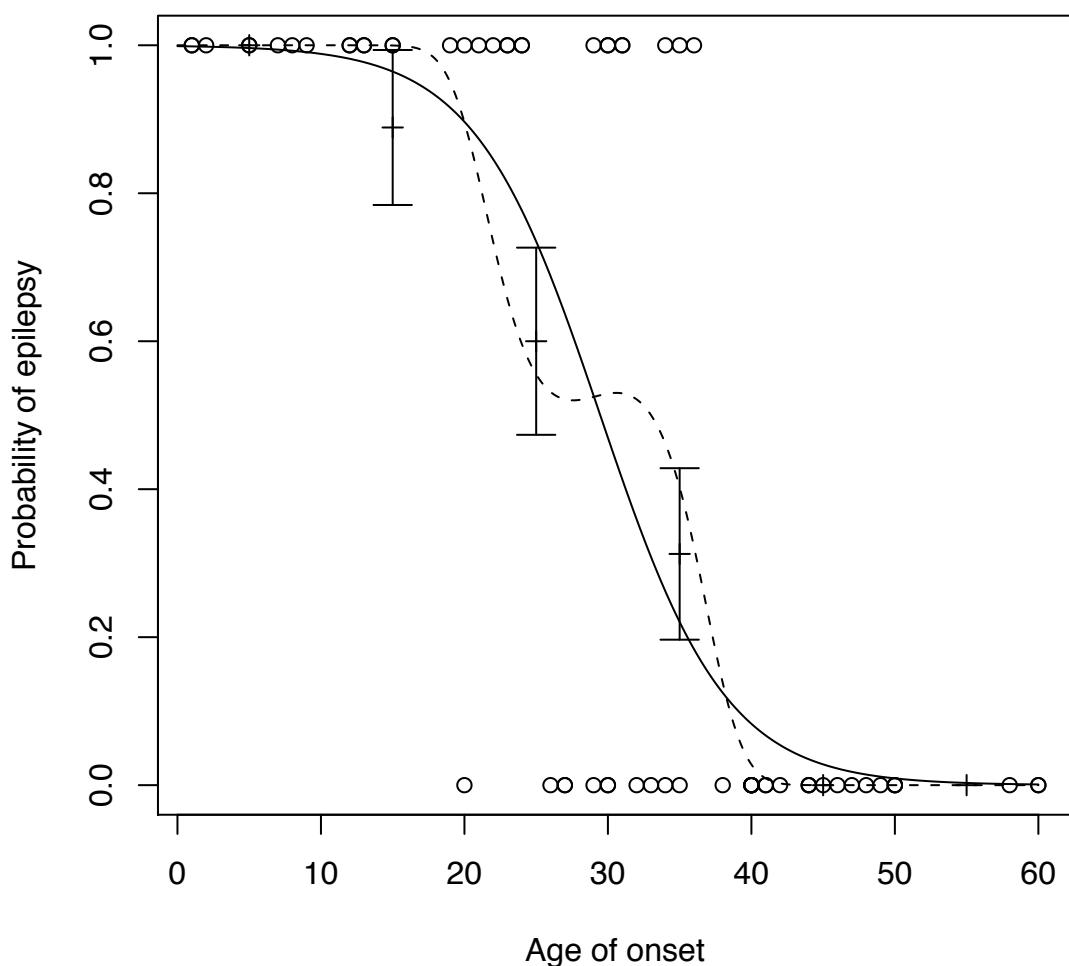
Figure 6.11: Probability of presenting with myoclonic epilepsy varies with age at onset. Results of logistic regression; actual data plotted as circles, simple logistic model plotted as line, polynomial logistic model plotted as dotted line. Prediction limits for polynomial model shown with error bars.
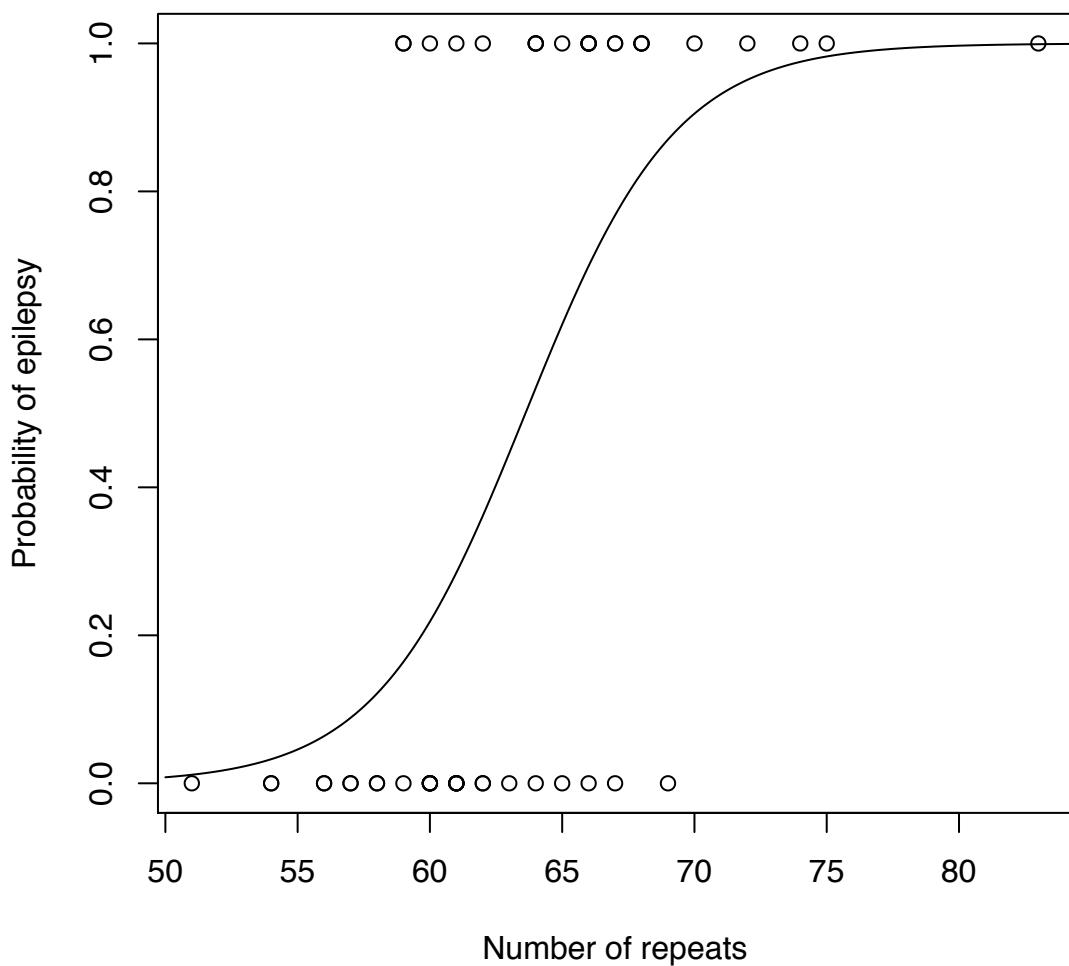
Figure 6.12: Probability of presenting with myoclonic epilepsy varies with number of repeats. Results of logistic regression.
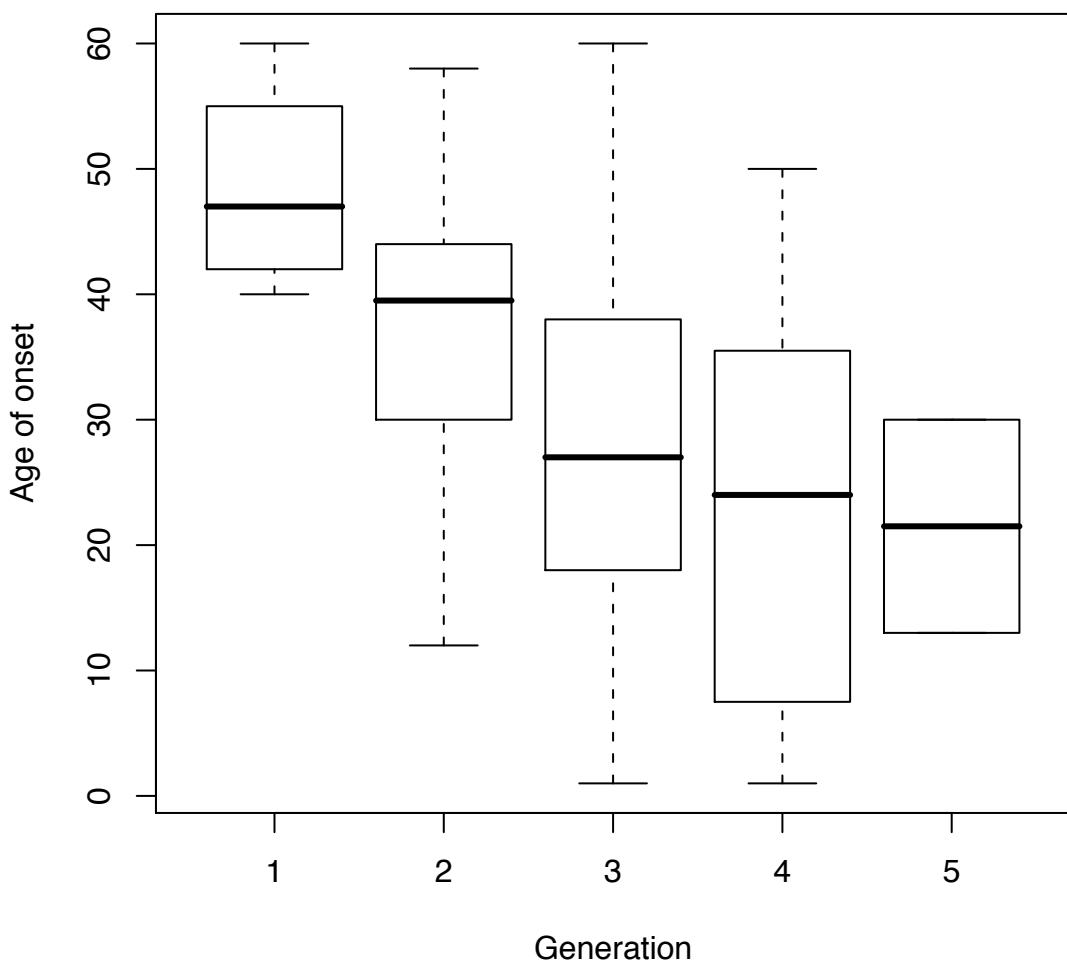
Figure 6.13: Crude relationship between age at onset and generation within family
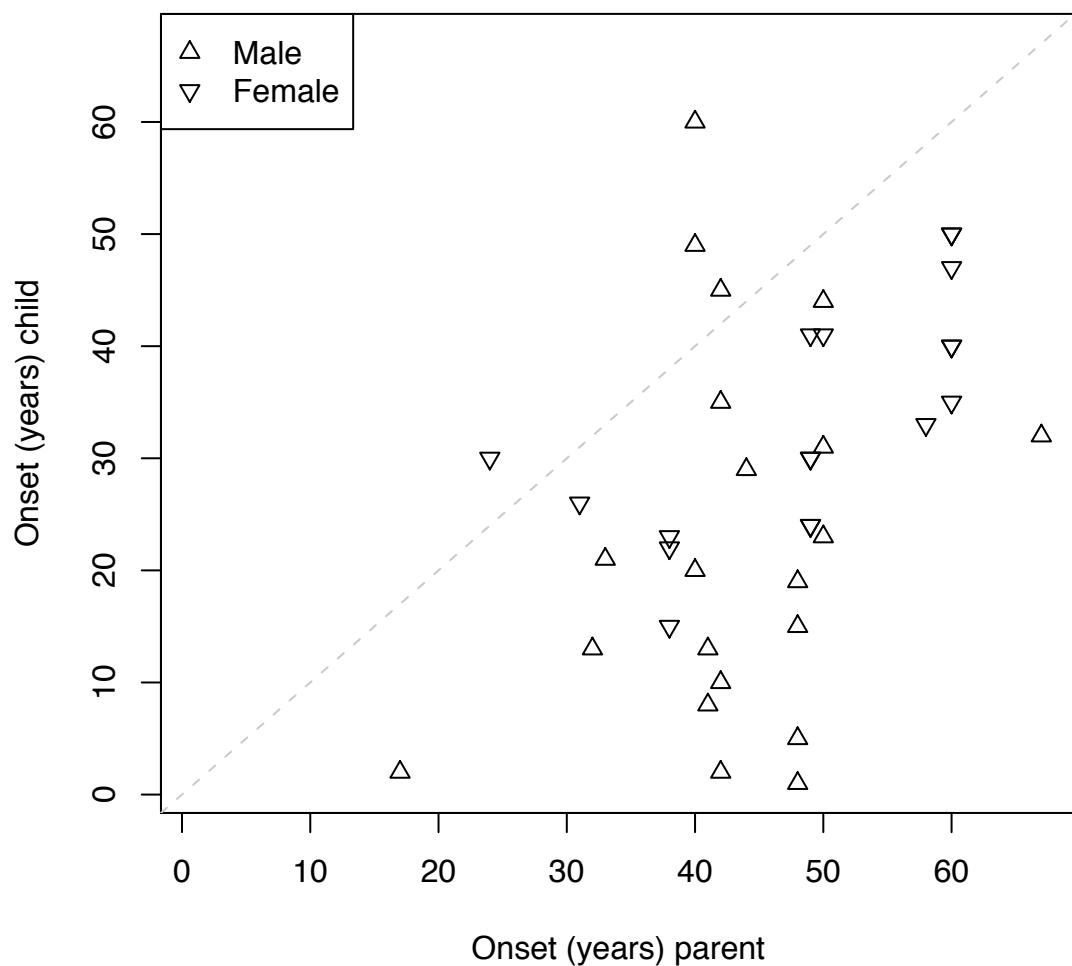
Figure 6.14: Intergenerational change in age at onset, grouped by parental sex.
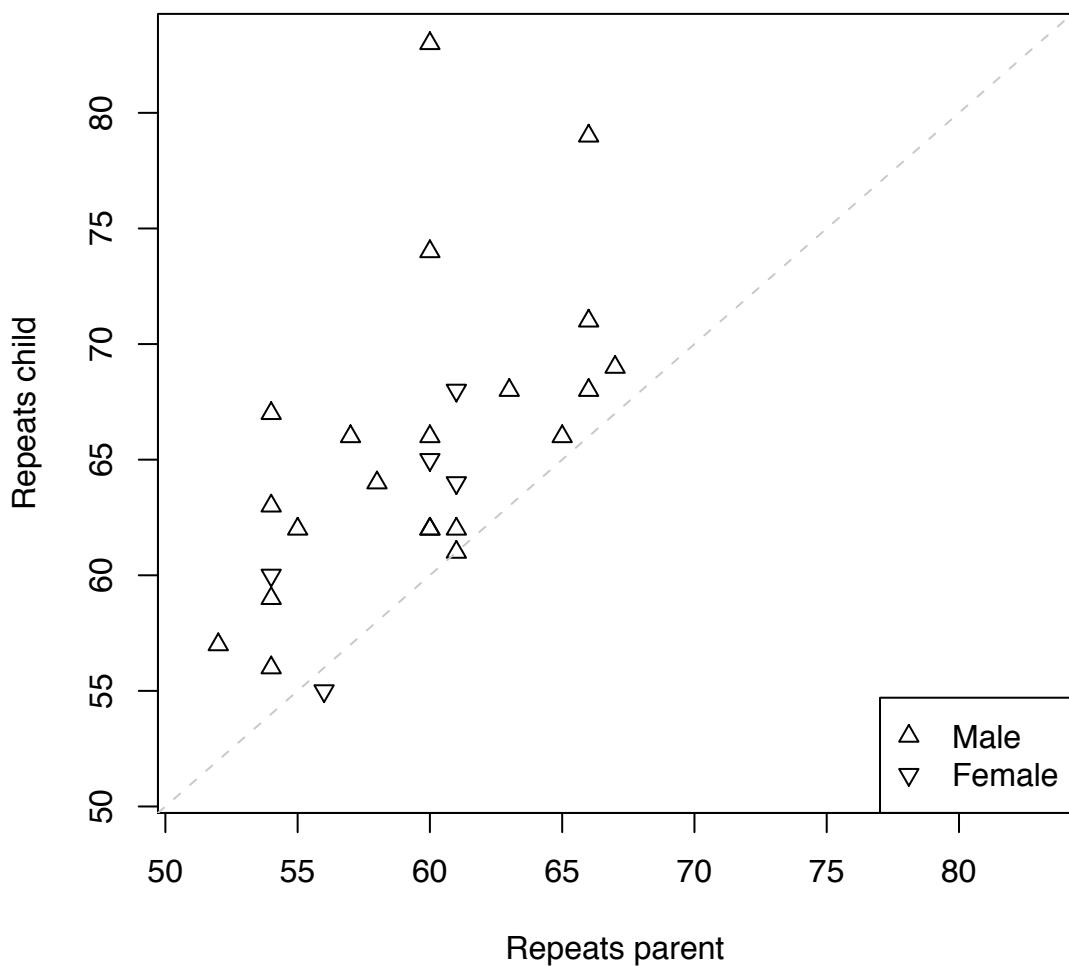
Figure 6.15: Intergenerational change in number of repeats, grouped by parental sex.
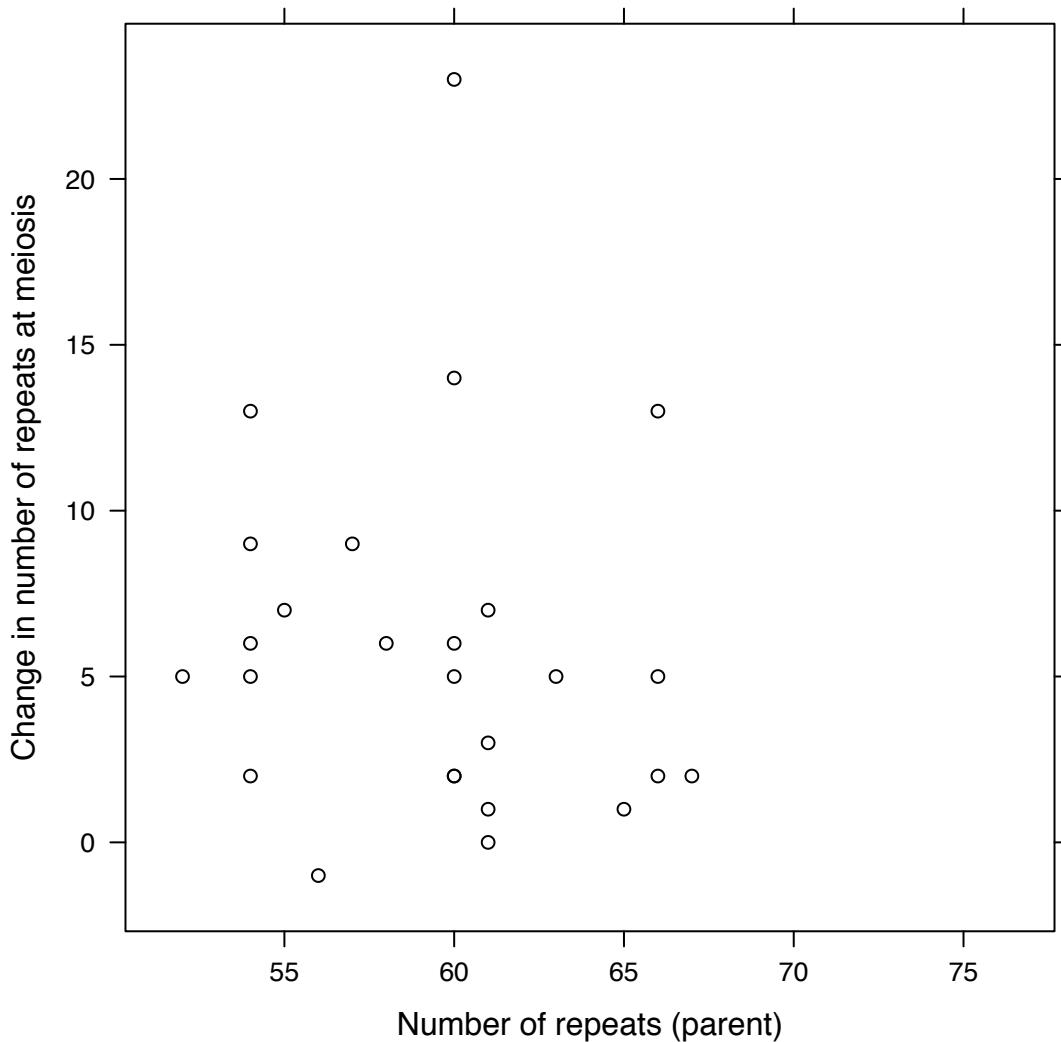
Figure 6.16: Intergenerational change in number of repeats based on parental number of repeats.

	Df	Sum Sq	Mean Sq	F value	Pr(>F)
pc	3	601.84	200.61	8.86	0.0001
Residuals	47	1063.84	22.63		

Table 6.2: ANOVA table for mode of presentation ("pc") and number of repeats.

6.4 Discussion

The majority of data regarding clinical phenomenology in DRPLA is sourced from Asian series and it remains unclear whether similar phenomena occur in non-Asian families. Individual studies to date in non-Asian families have been small and as such, detailed comparison has not been possible. For instance many Japanese studies have demonstrated a clear correlation between clinical phenotype and triplet repeat length,[59,67,89] but this relationship has been questioned in small non-Asian series which have not had the power in isolation to examine clinico-genetic phenomena such in detail.[99] Indeed, analysis of the 9 individuals from South Wales with detailed genetic data demonstrates no statistical relationship between repeat length and age at onset (Chapter 5). However, we have identified 183 individuals (90 male, 73 female and 20 unknown) in 27 non-Asian families reported in the literature since 1989 and have collated clinical and genetic data from all these families to facilitate such analysis. As such, this is the first detailed systematic study of non-Asian DRPLA.

The clinical phenotype and mode of presentation in non-Asian patients with DRPLA is highly dependent on repeat length (Figure 6.3) with 62% of the variability in age at onset explained by repeat length in non-Asian patients ($P < 0.0001$) mirroring previous reports in both Japanese DRPLA and HD.[2] The mode of presentation is also significantly determined by repeat length in non-Asian DRPLA. Three subtypes of DRPLA have previously been suggested including (a) ataxo-choreoathetoid type, (b) pseudo-Huntington type, and (c) a myoclonic-epileptic type,[57] but as with more recent reports[92] we have found distinguishing these subtypes difficult as a result of considerable phenotypic overlap and would therefore recommend restricting classification only to juvenile (onset < 20, repeat length > 65, myoclonic epilepsy type) and non-juvenile (onset

> 20, repeat length < 65). In non-juvenile cases, presenting features are heterogeneous and include ataxia, dementia, chorea and psychiatric disease but repeat length does not appear to be a significant determinant (Figure 6.3). In addition, the number of repeats on affected chromosomes was a significant determinant of age at death, although caution is advised as this is based on limited data (n=8). Similarly, the significance of repeat length is also emphasised by additional anecdotal evidence from Asian patients with homozygous expansions who have a more severe phenotype than predicted from heterozygote repeat lengths.[59] We did not find that length of the unaffected allele, gender, ethnicity and country of origin affected age at onset or presenting features.

Repeat length instability in non-Asian cases is also similar to that in Japanese series. There was a median inter-generational reduction in age at onset of -19 (-47 to 20, n=40) years per generation, with a corresponding increase of 5 (-1 to 23, n=26) repeats per generation (Figure 6.15). Reports from Japanese series suggest similar marked intergenerational instability but with a parental bias (paternal: 5.8 ± 0.9 repeats/generation; maternal: 1.3 ± 1.6 repeats/generation),[145] but we were unable to demonstrate a significant parental bias from our non-Asian series although power calculations confirm inadequate sample size. Indeed, the number of maternal meiotic events was 5 in this meta-analysis, and 5 and 4 respectively in comparable Japanese studies.[59,69] However, the two largest intergenerational increases in repeat length and age at onset were paternal (from 60 to 83 repeats and from 60 to 74 repeats) and the only contraction in repeat length was maternal in origin (from 56 to 55 repeats) suggesting there may be a parental gender effect on repeat length stability, but not allowing any definite conclusions to be made based on this limited data. In addition, there was no evidence that repeat length instability was dependent on parental repeat length ($P = 0.6$, Figure 6.16) suggesting that once a critical threshold is reached, tandem repeats are unstable with instability determined by factors other than absolute repeat length.

This study has many limitations. Data on age at onset and repeat length are sourced from multiple independent studies each with potential methodological differences potentially underestimating the true strength of the relationship between repeat length and age at onset. Different investigators may use variable definitions of age at onset and presenting features, perhaps neglecting and under-

representing clinical features not commonly examined by neurologists, such as psychiatric manifestations of disease. Further prospective study of DRPLA in non-Asian families is required to avoid such study variability and bias. In addition, we have assumed a linear relationship between repeat length and age at onset because logarithmic transformation did not improve the model's explanatory power with our limited data set (n=53). However, such a linear model results in predictions of negative ages of onset and is not as biologically intuitive compared to a model with a logarithmic transformation.

Data regarding anticipation and correlation between repeat length and clinical phenotype are critical in determining the origins of DRPLA in a population. Marked anticipation and a direct link between repeat length and phenotype suggest triplet repeat expansions should not persist within a population unless there is active and on-going *de novo* expansion. Certainly data suggest that anticipation in DRPLA is high but these conclusions are based on retrospective analysis of affected individuals with very limited information reported regarding intergenerational instability from individuals with normal-range repeat lengths. Our data suggest that disease-range DRPLA alleles are unstable but that such instability is not related to absolute repeat length. However, this study is limited to disease-range alleles and as such, we cannot make any firm conclusions regarding instability from normal or intermediate-length alleles. Intermediate length alleles are described in HD[39,88] and SCA7[130] and are more unstable than normal sized repeats, but less stable than fully expanded repeats with a variable risk of expansion of 2–10%. Expansion appears to be determined by sequence interruptions (a pure CAG tract is associated with marked instability), chromosomal haplotype, sex of the transmitting parent, sperm mosaicism and other, as yet, unknown factors.[17,40] However, intermediate length alleles have not so far been identified in DRPLA and indeed we failed to identify intermediate-length alleles in our 612 control alleles (Chapter 5). The highest high-normal repeat length published is 34 (in Japan) and the lowest disease range repeat 51 in an asymptomatic elderly patient.[52,89]

We postulate two alternative theories for the origins of expanded DRPLA alleles within a population. Firstly, identification of asymptomatic elderly patients with low-end disease range expansions suggests that penetrance is variable and

dependent on repeat length.[52] As such, intergenerational expansion from poorly penetrant disease range alleles may then result in apparent sporadic disease in offspring. A reservoir of unaffected individuals with intermediate or disease-range repeat lengths may therefore allow poorly penetrant repeat lengths to pass from generation to generation without further expansion causing propagation of disease within the population without requiring continuing new spontaneous mutation. Secondly, expansions may occur *de novo* from high-normal range expansions and indeed, such a theory is supported by a compelling association between high-normal repeats and disease prevalence (Chapters 3 and 5).[137]

However, there may be factors other than crude repeat length associated with *de novo* and inter-generational triplet repeat expansion. For instance, two intragenic biallelic polymorphisms have been described that form three known haplotypes: A1-B1, A1-B2 and A2-B2. The *A* system results from a single nucleotide substitution in intron 1 and the *B* system is situated in intron 3. All of the expanded and high-normal alleles described from Japanese and Portuguese affected patients are segregated with the A1-B1 haplotype[76,169] and this haplotype is found in 50% of Japanese controls compared to only 8% of Caucasians, prompting the suggestion of a common Asian founder for Caucasian patients and a possible explanation for geographic variability and expansion. Families from South Wales all share the A1 haplotype (Chapter 5), but all were heterozygous at B and it was not possible to determine which allele segregated with the expanded CAG repeat.

DRPLA is a rare neurodegenerative disorder that, despite previous assertions, is found in non-Asian populations. The clinico-genetic phenomenology appear similar to Japanese series, and our study confirms marked genetic anticipation together with a clear association between repeat length and clinical phenotype and disease severity. We suggest DRPLA is not as geographically or ethnically restricted as previous thought and the diagnosis should be considered in the differential diagnosis of a wide spectrum of neurological disease especially if there is a dominant family history of dementia or movement disorder.

Clinical characteristics and natural history of chronic progressive cerebellar ataxia

7.1 Introduction

As outlined in Chapter 1, chronic progressive late-onset cerebellar ataxia (LOCA) may result from a wide spectrum clinical disorders and such overlap has resulted in historical difficulties with clinical characterisation and classification.[50,51] While the nosology of inherited ataxias has been transformed by advances in molecular genetics,[24,27] the classification of sporadic disease remains problematic resulting in difficulties for both researchers and clinicians. Indeed, while hereditary ataxias are well-described in the literature, the investigation and study of sporadic disease is traditionally neglected and likely under-reported.[48] Study of sporadic disease is complicated by the observed clinical, radiological and pathological heterogeneity[1,65] together with a frequently dynamic and evolving clinical course. As such, longitudinal follow-up may subsequently identify a previously neglected symptomatic cause or indeed confirm evolving clinical features suggesting an alternative neurodegeration diagnosis, such as multiple system atrophy (MSA).

We have performed a pragmatic study on a population-based group of patients with chronic progressive LOCA from a well-defined geographical region of the United Kingdom (UK). We combined cross-sectional and longitudinal data to describe the clinical features and natural history of LOCA from a population-based sample, determine factors affecting prognosis and identify symptoms at disease onset predictive of prognosis and aetiology.

7.2 Patients and methods

7.2.1 Patients

Patients with chronic progressive LOCA resident in south east Wales (UK) were identified between 1999 and 2007 with regular systematic searches of multiple sources to create a contemporary centralised ataxia register held at the regional neurology unit in Cardiff. Ascertainment sources have included: local general practitioners, departmental databases in the Department of Neurology and Institute of Medical Genetics, liaison with and personal notifications

from regional consultant neurologists over the study period, self-referral via other family members or response to advertisement in the Ataxia UK newsletter (`http://www.ataxia.org.uk`) and regional NHS administrative databases searching for a diagnosis of "ataxia" according to the 9th and 10th editions of the International classification of diseases (ICD). In addition clinicians who had requested any form of spinocerebellar ataxia (SCA) testing were identified from a laboratory-based genetic database to prompt consideration of referral to a dedicated central clinic.

Patients were evaluated in two stages to determine whether they met inclusion and exclusion criteria. In the first stage general practitioners or nominated hospital clinicians were asked to confirm diagnosis and inform patients of the research project. After obtaining informed consent, patients underwent a systematic personal clinical evaluation at home or in hospital. The inclusion criteria were: patients with chronic progressive cerebellar ataxia, no identified symptomatic cause, disease duration of greater than one year and age at onset of 18 or over. Patients were excluded when ataxia was only a minor feature, a symptomatic cause was subsequently identified or ataxia was congenital or non-progressive. Whilst patients with a history of chronic alcoholism were excluded, we included and flagged patients with occasional moderate alcohol use.

Where possible, patients were recalled prospectively for re-assessment after intervals of at least two years. Centralised national health service (NHS) databases and general practitioner records were used to identify patients who died during or after the study period. A standardised data collection protocol was used to document clinical and investigative results and data were stored in a dedicated database in accordance with the Data Protection Act, 1998. Patients were systematically investigated for SCA1, SCA2, SCA3, SCA6, SCA7, SCA8, SCA10, SCA10, SCA17, DRPLA, FXTAS and Friedreich's ataxia (FA), with appropriate review of neuro-imaging where possible.

The project was approved by the relevant local ethics committee and NHS research and development office.

7.2.2 Neurological evaluation

Neurological history included questions concerning age at onset, symptoms at onset, symptom and disability accumulation and current and previous medical, surgical and drug history with particular attention given to a history of malignancy, auto-immune disorder and psychosis together with alcohol, tobacco and recreational drug use. Auto-immune diseases selected for study were the most prevalent and most commonly studied[10] and included pernicious anaemia, hyper- and hypothyroidism, diabetes mellitus type I, systemic lupus erythematosus, myasthenia gravis and Addison's disease. Disease stage was defined on a five-point scale (0 = no gait difficulties, 1 = disease onset, 2 = loss of independent gait, as defined by permanent use of walking aid, 3 = use of wheelchair, 4 = death).[65] The presence and evolution of gait disturbance, limb incoordination and weakness, sensory disturbance, dysphagia, dysarthria, urinary frequency, urinary urgency, incontinence, erectile dysfunction and cognitive deterioration were graded on a two-point scale (0 = absent, 1 = present) with data on age at onset derived prospectively when possible, but retrospectively when symptom onset preceded the first clinical evaluation. The presence or absence of wasting, spasticity, rigidity, tremor (resting, postural or intention), bradykinesia, dystonia, chorea, dysdiadochokinesis, scoliosis, foot deformity, postural hypotension, dysarthria, oculomotor abnormalities, deafness and sensory disturbance (including joint position, vibration, temperature and pinprick) were recorded for all patients (0 = absent, 1 = present). Muscle strength was assessed using the British Medical Research Council scale.[79] Deep tendon reflexes were assessed on a five-point scale (0 = absent, 1 = with reinforcement, 2 = normal lower range, 3 = normal upper range, 4 = brisk) with the Babinski response recorded as a three-point scale (0 = mute, 1 = flexor, 2 = extensor). Cognitive status was assessed using the mini-mental state examination (MMSE)[33] and all patients were judged according to published criterion for a potential diagnosis of MSA.[36] In addition, several standardised assessment tools were used including International Cooperative Ataxia Rating Scale (ICARS) (Appendix B.6),[144] Barthel ADL index (Appendix B.7),[150] SF-36 (Appendix B.8)[61] and Freidreich's ataxia impact scale (FAIS) (Appendix B.9; unpublished, J. Hobart: personal communication) to systematically assess the

severity of ataxia, activities of daily living and quality of life issues respectively. We used a structured genealogical questionnaire to identify patients with consanguinity or a possible family history of ataxia and when indicated and with consent, these relatives were subsequently reviewed personally.

7.2.3 Clinical characterisation

Patients were characterised systematically into clinically and genetically defined groups for further analysis. In all cases, patients were defined by a proven genetic diagnosis when possible, but otherwise were grouped clinically into familial (dominant or other) and sporadic (meeting criteria for MSA or not). Only patients designated as "Probable MSA" according to published criterion have been labelled as MSA.[36] To inform counselling and determination of prognosis, patients with a proven genetic aetiology were also grouped clinically providing an opportunity to compare patients with a specific clinical phenotype without a defined genetic diagnosis with those who had molecular confirmation of a genetic diagnosis.

7.2.4 Statistical analysis

All analysis was performed using "R: A Language and Environment for Statistical Computing".[104] Crude prevalence and confidence intervals were determined by a Poisson exact method. We used contingency tests including χ^2 test with Yates' correction and Fisher's exact test to examine clinical features in different subgroups, but extended this when appropriate with linear and logistic statistical modelling to explore interactions between covariates. Exact binomial test was used to compare co-morbidity frequencies with previously published series. Modelling age at onset data involved analysis of gender, the presence or absence of proven FA, SCA, a positive family history and prior auto-immune disease. To examine the relationship between ICARS scores and disease duration, we used linear mixed modelling and included gender, age at onset and clinical phenotype as covariates together with random effects to account for patient and investigator variability. Modelling was performed systematically, with a saturated model fitted first with sequential dropping of insignificant terms and sequential likelihood tests

together with assessment of standardised information criteria. Proportional hazards regression analysis was used to analyse survival data and determine factors associated with a poor prognosis. Need for ambulatory support was used as the primary outcome measure and we included gender, a family history, any proven genetic diagnosis, or an antecedent history of moderate alcohol use, carcinoma, auto-immune disease, ischaemic heart disease and hypertension as covariates. Patients with a proven diagnosis of FA were excluded from this analysis.

7.3 Results

7.3.1 Patients

161 patients were reviewed and assessed. Overall, there was a male predominance (60.2%) but we observed a female predominance in those presenting below the age of 40. 111 patients (69.6%) had no identified genetic cause and no family history of similar disorder and were designated "idiopathic sporadic", of which 20 patients (18.0%) met clinical criterion for a diagnosis of "Probable MSA" and 45 (40.5%) "Possible MSA". Six patients had genetically-confirmed dentatorubral pallidoluysian atrophy (DRPLA), 3 FA, 1 SCA8 and 4 SCA6. In addition, there were 15 with a dominant family history and 20 with a family history that could not be classified as either dominant, recessive or X-linked with no identified genetic cause. Family history (relative risk 1.3, 95% CI 1.2–1.4) and chorea (relative risk 1.6, 95% CI 1.3-2.1) were associated with identification of a proven underlying genetic cause and only age at onset discriminated familial and sporadic cases (P <0.01). A breakdown of clinical features is shown in Table 7.1 (and in more detail in Tables 7.3 and 7.6) with patients with a proven dominant inherited cause included in the dominant familial group, patients with FA excluded and a single patient with "Possible FXTAS" included within the sporadic group. No patient had a history of consanguinity. A detailed breakdown of patient groups is shown in Table 7.7.

7.3.2 Clinical features

Median age at onset was 48.5 (SD 15.2) years with ataxia of gait (89.3%), limb (31.9 %), speech (17.0%) the commonest presenting features.

The median disease duration was 9 years (SD 8.5) at the most recent clinical evaluation. 20.1% of patients had a disease duration of less than five years, 35.6% between five and ten years, 20.1% between ten and fifteen years and 24.2% greater than fifteen years. Examination identified 97.3% with gait ataxia, 34.8% with truncal ataxia and while 28.2% did not require any ambulatory aids, 38.3% required unilateral or bilateral support and 33.6% needed a wheelchair.

Many patients were considerably disabled and needed assistance with activities of daily living, including getting dressed (20.7%), bathing (42.8%), toileting (2.1%), feeding (17.2%), transferring (33.8%), mobility (80.7%) and stairs (99.3%). Quality of life data are shown in Tables 7.8 and 7.9.

Dysarthria affected 71.4%, gaze-evoked nystagmus 62.9%, broken-up smooth pursuit 62.1% and saccadic dysmetria 23.8%. Dysdiadochokinesia was found in 89.8%, upper limb dysmetria in 82.3%, intention tremor in 81.6% and postural tremor in 80.3%. In the lower limbs, heel-shin dysmetria was common (81.6%) together with tremor (66.7%).

Extracerebellar signs included reduced vibration (33.3%), temperature (9.2%), pinprick (10.0%) and joint position (30.0%) sensation, bradykinesia (12.2%), rigidity (5.3%), resting tremor (1.5%) and dystonia (4.5%). 10.9% had a MMSE< 26 and 2.9% had a MMSE< 22.

The most important co-morbidities were hypertension (19.3%), epilepsy (6.8%), and a prior history of alcohol use (12.4%). A significant association was seen between age at onset and presence of hypertension (P <0.01) with the raw data shown in Table 7.10.

A history of auto-immune disease was obtained in 12.1% of sporadic patients compared to 0.0% of patients with a family history of ataxia or a proven genetic aetiology. Contingency tests confirmed a statistically significant difference in frequency between these groups (P <0.05). Comparison of the prevalence of auto-immune disease in patients with familial or sporadic ataxia to that of the background UK population identified an excess of hypothyroidism ($\chi^2 = 30.2$, P

<0.0001) and pernicious anaemia ($\chi^2 = 51.8$, P <0.0001).[10] We did not identify a statistically significant excess of hyperthyroidism, rheumatoid arthritis, type I diabetes mellitus, myasthenia gravis or Addison's disease. There were no patients with a history of coeliac disease.

A statistical comparison between clinical features and underlying characterisation and a detailed breakdown of clinical features and defined ataxia diagnosis are shown in Tables 7.4 and 7.5.

While 51.6% of patients had never smoked tobacco, 30.7% smoked at the time of evaluation and 17.6% had smoked in the past. No patient admitted to recreational drug use.

Table 7.1: Clinical features of patients with LOCA grouped by age at onset and clinical diagnosis. Full version shown in Table 7.3.

Feature	All	Age at onset			Familial		Not familial	
		< 40	40–60	> 60	Dominant	Other	MSA	Sporadic
Demographics								
n	161	47	72	33	26	20	20	92
Male (%)	60.2	48.9	63.9	60.6	46.2	50.0	70.0	64.1
Female (%)	39.8	51.1	36.1	39.4	53.8	50.0	30.0	35.9
Mean prevalent age (SD)	60.6 (13.8)	49.1 (11.6)	62.7 (8.7)	78.0 (5.7)	54.7 (15.4)	61.7 (12.3)	63.0 (11.4)	62.2 (13.5)
Mean age at onset (SD)	48.5 (15.2)	30.4 (8.0)	51.2 (5.7)	68.3 (4.9)	40.9 (10.9)	45.1 (12.7)	54.2 (12.7)	51.0 (15.6)
Mean disease duration (SD)	11.5 (8.5)	16.7 (10.7)	10.0 (6.7)	7.7 (5.1)	13.7 (10.8)	13.2 (8.4)	8.6 (7.0)	10.6 (7.0)
Mean Barthel ADL (SD)	16.5 (3.7)	16.0 (4.6)	16.4 (3.7)	17.4 (2.3)	16.2 (5.0)	17.0 (2.4)	14.4 (4.8)	17.2 (2.7)
Disease stage (%)								
I	28.2	31.1	27.8	25.0	37.5	41.2	5.3	27.9
II	38.3	28.9	37.5	53.1	29.2	35.3	47.4	40.7
III	33.6	40.0	34.7	21.9	33.3	23.5	47.4	31.4
Within two years (%)								
Barthel ADL < 25	3.5	2.4	2.9	6.2	4.8	0.0	10.5	2.4
Ambulatory support	26.8	14.3	29.9	37.5	12.5	13.3	50.0	28.8
Co-morbidities (%)								
Epilepsy	6.8	10.6	6.9	3.0	15.4	5.0	0.0	6.5
Hypertension	19.3	6.4	25.0	30.3	11.5	0.0	25.0	25.0
Moderate alcohol use	12.4	8.5	18.1	6.1	7.7	5.0	20.0	14.1
Autoimmune disease	8.7	10.6	6.9	12.1	0.0	0.0	10.0	12.0

Table 7.1: *(continued)*

		< 40	40–60	> 60	Dominant	Other	MSA	Sporadic
Clinical features (%)								
Gait ataxia	97.3	93.2	98.6	100.0	91.7	94.1	100.0	98.8
Truncal ataxia	34.8	33.3	36.4	33.3	15.8	50.0	40.0	36.6
Dysarthria	71.4	72.7	80.0	50.0	91.3	64.7	78.9	64.7
Ocular								
Nystagmus	62.9	80.6	56.1	56.7	47.4	100.0	45.0	65.9
Broken pursuit	62.1	72.2	60.6	53.3	57.9	100.0	75.0	54.9
Ophthalmoplegia	1.5	0.0	1.5	3.3	0.0	0.0	5.0	1.2
Supranuclear palsy	3.1	2.8	1.6	6.7	0.0	0.0	5.3	3.7
Limb								
Wasting	19.1	13.9	15.4	33.3	0.0	28.6	25.0	20.7
Spasticity	12.2	8.3	16.9	6.7	0.0	42.9	10.0	12.2
Ankle clonus	5.4	8.6	6.2	0.0	0.0	0.0	10.0	6.1
Absent ankle jerks	25.4	27.8	17.2	40.0	10.5	14.3	30.0	25.9
Extensor plantars	15.3	11.1	16.9	16.7	15.8	0.0	25.0	14.6
Brisk ankle or knee jerks	17.7	22.2	15.6	16.7	15.8	14.3	25.0	17.3
Finger-nose dysmetria	82.3	86.4	75.7	93.8	73.9	82.4	89.5	82.4
Finger-nose tremor	81.6	84.1	80.0	84.4	69.6	82.4	89.5	82.4
Postural tremor	80.3	80.6	80.3	80.0	82.4	85.7	75.0	80.0
Dysdiadochokinesis	89.8	90.9	90.0	87.5	78.3	94.1	100.0	89.4
Heel-shin dysmetria	81.6	86.4	78.6	81.2	69.6	88.2	89.5	81.2
Heel-shin tremor	66.7	75.0	67.1	53.1	65.2	70.6	68.4	64.7
Extrapyramidal	12.2	5.6	10.8	23.3	15.8	0.0	25.0	9.8
Sensory loss	43.1	33.3	40.0	62.1	10.5	42.9	50.0	48.1
Autonomic dysfunction	46.9	43.9	45.7	53.1	50.0	41.2	100.0	34.9
Chorea	2.3	5.6	1.5	0.0	10.5	0.0	0.0	1.2
Head tremor	11.4	5.6	18.2	3.3	10.5	37.5	10.0	9.8
Deafness	4.5	5.6	4.5	3.3	0.0	0.0	5.0	6.1
Cognitive impairment	10.9	7.9	15.9	3.2	23.8	11.8	0.0	10.1

7.3.3 Disease progression

Indicators of ambulation (P <0.05), ataxia severity (ICARS; $P < 0.0001$) and disability (Barthel ADL; P <0.01) were all highly correlated with disease duration. Linear mixed modelling confirmed progressive ataxia severity, increasing by 1.7 (95% CI 0.9–2.6) points on the ICARS scale per year of disease duration (Figure 7.2). In addition, the presence of extracerebellar features sufficient to suggest a diagnosis of "probable MSA" (sporadic patients only) had a significant effect (an additional 10.7 points per year, 95% CI 1.9–19.5). A prior history of ischaemic heart disease, hypertension, organ-specific autoimmune disease or carcinoma was not significant.

Examination of raw cross-sectional data from Tables 7.1 and 7.6 identified several clear patterns in disease progression and prognosis. Patients with a diagnosis of "probable MSA" by clinical criteria[36] had the most aggressive disease course with 47.4% requiring a wheelchair compared to 31.5% who do not meet criteria. Important possible confounding issues include different baseline characteristics such as age at onset, gender and disease duration. However, direct comparison of these between patient groups suggests that these are not important confounders: for example median disease duration in patients with "Probable MSA" was 6 years compared to 10 years for other patients. However, patients with MSA were older.

To account for possible confounding issues, Cox proportional hazards modelling identified age at disease onset, disease duration, a clinical diagnosis of MSA and a history of carcinoma or auto-immune disorder as significant influences on progression to ambulatory support (Table 7.2). Each additional decade of disease onset increased the risk of entering advanced disease stages (relative risk 1.44; 95% CI 1.12–1.85). Each decade of disease duration similarly increased the probability of requiring ambulatory support by 1.58, although this parameter was not significant alone and when the interaction of disease duration and disease onset was studied, later disease onset and increasing disease duration appeared to reduce the probability of requiring ambulatory support (relative risk 0.77; 95% CI 0.64–0.91).

The presence of clinical features compatible with a diagnosis of MSA was highly significant (Figure 7.1) and increased the risk of ambulatory support by

a factor of 3.28 (95% CI 1.8–5.98). Other important covariates included a prior history of malignancy (relative risk 2.56; 95% CI 1.28–5.12) and autoimmune disorder (relative risk 1.39; 95% CI 0.69–2.77).

The median delay from age at onset to ambulatory support was 7 (95% CI 5–9) years. However, the median delay for patients meeting diagnostic criterion for "Probable MSA" was only 3 (95% CI 2–6) years, and 8 (95% CI 7–11) years for other patients. It was not possible to derive robust estimates of delay to wheelchair use or death using our cohort as there were few patients who reached these endpoints. Crude estimates of median survival to wheelchair use and death for patients with MSA were 6 years and 17 years respectively. We estimate a median delay to wheelchair use for other patients to be 20 years from disease onset.

A history of erectile dysfunction, urinary incontinence or urinary urgency within one year of disease onset was poorly predictive of a diagnosis of MSA (positive predictive value 27%) because a similar history was observed in other patients. However the absence of these features at disease onset essentially excluded a subsequent diagnosis of MSA during the study period (negative predictive value 99%). Factors including age at disease onset and gender were not significant in multiple logistic regression.
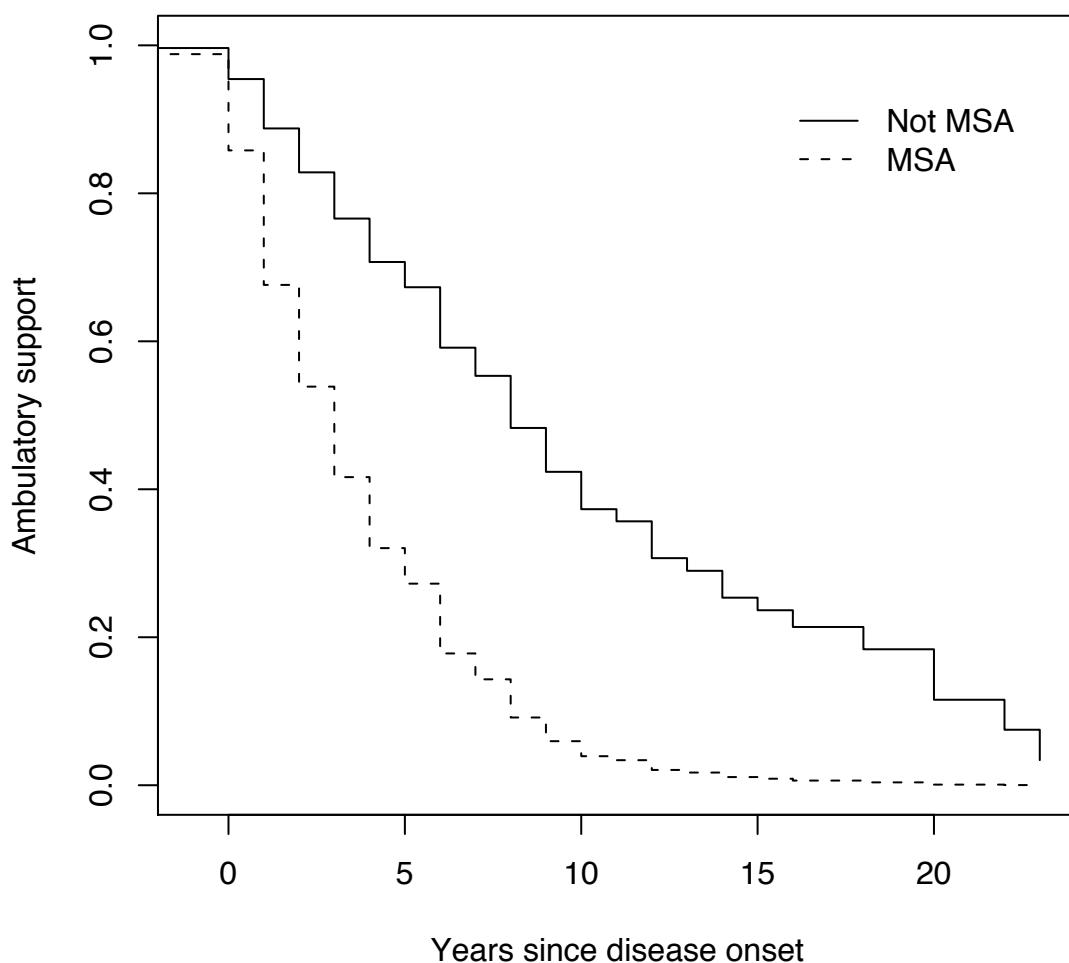
Figure 7.1: Survival curves showing latency to become dependent on walking aids estimated for patients with or without a diagnosis of "Probable MSA" with disease onset aged 50 and disease duration of 10 years and no history of malignancy or autoimmune disease.

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Covariate	coef	exp(coef)	se(coef)	z	p	95% CI
Age at onset †	0.36	1.44	0.13	2.83	<0.01	1.12–1.85
Disease duration †	0.46	1.58	0.40	1.15	0.2	0.73–3.45
"Probable MSA"	1.19	3.28	0.31	3.89	<0.0001	1.80–5.98
Carcinoma	0.94	2.56	0.35	2.66	<0.01	1.28–5.12
Auto-immune disease	0.33	1.39	0.35	0.92	0.4	0.69–2.77
Onset:duration †	−0.27	0.77	0.09	−2.98	<0.01	0.64–0.91

Table 7.2: Cox regression model fitted to survival data. † signifies coefficient calculated per ten years. Covariates are listed with associated relative risks (as exponents of each coefficient) and 95% confidence intervals. "Onset:duration" refers to an interaction between these two variables.

7.4 Discussion

This is a systematic study of chronic progressive LOCA using intensive population-based recruitment from a geographically-defined region of the United Kingdom. Unlike clinic-based cohorts, such a population-based approach provides robust estimates of the relative importance of different disorders causing LOCA and confirms that the majority of patients in this region remain "idiopathic" despite extensive systematic investigation.

Our study also documents the considerable burden that LOCA imposes on patients, families and carers as well as local health and social services. In addition, patients commonly demonstrate significant disease progression with time, becoming decreasingly ambulant, increasingly dependent and suffer a considerable burden of morbidity and mortality. Furthermore we have shown sporadic LOCA is clinically heterogeneous, with evidence of a subset of patients with defined extra-cerebellar symptoms and signs who, despite having a shorter disease duration, are less ambulant, more disabled and have a significantly worse prognosis. Our data for patients meeting a diagnosis of MSA is broadly in agreement with previous studies which document similar estimates of time to ambulatory support and wheelchair use.[35,64,115,161] However, estimates of survival in this population are longer than previous studies (17 years vs. 9 years typically), although comparative studies of cerebellar predominant disease (MSA-C) are limited. Studies investigating those with marked extrapyramidal signs (MSA-P) suggest an even worse prognosis than those of the cerebellar type, estimating a median survival of 6 years.[161] There are a number of possible explanations for the differences between our cohort and other studies. Patients in our population in South Wales were recruited only if cerebellar ataxia was a predominant feature, and therefore the observed difference in survival may be due to genuine differences in prognosis between MSA sub-types. However, in restricting cases to those with disease duration of greater than one year, we may have excluded those patients with the worst prognosis and most aggressive deterioration and selected a sub-group with a more benign disease course. In addition, our parameter estimates for survival are based on few events within a large cohort and we have been unable to derive secure confidence intervals for these estimates, prompting caution in over-interpretation.
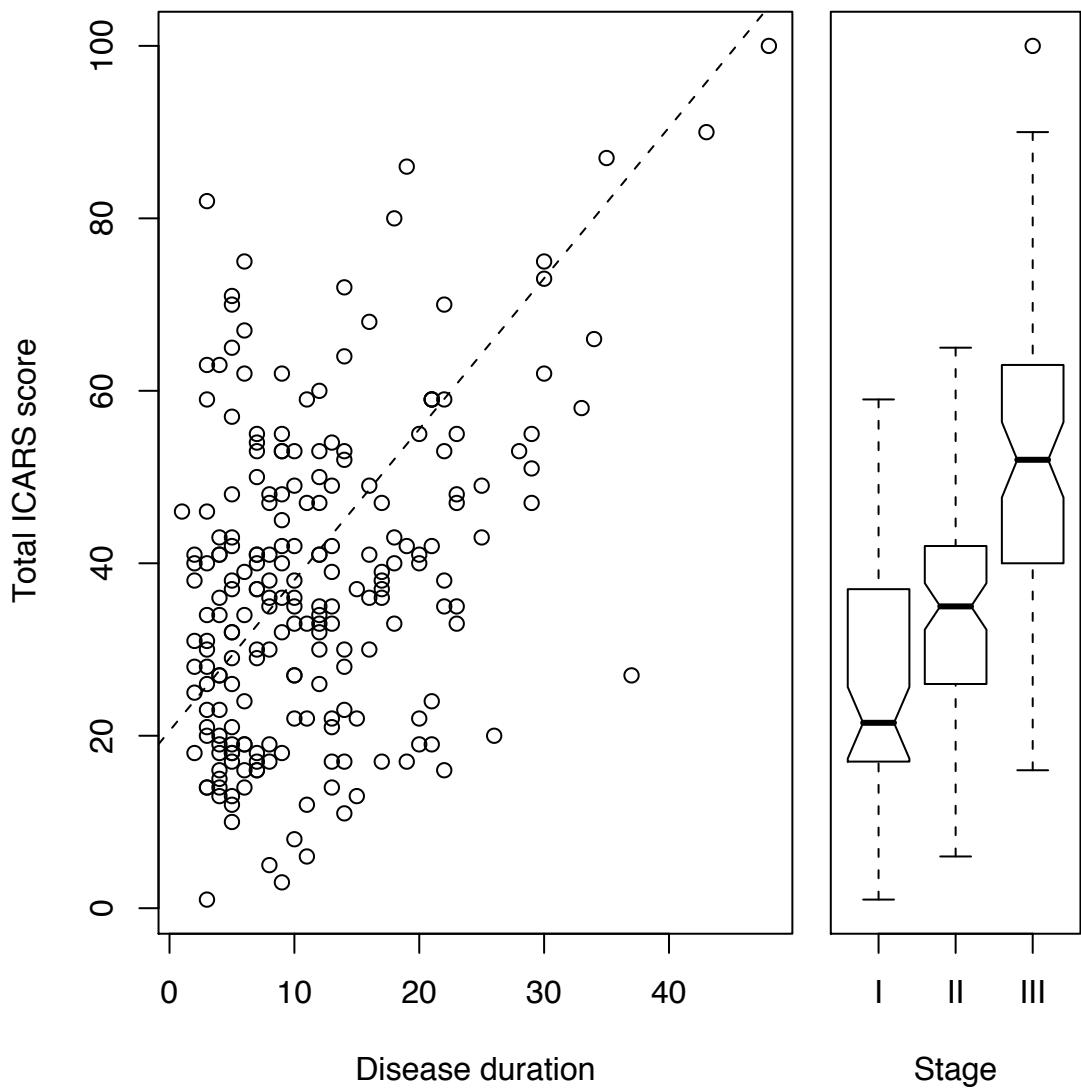
Figure 7.2: Relationship between ICARS score, disease duration and ambulatory support. I:disease onset, II: support required, III: wheelchair.
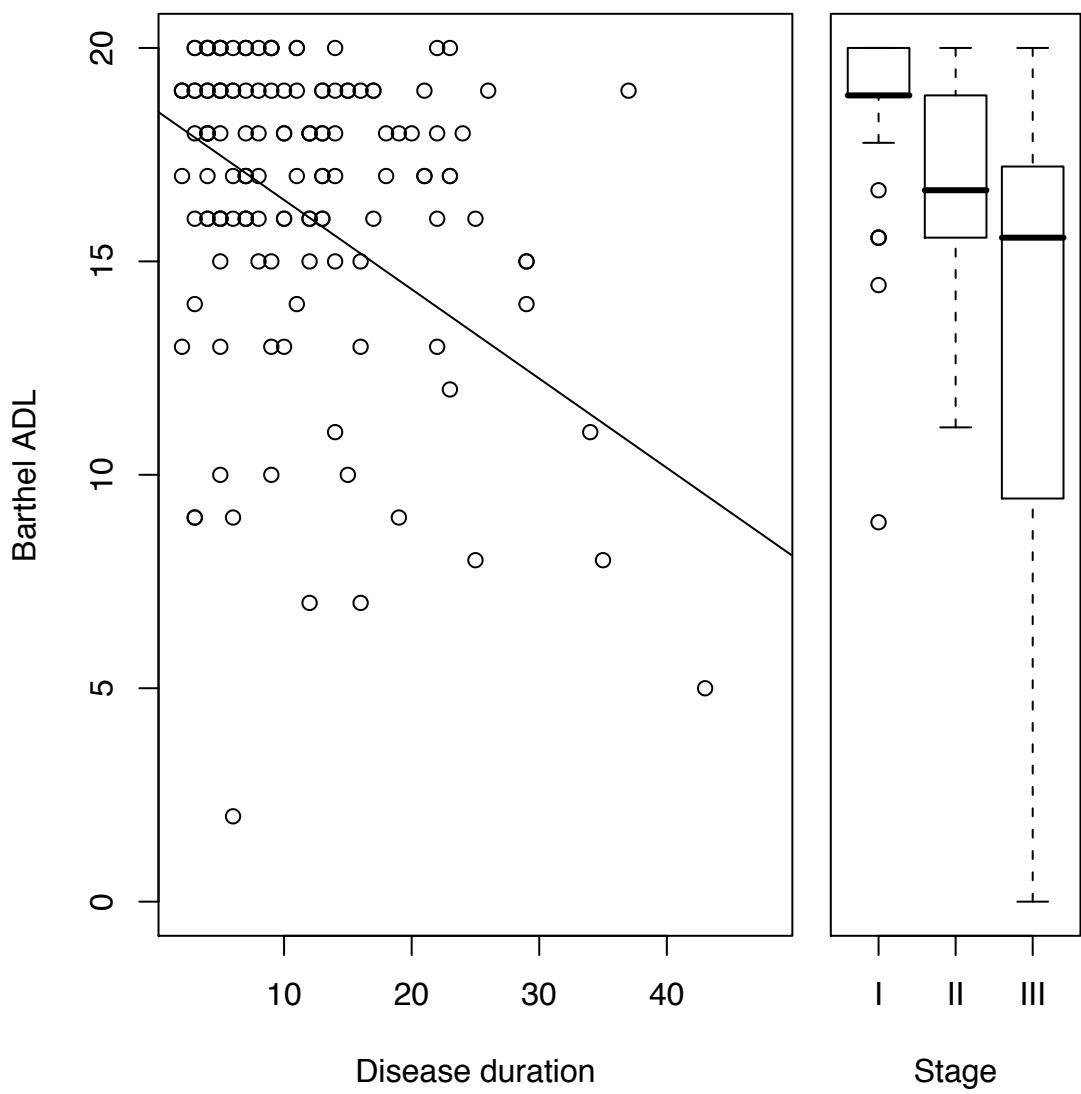
Figure 7.3: Relationship between Barthel ADL, disease duration and ambulatory support.

Notwithstanding these limitations, patients with a diagnosis of MSA at evaluation still had a significantly worse prognosis than the rest of our group even though disease duration for these patients was on average lower. Data on progression to ambulatory support or wheelchair use also demonstrates an unequivocal difference between those with extra-cerebellar signs and those without.

While age at disease onset was highly variable, patients with FA or a positive family history presented at a significantly younger age than other patients and while there was a female predominance in these groups, gender was not a significant independent influence on age at onset. It was expected that patients presenting with extra-cerebellar features meeting the criteria for MSA would be more elderly[64] but although there was a small difference in observed age at disease onset, any difference was not significant in linear regression.

We found an overall significant excess of patients with a reported history of auto-immune disease compared to previously published reports for the UK population (8.7% vs. 2.5%, $\chi^2 = 22.9$, P <0.0001).[10] Such results must be interpreted with caution as they are not the result of a rigorous case-control study with locally-ascertained age- and sex-matched controls. However our data highlights a significant difference between sporadic and familial cases, with an excess of auto-immune disease in the former group (P <0.05) and hypothesise that this has implications for understanding the aetiology of sporadic cerebellar ataxia. While cerebellar ataxia may result from untreated hypothyroidism and may be mimicked by untreated pernicious anaemia, all included patients were on treatment and did not have abnormal thyroid function or vitamin B12 levels when included in the study. It is widely recognised that organ-specific and systemic auto-immune diseases may occur together in a single patient and it suggested that common genetic susceptibility factors co-exist with additional disease-specific environmental or genetic factors. Therefore, the identified excess of auto-immunity in patients from South Wales may suggest a hitherto unrecognised auto-immune process in a proportion of patients. In addition there remains controversy surrounding the positive identification and significance of a range of antibodies in patients with ataxia (for example anti-gliaden antibodies, anti-GAD antibodies)[43,54] and while our data suggests some patients with sporadic ataxia may have an immune-mediated cause, it is conceivable that the identification of an excess of a range of auto-antibodies

is to be expected. Further work will be necessary to determine whether there is an excess frequency of positive auto-antibodies in sporadic cerebellar ataxia, and to establish whether they are directly pathogenic or merely a marker of increased auto-immunity generally.

This study has a number of limitations. While a population-based approach minimises bias due to selective ascertainment, it can result in unrepresentative conclusions limited to the population under study. Certainly the proportion of patients with a confirmed genetic aetiology was low within our cohort and we have therefore avoided making any conclusions about clinical heterogeneity and disease progression in these groups. For instance our data suggest family history, chorea and epilepsy are associated with a positive identification of an underlying genetic diagnosis but this is not surprising given an unusual excess of patients with DRPLA within our familial subgroup. However, our study includes a large number of patients presenting with LOCA and we suggest conclusions derived from our population-based cohort are applicable to a wider population of patients. Unfortunately, there is evidence of informative case-ascertainment bias within these mixed cross-sectional and longitudinal data: the older a patient is at disease onset the more likely they are to require ambulatory support, but after disease onset, there is a small, but significant reduction in hazard. This highlights an important problem of case ascertainment in cross-sectional and retrospective studies. While prospective studies can include all new incident cases and minimise ascertainment bias, our study has only been recruiting patients between 1999 and 2007. Median disease duration for our cohort was 11.5 years (range 2–48) demonstrating an unintentional bias against those patients with short disease duration. The negative parameter estimate for an interaction between disease onset and disease duration affecting time to ambulatory support is principally based on cross-sectional data and may result from bias caused by patients with a long and benign disease course. Indeed, patients with aggressive disease appear to accrue most disability within the first decade. The observed effect of disease duration is highlighted in Figure 7.4.

Such problems are not seen in our prospective data collected at each visit. Indeed, we demonstrate a very clear and statistically significant relationship between disease duration and outcome: disease stage as defined by walking aid or

wheelchair use, ataxia severity as defined by ICARS and disability measured by Barthel ADL. In these analyses, the presence of extracerebellar features is associated with a poor prognosis. Other factors associated with a poor prognosis included a past history of carcinoma or organ-specific auto-immune disease, although these were only identified during analysis of ambulatory data rather than for ICARS.

None of our patients have had a post-mortem examination to confirm a pathological diagnosis. While we have demonstrated a clinical diagnosis of "probable MSA" to be highly predictive of subsequent disease progression and outcome, we would avoid making definitive conclusions regarding the evolution of sporadic ataxia into MSA based on our data. However our data is similar to previous reports[35] with 20 patients (18.0%) of the 111 patients with sporadic ataxia included meeting diagnostic criteria for MSA during a median follow-up of 6 years. The absence of a history of autonomic dysfunction at disease onset essentially excluded a subsequent diagnosis of MSA during the study period (predictive value 99%). Further work is necessary to study the natural history of sporadic ataxia and such work will need to assess patients at disease onset, perform repeated longitudinal assessments and confirm pathological diagnosis.

Table 7.3: Clinical features of patients with LOCA grouped by age at onset and clinical diagnosis. (Abridged version shown in Table 7.1)

Feature	All	Age at onset			Familial		Not familial	
		< 40	40–60	> 60	Dominant	Other	MSA	Sporadic
Demographics								
n	161	47	72	33	26	20	20	92
Male	60.2%	48.9%	63.9%	60.6%	46.2%	50.0%	70.0%	64.1%
Female	39.8%	51.1%	36.1%	39.4%	53.8%	50.0%	30.0%	35.9%
Mean prevalent age (SD)	60.6 (13.8)	49.1 (11.6)	62.7 (8.7)	78.0 (5.7)	54.7 (15.4)	61.7 (12.3)	63.0 (11.4)	62.2 (13.5)
Mean age at onset (SD)	48.5 (15.2)	30.4 (8.0)	51.2 (5.7)	68.3 (4.9)	40.9 (10.9)	45.1 (12.7)	54.2 (12.7)	51.0 (15.6)
Disease duration								
Mean (SD)	11.5 (8.5)	16.7 (10.7)	10.0 (6.7)	7.7 (5.1)	13.7 (10.8)	13.2 (8.4)	8.6 (7.0)	10.6 (7.0)
< 5 years	20.1%	8.9%	19.4%	37.5%	29.2%	5.9%	31.6%	18.6%
5 − 10 years	35.6%	22.2%	44.4%	34.4%	16.7%	41.2%	42.1%	38.4%
10 − 15 years	20.1%	17.8%	19.4%	25.0%	16.7%	23.5%	10.5%	23.3%
> 15 years	24.2%	51.1%	16.7%	3.1%	37.5%	29.4%	15.8%	19.8%
Co-morbidities								
Epilepsy	6.8%	10.6%	6.9%	3.0%	15.4%	5.0%	0.0%	6.5%
Hypertension	19.3%	6.4%	25.0%	30.3%	11.5%	0.0%	25.0%	25.0%
Asthma	5.0%	8.5%	4.2%	3.0%	7.7%	5.0%	5.0%	4.3%
Ischaemic heart disease	5.6%	2.1%	9.7%	3.0%	7.7%	0.0%	5.0%	6.5%
Moderate alcohol use	12.4%	8.5%	18.1%	6.1%	7.7%	5.0%	20.0%	14.1%
Carcinoma	6.2%	4.3%	5.6%	12.1%	0.0%	10.0%	0.0%	8.7%
Autoimmune disease								
Thyroid disease	6.2%	6.4%	5.6%	9.1%	0.0%	0.0%	10.0%	7.6%
Rheumatoid arthritis	0.6%	0.0%	0.0%	3.0%	0.0%	0.0%	0.0%	1.1%
Pernicious anaemia	2.5%	6.4%	1.4%	0.0%	0.0%	0.0%	0.0%	3.3%
Vitiligo	0.6%	2.1%	0.0%	0.0%	0.0%	0.0%	0.0%	1.1%
Any autoimmune	8.7%	10.6%	6.9%	12.1%	0.0%	0.0%	10.0%	12.0%

Table 7.3: *(continued)*

	< 40	40–60	> 60	Dominant	Other	MSA	Sporadic
Disability							
Mean Barthel ADL	16.5	16	16.4	17.4	16.2	17	14.4	17.2
Independent	17.2%	18.6%	15.9%	18.2%	18.2%	11.8%	10.0%	19.3%
Mild	64.8%	62.8%	60.9%	75.8%	63.6%	76.5%	60.0%	66.3%
Moderate	10.3%	4.7%	17.4%	3.0%	9.1%	11.8%	5.0%	12.0%
Severe	6.2%	11.6%	4.3%	3.0%	4.5%	0.0%	20.0%	2.4%
Very severe	1.4%	2.3%	1.4%	0.0%	4.5%	0.0%	5.0%	0.0%
Need help with:							
Dressing	20.7%	18.6%	23.2%	18.2%	18.2%	11.8%	45.0%	15.7%
Grooming	6.2%	7.0%	7.2%	3.0%	9.1%	0.0%	15.0%	3.6%
Bathing	42.8%	46.5%	40.6%	42.4%	31.8%	47.1%	65.0%	38.6%
Toilet use	6.9%	9.3%	7.2%	3.0%	18.2%	0.0%	25.0%	0.0%
Feeding	17.2%	16.3%	20.3%	12.1%	13.6%	29.4%	25.0%	12.0%
Transfer	33.8%	34.9%	31.9%	36.4%	22.7%	35.3%	40.0%	33.7%
Mobility	80.7%	81.4%	79.7%	81.8%	81.8%	88.2%	85.0%	78.3%
Stairs	35.9%	41.9%	42.0%	15.2%	45.5%	35.3%	50.0%	28.9%
Rate of progression							
Within two years							
Barthel ADL < 25	3.5%	2.4%	2.9%	6.2%	4.8%	0.0%	10.5%	2.4%
ICARS > 25	80.0%	100.0%	50.0%	100.0%	100.0%	NaN%	100.0%	50.0%
Wheelchair	4.2%	2.4%	6.0%	3.1%	4.2%	0.0%	15.0%	2.5%
Ambulatory support	26.8%	14.3%	29.9%	37.5%	12.5%	13.3%	50.0%	28.8%
Posture and gait							
Gait ataxia							
Mild	35.1%	36.4%	36.6%	31.2%	41.7%	23.5%	10.5%	42.4%
Moderate	37.8%	31.8%	32.4%	56.2%	37.5%	58.8%	52.6%	30.6%
Severe	27.0%	31.8%	31.0%	12.5%	20.8%	17.6%	36.8%	27.1%
Truncal ataxia	34.8%	33.3%	36.4%	33.3%	15.8%	50.0%	40.0%	36.6%
Romberg	29.1%	36.4%	32.4%	12.5%	20.8%	29.4%	47.4%	24.7%

Table 7.3: *(continued)*

	< 40	40–60	> 60	Dominant	Other	MSA	Sporadic
Disease stage							
I	28.2%	31.1%	27.8%	25.0%	37.5%	41.2%	5.3%	27.9%
II	38.3%	28.9%	37.5%	53.1%	29.2%	35.3%	47.4%	40.7%
III	33.6%	40.0%	34.7%	21.9%	33.3%	23.5%	47.4%	31.4%
Ocular							
Nystagmus	62.9%	80.6%	56.1%	56.7%	47.4%	100.0%	45.0%	65.9%
Broken pursuit	62.1%	72.2%	60.6%	53.3%	57.9%	100.0%	75.0%	54.9%
Ophthalmoplegia	1.5%	0.0%	1.5%	3.3%	0.0%	0.0%	5.0%	1.2%
Supranuclear palsy	3.1%	2.8%	1.6%	6.7%	0.0%	0.0%	5.3%	3.7%
Ptosis	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%

Table 7.3: *(continued)*

	< 40	40–60	> 60	Dominant	Other	MSA	Sporadic
Limb							
Spasticity	12.2%	8.3%	16.9%	6.7%	0.0%	42.9%	10.0%	12.2%
Ankle clonus	5.4%	8.6%	6.2%	0.0%	0.0%	0.0%	10.0%	6.1%
Absent ankle jerks	25.4%	27.8%	17.2%	40.0%	10.5%	14.3%	30.0%	25.9%
Extensor plantars	15.3%	11.1%	16.9%	16.7%	15.8%	0.0%	25.0%	14.6%
Brisk ankle or knee jerks	17.7%	22.2%	15.6%	16.7%	15.8%	14.3%	25.0%	17.3%
Wasting	19.1%	13.9%	15.4%	33.3%	0.0%	28.6%	25.0%	20.7%
Finger-nose dysmetria							
None	17.7%	13.6%	24.3%	6.2%	26.1%	17.6%	10.5%	17.6%
Mild	61.9%	61.4%	51.4%	87.5%	60.9%	58.8%	52.6%	65.9%
Moderate	15.0%	15.9%	18.6%	6.2%	8.7%	23.5%	21.1%	12.9%
Severe	5.4%	9.1%	5.7%	0.0%	4.3%	0.0%	15.8%	3.5%
Finger-nose tremor							
None	18.4%	15.9%	20.0%	15.6%	30.4%	17.6%	10.5%	17.6%
Mild	70.7%	68.2%	70.0%	78.1%	65.2%	70.6%	68.4%	74.1%
Moderate	8.2%	9.1%	8.6%	6.2%	0.0%	5.9%	21.1%	7.1%
Severe	2.7%	6.8%	1.4%	0.0%	4.3%	5.9%	0.0%	1.2%
Postural tremor	80.3%	80.6%	80.3%	80.0%	82.4%	85.7%	75.0%	80.0%
Dysdiadochokinesis							
None	10.2%	9.1%	10.0%	12.5%	21.7%	5.9%	0.0%	10.6%
Mild	28.6%	31.8%	27.1%	25.0%	39.1%	29.4%	21.1%	27.1%
Moderate	59.9%	54.5%	62.9%	62.5%	34.8%	64.7%	78.9%	62.4%
Severe	1.4%	4.5%	0.0%	0.0%	4.3%	0.0%	0.0%	0.0%
Heel-shin dysmetria							
None	18.4%	13.6%	21.4%	18.8%	30.4%	11.8%	10.5%	18.8%
Mild	40.1%	36.4%	35.7%	56.2%	34.8%	41.2%	31.6%	43.5%
Moderate	23.8%	22.7%	24.3%	21.9%	21.7%	29.4%	36.8%	21.2%
Severe	17.7%	27.3%	18.6%	3.1%	13.0%	17.6%	21.1%	16.5%
Heel-shin tremor							

Table 7.3: *(continued)*

		< 40	40–60	> 60	Dominant	Other	MSA	Sporadic
None		33.3%	25.0%	32.9%	46.9%	34.8%	29.4%	31.6%	35.3%
Mild		44.9%	45.5%	42.9%	50.0%	47.8%	47.1%	42.1%	44.7%
Moderate		7.5%	6.8%	11.4%	0.0%	4.3%	5.9%	15.8%	7.1%
Severe		14.3%	22.7%	12.9%	3.1%	13.0%	17.6%	10.5%	12.9%
Extrapyramidal signs								
Rigidity		5.3%	2.8%	3.1%	13.3%	5.3%	0.0%	15.0%	3.7%
Bradykinesia		12.2%	5.6%	10.8%	23.3%	15.8%	0.0%	25.0%	9.8%
Resting tremor		1.5%	0.0%	1.5%	3.3%	0.0%	0.0%	10.0%	0.0%
Any above 3		12.2%	5.6%	10.8%	23.3%	15.8%	0.0%	25.0%	9.8%
Dystonia		4.5%	5.6%	4.6%	0.0%	15.0%	0.0%	5.0%	2.4%
Sensory loss								
Pinprick		10.0%	11.1%	10.8%	6.9%	0.0%	14.3%	15.0%	9.9%
Temperature		9.2%	8.3%	9.2%	10.3%	0.0%	14.3%	20.0%	7.4%
Vibration		33.3%	25.0%	33.8%	42.9%	5.3%	42.9%	40.0%	36.2%
Joint position		30.0%	25.0%	26.2%	44.8%	5.3%	42.9%	20.0%	35.8%
Any extracerebellar		58.0%	47.2%	60.0%	66.7%	47.4%	42.9%	75.0%	57.3%

Table 7.3: *(continued)*

	< 40	40–60	> 60	Dominant	Other	MSA	Sporadic
Speech and swallow							
Dysarthria							
None	28.6%	27.3%	20.0%	50.0%	8.7%	35.3%	21.1%	35.3%
Mild	29.9%	25.0%	34.3%	25.0%	26.1%	23.5%	36.8%	31.8%
Moderate	40.1%	43.2%	45.7%	25.0%	60.9%	41.2%	42.1%	31.8%
Severe	1.4%	4.5%	0.0%	0.0%	4.3%	0.0%	0.0%	1.2%
Autonomic							
Postural hypotension	2.4%	2.9%	0.0%	6.9%	0.0%	0.0%	10.0%	1.3%
Urinary urgency	28.7%	34.1%	22.9%	34.4%	25.0%	35.3%	65.0%	20.5%
Urinary frequency	26.6%	19.5%	27.1%	34.4%	45.0%	29.4%	30.0%	20.5%
Urinary hesitancy	11.3%	7.3%	10.3%	18.8%	5.0%	6.7%	25.0%	10.8%
Urinary incontinence	22.9%	22.0%	23.2%	23.3%	25.0%	18.8%	85.0%	8.6%
Faecal incontinence	7.1%	9.8%	7.2%	3.2%	0.0%	6.2%	25.0%	4.9%
Indwelling catheter	1.4%	0.0%	2.9%	0.0%	0.0%	0.0%	10.0%	0.0%
Intermittent catheter	1.4%	2.4%	1.5%	0.0%	0.0%	6.2%	5.3%	0.0%
Erectile dysfunction	41.8%	31.6%	44.2%	47.1%	42.9%	20.0%	84.6%	32.7%
Any autonomic dysfunction	46.9%	43.9%	45.7%	53.1%	50.0%	41.2%	100.0%	34.9%
Other							
Chorea	2.3%	5.6%	1.5%	0.0%	10.5%	0.0%	0.0%	1.2%
Head tremor	11.4%	5.6%	18.2%	3.3%	10.5%	37.5%	10.0%	9.8%
Jaw jerk	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
Deafness	4.5%	5.6%	4.5%	3.3%	0.0%	0.0%	5.0%	6.1%
Nail clubbing	2.8%	3.6%	1.9%	3.7%	0.0%	0.0%	14.3%	1.3%
Palmar erythema	9.3%	7.1%	11.5%	7.4%	16.7%	12.5%	28.6%	5.2%
Cognition							
MMSE < 26	10.9%	7.9%	15.9%	3.2%	23.8%	11.8%	0.0%	10.1%
MMSE 26 − 27	12.3%	15.8%	7.2%	19.4%	14.3%	5.9%	15.0%	12.7%
MMSE 28 − 29	39.9%	23.7%	43.5%	51.6%	28.6%	17.6%	70.0%	40.5%
MMSE 30	37.0%	52.6%	33.3%	25.8%	33.3%	64.7%	15.0%	36.7%

Table 7.4: Clinical features of patients with LOCA with results of repeated contingency tests for each category listed. Unless otherwise specified, results are shown as p-values. Mol. diagnosis = contingency test based on proven molecular diagnosis.

Feature	All	Gilman status	Age at onset	Sex	Familial vs. sporadic	Mol. diagnosis	Ataxia diagnosis
Demographics							
n	161	161	161	161	161	161	161
Male (%)	60.2%	0.4	0.3	<0.0001	0.1	0.8	<0.05
Female (%)	39.8%	0.4	0.3	<0.0001	0.1	0.8	<0.05
Mean prevalent age (SD)	60.6 (13.8)	60.6 (13.8)	60.6 (13.8)	60.6 (13.8)	60.6 (13.8)	60.6 (13.8)	60.6 (13.8)
Mean age at onset (SD)	48.5 (15.2)	48.5 (15.2)	48.5 (15.2)	48.5 (15.2)	48.5 (15.2)	48.5 (15.2)	48.5 (15.2)
Mean disease duration (SD)	11.5 (8.5)	11.5 (8.5)	11.5 (8.5)	11.5 (8.5)	11.5 (8.5)	11.5 (8.5)	11.5 (8.5)
Mean Barthel ADL (SD)	16.5 (3.7)	16.5 (3.7)	16.5 (3.7)	16.5 (3.7)	16.5 (3.7)	16.5 (3.7)	16.5 (3.7)
Disease stage (%)							
I	28.2%	<0.05	0.8	0.3	0.1	0.8	0.7
II	38.3%	0.5	0.1	0.2	0.5	0.3	0.6
III	33.6%	0.5	0.2	0.9	0.5	0.3	0.5
Within two years (%)							
Barthel ADL < 25	3.5%	0.3	0.6	0.7	0.8	0.9	1
Ambulatory support	26.8%	0.1	0.1	0.2	<0.05	0.2	NA
Co-morbidities (%)							
Epilepsy	6.8%	0.6	0.4	0.9	0.3	0.1	<0.01
Hypertension	19.3%	<0.05	<0.05	0.1	<0.01	0.3	0.2
Moderate alcohol use	12.4%	0.7	0.1	0.1	0.3	0.8	0.4
Autoimmune disease	8.7%	0.3	0.6	1	<0.05	0.9	<0.05

Table 7.4: *(continued)*

Clinical features (%)							
Gait ataxia	97.3%	0.3	0.1	0.9	0.1	0.8	0.2
Truncal ataxia	34.8%	0.5	0.9	0.8	0.5	1	0.4
Dysarthria	71.4%	0.4	<0.01	0.1	0.3	0.2	0.2
Ocular							
Nystagmus	62.9%	0.1	<0.05	0.9	0.9	0.3	0.1
Broken pursuit	62.1%	<0.05	0.3	0.3	0.5	0.8	0.2
Ophthalmoplegia	1.5%	0.4	0.5	0.7	0.9	0.5	1
Supranuclear palsy	3.1%	0.2	0.4	1	0.7	0.9	1
Limb							
Wasting	19.1%	0.3	0.1	0.7	0.2	1	0.2
Spasticity	12.2%	0.4	0.3	0.8	0.8	0.9	<0.05
Ankle clonus	5.4%	0.8	0.3	0.5	0.4	0.8	1
Absent ankle jerks	25.4%	0.8	0.1	0.7	<0.05	0.1	<0.01
Extensor plantars	15.3%	0.6	0.7	0.7	0.8	0.7	0.8
Brisk ankle or knee jerks	17.7%	0.8	0.7	<0.01	1	0.2	0.8
Finger-nose dysmetria	82.3%	0.2	0.1	0.1	0.4	0.5	0.6
Finger-nose tremor	81.6%	0.1	0.8	0.8	0.3	0.9	0.7
Postural tremor	80.3%	<0.05	1	0.6	1	0.4	0.9
Dysdiadochokinesis	89.8%	<0.05	0.9	0.7	0.3	0.4	0.1
Heel-shin dysmetria	81.6%	0.4	0.6	0.8	0.5	0.9	0.7
Heel-shin tremor	66.7%	0.9	0.1	0.7	0.8	0.3	0.8
Extrapyramidal	12.2%	0.1	0.1	0.4	0.8	0.9	0.9
Sensory loss	43.1%	NA	0.1	0.9	<0.01	0.5	0.1
Autonomic dysfunction	46.9%	NA	0.7	0.1	0.9	0.2	0.7
Chorea	2.3%	0.9	0.3	0.7	0.2	<0.05	<0.0001
Head tremor	11.4%	0.8	<0.05	<0.05	0.3	1	<0.05
Deafness	4.5%	0.8	0.9	0.9	0.5	0.9	1
Cognitive impairment	10.9%	<0.01	0.1	0.8	0.1	0.8	0.3

Table 7.5: Clinical features of patients with LOCA by ataxia diagnosis.

Feature	All patients	Ataxia diagnosis							
		DRPLA	Dominant LOCA	FRDA	FXTAS	Familial LOCA	SCA-6	SCA-8	Sporadic LOCA
Demographics									
n	161	6	15	3	1	20	4	1	111
Male (%)	60.2	83.3	40.0	66.7	0.0	50.0	0.0	100.0	65.8
Female (%)	39.8	16.7	60.0	33.3	100.0	50.0	100.0	0.0	34.2
Mean prevalent age (SD)	60.6 (13.8)	51.7 (10.5)	51.7 (16.8)	47.3 (16.5)	88.0 (NA)	61.7 (12.3)	63.2 (8.2)	82.0 (NA)	62.1 (13.0)
Mean age at onset (SD)	48.5 (15.2)	39.3 (8.8)	37.8 (10.6)	18.7 (2.1)	55.0 (NA)	45.1 (12.7)	51.5 (10.1)	52.0 (NA)	51.6 (15.2)
Mean disease duration (SD)	11.5 (8.5)	10.4 (7.4)	14.3 (12.1)	28.3 (18.9)	29.0 (NA)	13.2 (8.4)	11.8 (8.8)	29.0 (NA)	10.1 (6.8)
Mean Barthel ADL (SD)	16.5 (3.7)	12.4 (8.6)	17.8 (2.7)	11.0 (7.9)	14.0 (NA)	17.0 (2.4)	16.5 (3.9)	15.0 (NA)	16.7 (3.4)
Disease stage (%)									
I	28.2	40.0	42.9	33.3	0.0	41.2	25.0	0.0	24.0
II	38.3	20.0	35.7	0.0	100.0	35.3	25.0	0.0	41.3
III	33.6	40.0	21.4	66.7	0.0	23.5	50.0	100.0	34.6
Within two years (%)									
Barthel ADL < 25	3.5	0.0	8.3	0.0	0.0	0.0	0.0	0.0	4.0
Ambulatory support	26.8	16.7	15.4	0.0	NaN	13.3	0.0	0.0	33.0
Co-morbidities (%)									
Epilepsy	6.8	50.0	6.7	0.0	0.0	5.0	0.0	0.0	5.4
Hypertension	19.3	0.0	13.3	0.0	0.0	0.0	25.0	0.0	25.2
Moderate alcohol use	12.4	33.3	0.0	0.0	0.0	5.0	0.0	0.0	15.3
Autoimmune disease	8.7	0.0	0.0	33.3	100.0	0.0	0.0	0.0	10.8

Table 7.5: *(continued)*

	DRPLA	Dominant LOCA	FRDA	FXTAS	Familial LOCA	SCA-6	SCA-8	Sporadic LOCA
Clinical features (%)								
Gait ataxia	97.3	100.0	85.7	100.0	100.0	94.1	100.0	100.0	99.0
Truncal ataxia	34.8	40.0	10.0	33.3	100.0	50.0	0.0	0.0	36.6
Dysarthria	71.4	100.0	85.7	100.0	0.0	64.7	100.0	100.0	68.0
Ocular								
Nystagmus	62.9	40.0	60.0	100.0	0.0	100.0	33.3	0.0	62.4
Broken pursuit	62.1	40.0	60.0	100.0	100.0	100.0	66.7	100.0	58.4
Ophthalmoplegia	1.5	0.0	0.0	0.0	0.0	0.0	0.0	0.0	2.0
Supranuclear palsy	3.1	0.0	0.0	0.0	0.0	0.0	0.0	0.0	4.0
Limb								
Wasting	19.1	0.0	0.0	33.3	100.0	28.6	0.0	0.0	20.8
Spasticity	12.2	0.0	0.0	33.3	100.0	42.9	0.0	0.0	10.9
Ankle clonus	5.4	0.0	0.0	0.0	0.0	0.0	0.0	0.0	6.9
Absent ankle jerks	25.4	0.0	0.0	100.0	100.0	14.3	33.3	100.0	26.0
Extensor plantars	15.3	0.0	20.0	0.0	0.0	0.0	33.3	0.0	16.8
Brisk ankle or knee jerks	17.7	0.0	30.0	0.0	0.0	14.3	0.0	0.0	19.0
Finger-nose dysmetria	82.3	100.0	64.3	100.0	100.0	82.4	75.0	100.0	83.5
Finger-nose tremor	81.6	75.0	64.3	100.0	100.0	82.4	75.0	100.0	83.5
Postural tremor	80.3	80.0	75.0	100.0	100.0	85.7	100.0	100.0	78.8
Dysdiadochokinesis	89.8	100.0	64.3	100.0	100.0	94.1	100.0	100.0	91.3
Heel-shin dysmetria	81.6	75.0	64.3	100.0	100.0	88.2	75.0	100.0	82.5
Heel-shin tremor	66.7	75.0	57.1	100.0	100.0	70.6	75.0	100.0	65.0
Extrapyramidal	12.2	20.0	20.0	0.0	0.0	0.0	0.0	0.0	12.9
Sensory loss	43.1	0.0	10.0	66.7	100.0	42.9	33.3	0.0	48.0
Autonomic dysfunction	46.9	33.3	70.0	33.3	0.0	41.2	33.3	0.0	48.0
Chorea	2.3	40.0	0.0	0.0	0.0	0.0	0.0	0.0	1.0
Head tremor	11.4	0.0	20.0	0.0	100.0	37.5	0.0	0.0	8.9
Deafness	4.5	0.0	0.0	0.0	0.0	0.0	0.0	0.0	5.9
Cognitive impairment	10.9	40.0	25.0	0.0	0.0	11.8	0.0	0.0	8.2

Table 7.6: Clinical features by disease stage

Feature	All patients	Gender		Disease stage		
		Female	Male	I	II	III
Demographics						
n	161	64	97	42	57	50
Male	60.2%	0.0%	100.0%	66.7%	50.9%	60.0%
Female	39.8%	100.0%	0.0%	33.3%	49.1%	40.0%
Mean prevalent age (SD)	60.6 (13.8)	61.7 (14.4)	59.9 (13.5)	57.9 (16.0)	63.8 (12.7)	61.0 (12.5)
Mean age at onset (SD)	48.5 (15.2)	47.6 (14.9)	49.1 (15.5)	47.6 (14.9)	51.7 (14.8)	46.3 (15.2)
Disease duration						
Mean (SD)	11.5 (8.5)	12.5 (9.4)	10.8 (7.8)	9.6 (6.1)	10.6 (7.9)	14.1 (10.3)
< 5 years	20.1%	21.0%	19.5%	26.2%	21.1%	14.0%
5 − 10 years	35.6%	32.3%	37.9%	33.3%	40.4%	32.0%
10 − 15 years	20.1%	16.1%	23.0%	21.4%	19.3%	20.0%
> 15 years	24.2%	30.6%	19.5%	19.0%	19.3%	34.0%
Co-morbidities						
Epilepsy	6.8%	6.2%	7.2%	4.8%	7.0%	10.0%
Hypertension	19.3%	12.5%	23.7%	14.3%	19.3%	26.0%
Asthma	5.0%	7.8%	3.1%	2.4%	5.3%	8.0%
Ischaemic heart disease	5.6%	4.7%	6.2%	4.8%	8.8%	4.0%
Moderate alcohol use	12.4%	6.2%	16.5%	9.5%	7.0%	20.0%
Carcinoma	6.2%	9.4%	4.1%	2.4%	8.8%	8.0%
Autoimmune disease						
Thyroid disease	6.2%	6.2%	6.2%	2.4%	5.3%	12.0%
Rheumatoid arthritis	0.6%	0.0%	1.0%	0.0%	1.8%	0.0%
Pernicious anaemia	2.5%	3.1%	2.1%	0.0%	3.5%	4.0%
Vitiligo	0.6%	0.0%	1.0%	0.0%	0.0%	2.0%
Any autoimmune	8.7%	7.8%	9.3%	2.4%	8.8%	16.0%

Table 7.6: *(continued)*

		Female	Male	I	II	III
Disability						
Mean Barthel ADL	16.5	16.4	16.6	18.7	17.3	14.1
Independent	17.2%	10.0%	22.4%	35.9%	12.3%	6.4%
Mild	64.8%	70.0%	61.2%	61.5%	78.9%	53.2%
Moderate	10.3%	13.3%	8.2%	2.6%	8.8%	19.1%
Severe	6.2%	6.7%	5.9%	0.0%	0.0%	19.1%
Very severe	1.4%	0.0%	2.4%	0.0%	0.0%	2.1%
Need help with:						
Dressing	20.7%	20.0%	21.2%	5.1%	14.0%	40.4%
Grooming	6.2%	5.0%	7.1%	0.0%	0.0%	17.0%
Bathing	42.8%	48.3%	38.8%	15.4%	42.1%	66.0%
Toilet use	6.9%	8.3%	5.9%	2.6%	0.0%	17.0%
Feeding	17.2%	15.0%	18.8%	7.7%	8.8%	34.0%
Transfer	33.8%	43.3%	27.1%	15.4%	33.3%	48.9%
Mobility	80.7%	90.0%	74.1%	59.0%	87.7%	91.5%
Stairs	35.9%	36.7%	35.3%	7.7%	29.8%	66.0%
Rate of progression						
Within two years						
Barthel ADL < 25	3.5%	5.0%	2.4%	2.6%	5.3%	2.1%
ICARS > 25	80.0%	100.0%	50.0%	0.0%	100.0%	100.0%
Wheelchair	4.2%	3.7%	4.5%	0.0%	0.0%	12.2%
Ambulatory support	26.8%	33.3%	22.7%	0.0%	46.8%	32.7%
Posture and gait						
Gait ataxia						
Mild	35.1%	31.1%	37.9%	76.2%	29.8%	6.2%
Moderate	37.8%	41.0%	35.6%	21.4%	54.4%	31.2%
Severe	27.0%	27.9%	26.4%	2.4%	15.8%	62.5%
Truncal ataxia	34.8%	37.3%	33.3%	17.6%	39.2%	43.5%
Romberg	29.1%	34.4%	25.3%	9.5%	24.6%	52.1%

Table 7.6: *(continued)*

	Female	Male	I	II	III
Disease stage					
I	28.2%	22.6%	32.2%	100.0%	0.0%	0.0%
II	38.3%	45.2%	33.3%	0.0%	100.0%	0.0%
III	33.6%	32.3%	34.5%	0.0%	0.0%	100.0%
Ocular					
Nystagmus	62.9%	62.7%	63.0%	58.8%	64.7%	65.2%
Broken pursuit	62.1%	68.6%	58.0%	52.9%	62.7%	69.6%
Ophthalmoplegia	1.5%	0.0%	2.4%	0.0%	3.9%	0.0%
Supranuclear palsy	3.1%	2.0%	3.8%	0.0%	3.9%	4.4%
Ptosis	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%

Table 7.6: *(continued)*

	Female	Male	I	II	III
Limb					
Spasticity	12.2%	12.0%	12.3%	9.1%	7.8%	19.6%
Ankle clonus	5.4%	8.2%	3.7%	0.0%	3.9%	11.1%
Absent ankle jerks	25.4%	28.0%	23.8%	21.2%	23.5%	31.1%
Extensor plantars	15.3%	18.0%	13.6%	9.1%	17.6%	17.4%
Brisk ankle or knee jerks	17.7%	30.0%	10.0%	3.0%	21.6%	24.4%
Wasting	19.1%	22.0%	17.3%	9.1%	19.6%	26.1%
Finger-nose dysmetria					
None	17.7%	11.5%	22.1%	33.3%	7.1%	14.6%
Mild	61.9%	68.9%	57.0%	59.5%	76.8%	47.9%
Moderate	15.0%	14.8%	15.1%	7.1%	14.3%	22.9%
Severe	5.4%	4.9%	5.8%	0.0%	1.8%	14.6%
Finger-nose tremor					
None	18.4%	16.4%	19.8%	28.6%	16.1%	10.4%
Mild	70.7%	70.5%	70.9%	66.7%	78.6%	66.7%
Moderate	8.2%	8.2%	8.1%	4.8%	5.4%	14.6%
Severe	2.7%	4.9%	1.2%	0.0%	0.0%	8.3%
Postural tremor	80.3%	83.7%	78.2%	75.8%	76.5%	90.5%
Dysdiadochokinesis					
None	10.2%	8.2%	11.6%	11.9%	12.5%	6.2%
Mild	28.6%	21.3%	33.7%	42.9%	19.6%	25.0%
Moderate	59.9%	68.9%	53.5%	45.2%	67.9%	64.6%
Severe	1.4%	1.6%	1.2%	0.0%	0.0%	4.2%
Heel-shin dysmetria					
None	18.4%	16.4%	19.8%	35.7%	14.3%	8.3%
Mild	40.1%	45.9%	36.0%	42.9%	50.0%	27.1%
Moderate	23.8%	21.3%	25.6%	16.7%	21.4%	31.2%
Severe	17.7%	16.4%	18.6%	4.8%	14.3%	33.3%
Heel-shin tremor					

Table 7.6: *(continued)*

	Female	Male	I	II	III
None	33.3%	36.1%	31.4%	47.6%	35.7%	18.8%
Mild	44.9%	42.6%	46.5%	45.2%	50.0%	39.6%
Moderate	7.5%	8.2%	7.0%	4.8%	7.1%	10.4%
Severe	14.3%	13.1%	15.1%	2.4%	7.1%	31.2%
Extrapyramidal signs					
Rigidity	5.3%	4.0%	6.2%	0.0%	7.8%	6.5%
Bradykinesia	12.2%	8.0%	14.8%	12.1%	13.7%	10.9%
Resting tremor	1.5%	2.0%	1.2%	0.0%	2.0%	2.2%
Any above 3	12.2%	8.0%	14.8%	12.1%	13.7%	10.9%
Dystonia	4.5%	2.0%	6.1%	6.1%	0.0%	6.5%
Sensory loss					
Pinprick	10.0%	14.3%	7.4%	3.1%	5.9%	19.6%
Temperature	9.2%	10.2%	8.6%	0.0%	5.9%	19.6%
Vibration	33.3%	31.2%	34.6%	25.0%	31.4%	40.0%
Joint position	30.0%	32.7%	28.4%	21.9%	31.4%	34.8%
Any extracerebellar	58.0%	58.0%	58.0%	42.4%	60.8%	65.2%

Table 7.6: *(continued)*

	Female	Male	I	II	III
Speech and swallow					
Dysarthria					
None	28.6%	36.1%	23.3%	33.3%	39.3%	12.5%
Mild	29.9%	23.0%	34.9%	31.0%	33.9%	22.9%
Moderate	40.1%	39.3%	40.7%	35.7%	26.8%	60.4%
Severe	1.4%	1.6%	1.2%	0.0%	0.0%	4.2%
Autonomic					
Postural hypotension	2.4%	2.1%	2.5%	0.0%	2.0%	2.3%
Urinary urgency	28.7%	29.8%	27.9%	17.9%	29.1%	38.3%
Urinary frequency	26.6%	22.8%	29.1%	25.6%	27.3%	27.7%
Urinary hesitancy	11.3%	3.6%	16.5%	5.1%	15.1%	12.8%
Urinary incontinence	22.9%	19.3%	25.3%	10.3%	22.6%	32.6%
Faecal incontinence	7.1%	5.3%	8.3%	2.6%	5.7%	12.8%
Indwelling catheter	1.4%	1.8%	1.2%	0.0%	1.9%	2.1%
Intermittent catheter	1.4%	1.8%	1.2%	2.6%	1.9%	0.0%
Erectile dysfunction	41.8%	NaN%	41.8%	32.0%	44.0%	46.4%
Any autonomic dysfunction	46.9%	36.8%	53.5%	35.9%	49.1%	53.2%
Other					
Chorea	2.3%	2.0%	2.5%	0.0%	0.0%	6.5%
Head tremor	11.4%	19.6%	6.2%	2.9%	9.8%	19.6%
Jaw jerk	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
Deafness	4.5%	5.9%	3.7%	5.9%	3.9%	4.3%
Nail clubbing	2.8%	2.5%	3.0%	3.6%	0.0%	2.6%
Palmar erythema	9.3%	7.5%	10.4%	0.0%	10.0%	15.8%
Cognition					
MMSE < 26	10.9%	12.5%	9.8%	10.5%	7.4%	15.6%
MMSE $26 - 27$	12.3%	14.3%	11.0%	7.9%	11.1%	17.8%
MMSE $28 - 29$	39.9%	35.7%	42.7%	34.2%	48.1%	33.3%
MMSE 30	37.0%	37.5%	36.6%	47.4%	33.3%	33.3%

Age at onset	No family history		Positive family history		Proven genetic diagnosis				
	MSA	Not MSA	Dominant	Other	DRPLA	FA	FXTAS	SCA-6	SCA-8
No family history									
< 40	4	21	0	0	0	3	0	0	0
40 − 60	7	24	0	0	0	0	0	0	0
> 60	9	41	0	0	0	0	1	1	0
Unknown	0	5	0	0	0	0	0	0	0
Positive family history									
< 40	0	0	8	7	3	0	0	1	0
40 − 60	0	0	0	2	0	0	0	0	0
> 60	0	0	6	8	3	0	0	2	1
Unknown	0	0	1	3	0	0	0	0	0
Total	20	91	15	20	6	3	1	4	1

Table 7.7: Breakdown of genetic and clinical diagnoses by age at onset and presence of family history

Table 7.8: Quality of life in LOCA.

Feature	All patients	Age at onset			Familial		Not familial	
		< 40	40–60	> 60	Dominant	Other	MSA	Sporadic
Quality of life								
Balance transfers	86.4%	88.9%	85.7%	84.6%	71.4%	85.7%	100.0%	88.6%
Restless legs	62.7%	61.1%	67.9%	53.8%	71.4%	85.7%	62.5%	57.1%
Spasms	49.2%	44.4%	50.0%	53.8%	57.1%	57.1%	75.0%	42.9%
Nervous strangers	45.8%	38.9%	57.1%	30.8%	71.4%	42.9%	37.5%	45.7%
Writing	86.4%	94.4%	89.3%	69.2%	100.0%	85.7%	87.5%	82.9%
Using telephone	42.4%	27.8%	46.4%	53.8%	71.4%	28.6%	62.5%	37.1%
Cutting up food	47.5%	44.4%	53.6%	38.5%	57.1%	42.9%	62.5%	42.9%
Brushing teeth	30.5%	27.8%	32.1%	30.8%	42.9%	14.3%	62.5%	25.7%
Stairs	55.9%	61.1%	60.7%	38.5%	71.4%	57.1%	75.0%	51.4%
Public transport	67.8%	66.7%	75.0%	53.8%	100.0%	57.1%	87.5%	60.0%
In/out of car	62.7%	44.4%	67.9%	76.9%	71.4%	57.1%	75.0%	60.0%
Housework	69.5%	66.7%	75.0%	61.5%	85.7%	71.4%	87.5%	62.9%
Dressing	66.1%	61.1%	67.9%	69.2%	57.1%	85.7%	75.0%	62.9%
Frustration	84.7%	88.9%	85.7%	76.9%	100.0%	85.7%	87.5%	80.0%
Depressed/down	76.3%	66.7%	85.7%	69.2%	100.0%	85.7%	75.0%	71.4%
Frightened/scared	47.5%	44.4%	46.4%	53.8%	57.1%	71.4%	50.0%	42.9%
Cut off	61.0%	50.0%	71.4%	53.8%	85.7%	42.9%	75.0%	60.0%
Self-esteem	59.3%	55.6%	57.1%	69.2%	57.1%	85.7%	62.5%	57.1%
Loss confidence	67.8%	66.7%	67.9%	69.2%	85.7%	85.7%	75.0%	62.9%
Embarrassed	57.6%	66.7%	53.6%	53.8%	71.4%	71.4%	75.0%	51.4%

Table 7.9: Mean (SD) SF-36 results in LOCA for individual dimensions

Feature	All patients	Age at onset			Familial		Not familial	
		< 40	40–60	> 60	Dominant	Other	MSA	Sporadic
SF-36								
Physical function	28.7 (29.7)	23.3 (28.3)	31.7 (33.4)	27.9 (23.6)	32.5 (38.0)	15.0 (17.3)	21.0 (26.8)	31.1 (29.1)
Role limitation (physical)	24.3 (39.6)	16.7 (35.4)	30.6 (43.3)	17.9 (37.4)	6.2 (12.5)	0.0 (0.0)	30.0 (44.7)	28.9 (42.7)
Role limitation (emotional)	42.4 (50.2)	44.4 (52.7)	38.9 (50.2)	50.0 (54.8)	0.0 (0.0)	25.0 (50.0)	60.0 (54.8)	50.0 (51.4)
Social functioning	49.3 (33.1)	48.1 (38.5)	48.8 (34.7)	52.4 (24.6)	33.3 (28.7)	36.1 (29.2)	28.9 (44.2)	58.5 (29.1)
Mental health	63.6 (20.2)	61.3 (16.1)	65.8 (24.6)	61.1 (12.6)	59.0 (16.8)	63.0 (28.5)	59.2 (20.9)	65.5 (21.3)
Energy/vitality	38.2 (22.4)	33.3 (16.2)	38.9 (26.3)	42.9 (20.0)	32.5 (17.1)	27.5 (2.9)	35.0 (31.0)	42.6 (23.8)
Pain	63.7 (32.4)	54.3 (36.2)	66.7 (32.8)	68.3 (28.3)	52.8 (36.7)	50.0 (38.0)	57.8 (41.9)	69.6 (29.4)
General health perception	40.0 (21.4)	37.8 (17.0)	40.8 (24.1)	40.7 (21.9)	31.2 (25.3)	30.0 (4.1)	23.0 (22.0)	47.9 (20.3)

Table 7.10: Co-morbidities grouped by age at time of assessment

Feature	All patients	Age						
		(20,30]	(30,40]	(40,50]	(50,60]	(60,70]	(70,80]	(80,90]
Past history								
Epilepsy	6.8%	0.0%	12.5%	5.9%	9.6%	12.9%	0.0%	0.0%
Hypertension	19.3%	0.0%	0.0%	11.8%	19.2%	22.6%	27.6%	33.3%
Asthma	5.0%	0.0%	0.0%	23.5%	5.8%	0.0%	3.4%	0.0%
Ischaemic heart disease	5.6%	0.0%	0.0%	11.8%	3.8%	3.2%	10.3%	11.1%
Moderate alcohol use	12.4%	0.0%	12.5%	11.8%	23.1%	6.5%	3.4%	0.0%
Carcinoma	6.2%	0.0%	0.0%	5.9%	5.8%	19.4%	0.0%	0.0%
Autoimmune disease								
Thyroid disease	6.2%	0.0%	12.5%	0.0%	5.8%	9.7%	3.4%	22.2%
Rheumatoid arthritis	0.6%	0.0%	0.0%	0.0%	0.0%	3.2%	0.0%	0.0%
Pernicious anaemia	2.5%	0.0%	12.5%	5.9%	1.9%	3.2%	0.0%	0.0%
Vitiligo	0.6%	0.0%	0.0%	0.0%	1.9%	0.0%	0.0%	0.0%
Any autoimmune	8.7%	0.0%	12.5%	5.9%	7.7%	16.1%	3.4%	22.2%
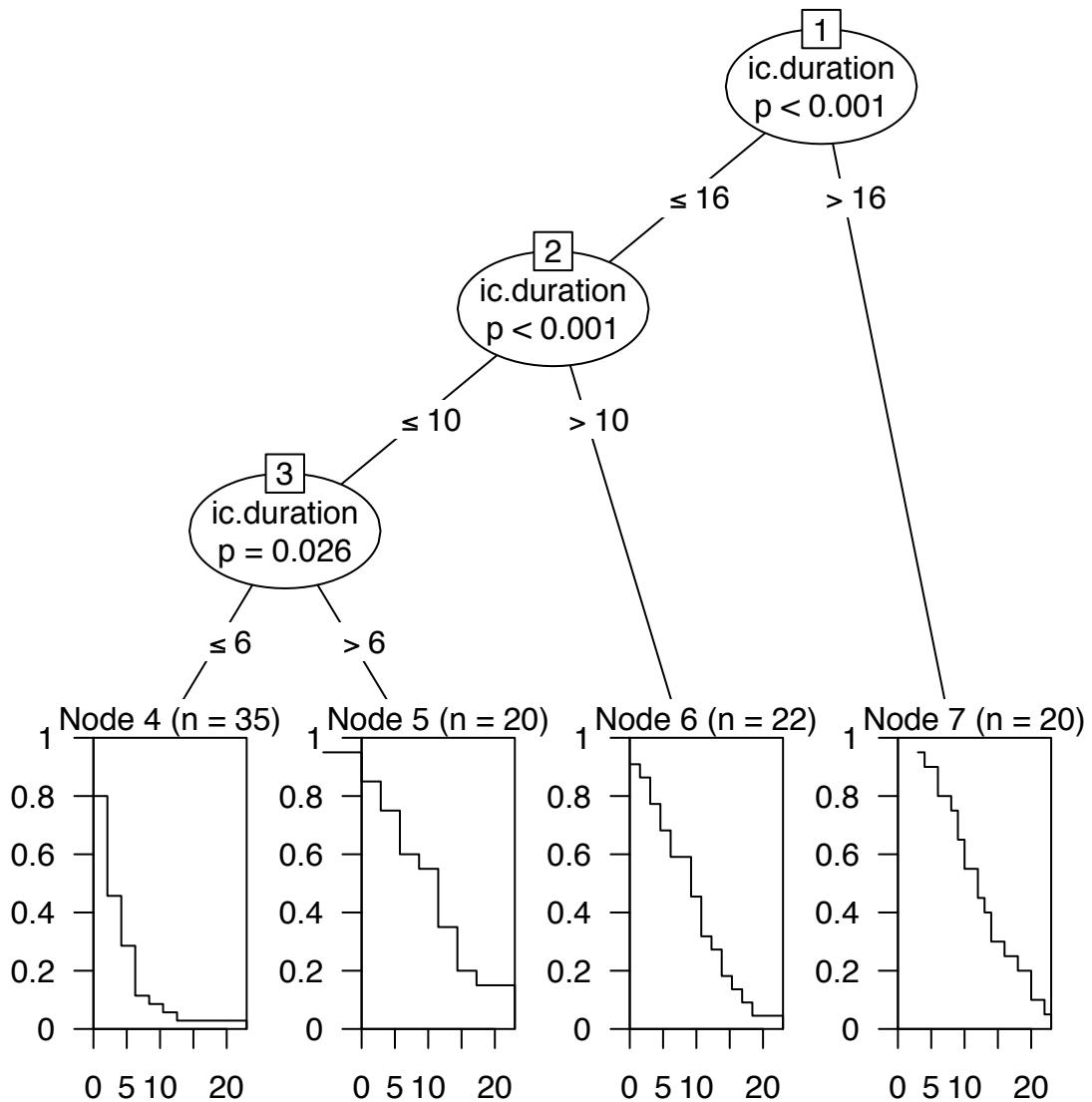
Figure 7.4: Recursive partitioning of survival data demonstrating confounding resulting informative drop-out of patients with aggressive disease on hazard estimates.

Psychometric properties of ICARS

8.1 Introduction

As outlined in Chapter 1.4, International Cooperative Ataxia Rating Scale (ICARS) was published in 1997 with the long-term goal of supporting double-blind controlled trials for treatments of ataxia.[144] However, while there have been several studies examining the psychometric properties of ICARS in a number of ataxic disorders, there have been few studies measuring its ability to assess change.

This chapter reports on a detailed investigation of ICARS in a heterogeneous group of 148 patients with chronic progressive cerebellar ataxia recruited and seen between 1999 and 2007 from a population-based study of ataxia in South Wales, UK.[86] In this study, we evaluate the fundamental psychometric properties of ICARS including correlates to detailed clinical characteristics and indicators of disease progression and disability together with an analysis of the responsiveness of the ICARS to detect clinically important change.

8.2 Materials and methods

8.2.1 Case ascertainment

Patients with chronic progressive LOCA were identified from multiple sources including (i) local general practitioners, (ii) departmental databases in the Department of Neurology and Institute of Medical Genetics, (iii) liaison and personal notifications from regional consultant neurologists over the study period and (iv) self-referral via other family members or response to an advertisement in the Ataxia UK newsletter (`http://www.ataxia.org.uk`). (v) regional NHS administrative databases searching for a diagnosis of "ataxia" according to the 9th and 10th editions of the International Classification of Diseases (ICD).

The inclusion criteria were: (i) patients with chronic progressive cerebellar ataxia, (ii) at least one year duration, (iii) age at onset of 16 or over. Patients were excluded if ataxia was only a minor feature or if a symptomatic cause was identified. After obtaining informed consent patients underwent a systematic clinical evaluation using a standardised data collection protocol with data stored in a

dedicated database in accordance with the Data Protection Act, 1998. Three experienced examiners administered the ICARS together with a full history and clinical examination, Barthel ADL,[150] SF-36[61] and assessment of disease stage, defined as I: no ambulatory support required, II: unilateral or bilateral support required, III: wheelchair bound.[64] Patients were categorised by defined genetic diagnosis when possible, but otherwise designated familial or sporadic based on the presence or absence of a family history of similar disorder in a first- or second-degree relative and with sporadic patients judged according to published criterion for a potential diagnosis of probable multiple system atrophy (MSA).[36]

To study inter-rater reliability, a subgroup of 19 patients were examined at a short time interval by two different investigators who completed assessments independently and without discussion. Similarly, a subgroup of 34 patients were revisited by a single investigator (MW) within 12 months to assess intra-rater reliability. A further subgroup of 24 patients were visited prospectively over the study period at a variable interval of between 2 and 8 (mean 4.2) years to assess longitudinal change. We administered transition questions to patients visited prospectively with self-reported change graded on a seven-point scale ("Much worse", "Moderately worse","A little worse", "No change", "A little better", "Moderately better" and "Much better") in response to the question "Overall, how do you think things have generally changed?". The project was approved by the relevant local ethics committee and NHS research and development office.

8.2.2   Statistical methodology

All analysis was performed using "R: A Language and Environment for Statistical Computing".[104] We have adopted standard methods in evaluating the fundamental psychometric properties of the ICARS scale with systematic study of scaling assumptions, targeting, reliability, validity and responsiveness.[16,106] Unless indicated to the contrary, we have adopted methods and criterion from these papers.

Since ICARS uses Likert's method to sum individual items into four subscales and one total score,[74,144] the inherent assumption that item scores can be summed without weighting or standardisation must be tested. As such, item means and standard deviations should be similar within each scale, item-total cor-

relations should be ≥ 0.30.[16] and item scores must correlate more highly with their own subscale total than to other subscales while still correlating with total ICARS score. Factor analysis (varimax rotation) and principal components analysis were employed to examine item-level grouping in more detail.

We assessed targeting by examining score distributions. It is recommended that scores span the full scale range, with sample mean scores being near the scale mid-point, skewness statistics between -1 and +1, and floor and ceiling effects (proportion of sample scoring at the extreme ends of each scale) being less than 20%).

Reliability was assessed by calculating internal consistency (using Cronbachs α) and mean item-item correlations (homogeneity coefficients) as alphas are dependent on the number of items in a scale. Test-retest reproducibility and inter-rater agreement (both expressed as intraclass correlation coefficients — ICC, one-way model with patients considered random effects, criterion ≥ 0.80).

Internal construct validity was determined by examining inter-correlations between ICARS subscales. These correlations are expected to be moderate ($0.30 \leq r \leq 0.70$) as the ICARS subscales purport to measure related but different aspects of ataxia. External construct validity was assessed by examining relationships between ICARS subscale scores and other scales (Barthel ADL and SF-36) and variables (disease duration, disease stage) and although late-onset cerebellar ataxia (LOCA) is heterogeneous, most patients have a progressive disease course accruing increasing impairment and disability with time. To examine the relationship between ICARS scores and disease duration, we used linear mixed modelling and included covariates including gender, age at onset and clinical phenotype together with random effects to account for patient and investigator variability and investigated the effect of classifying patients according to diagnostic criteria for multiple system atrophy.[36] Parameter estimates are given along with 95% confidence intervals where indicated. One-way analysis of variance (ANOVA) was used to compare scores for patients in different disease stages.

Responsiveness (the ability of a scale to measure clinically important change) was determined by calculating effect size for subscale and total ICARS scores, defined as the change in mean score (T1 - T2) divided by the standard deviation of each baseline score. We also computed standardised response mean (change

in mean score divided by standard deviation of change scores). These were interpreted according to Cohen's arbitrary criteria (≤ 0.2 =small, 0.5 =moderate, ≥ 0.8 =large).[63] We analysed response to transition questions and change in ICARS score with ANOVA. For hypothesis tests, including likelihood tests used in statistical modelling, $P \leq 0.05$ was considered statistically significant.

8.3   Results

A total of 148 patients were studied with 215 independent ICARS assessments by three different investigators. Patient age in 2007 was 61 (23–88) years, with a mean disease duration of 11 years (range 1–48) and a mean age at onset of 48.5 (range 17–78) years. 42 patients did not require ambulatory support (disease stage I), 57 required bilateral support (stage II) and 42 needed a wheelchair (stage III). A molecular diagnosis was known in 14 patients: 5 had DRPLA, 4 SCA6, 3 Friedreich's ataxia, 1 SCA8 and 1 with a probable diagnosis of FXTAS (Fragile-X-associated tremor/ataxia syndrome). Of the remainder, 103 patients were sporadic and 31 patients had a family history (14 dominant, 17 recessive). 19/103 (18.45%) of patients with sporadic disease reached diagnostic criteria for probable MSA during the study period.

Table 8.1: Targeting, scaling assumptions and reliability of ICARS (n=215)

Property	Posture and gait	Kinetic	Dysarthria	Oculomotor	Total
Targeting					
Number of items	7	13	2	3	25
Possible score range	0–34	0–52	0–8	0–6	0–100
Observed score range	0–34	0–52	0–8	0–6	1–100
Mean score (SD)	14.57 (7.79)	19.36 (10.34)	1.93 (1.76)	2.00 (1.73)	37.74 (18.24)
Scale midpoint	17	26	4	3	50
Floor/ceiling effect (%)	0.9 / 1.9	1.9 / 0.5	35.5 / 0.5	22 / 4.7	0 / 0.5
Skewness	0.70	0.34	0.45	0.68	0.58
Scaling assumptions					
Item-total correlations					
Mean	0.75	0.7	0.87	0.52	0.61
Range	0.56–0.87	0.59–0.80	0.87–0.87	0.47–0.57	0.31–0.80
Reliability					
Internal consistency					
Cronbach's α	0.91	0.93	0.93	0.66	0.94
Mean inter-item correlation	0.61	0.53	0.87	0.45	0.4
Reproducibility					
Intra-rater reliability (ICC)	0.93	0.9	0.85	0.74	0.93
(95% CI)	0.87–0.96	0.8–0.95	0.72–0.92	0.54–0.86	0.87–0.97
Inter-rater reliability (ICC)	0.89	0.89	0.41	0.67	0.91
(95% CI)	0.73–0.96	0.73–0.96	-0.08–0.74	0.29–0.87	0.76–0.97

Table 8.2: ICARS item-own (corrected) and item-other correlations. Boldface indicates highest item-subscale correlations.

Property	Posture and gait	Kinetic	Dysarthria	Oculomotor	Total
Posture and Gait					
Walking	**0.85**	0.67	0.39	0.35	0.80
Gait	**0.72**	0.57	0.26	0.28	0.68
Standing	**0.87**	0.61	0.34	0.36	0.78
Feet spread	**0.70**	0.46	0.35	0.26	0.61
Body sway eyes open	**0.82**	0.63	0.10	0.27	0.74
Body sway eyes closed	**0.75**	0.57	0.05	0.25	0.66
Sitting quality	0.56	**0.62**	0.10	0.24	0.63
Kinetic					
Knee shin dysmetria right	0.61	**0.79**	0.09	0.24	0.74
Knee shin dysmetria left	0.59	**0.80**	0.11	0.23	0.74
Knee shin tremor left	0.59	**0.77**	0.15	0.20	0.72
Knee shin tremor right	0.60	**0.76**	0.13	0.20	0.72
Finger nose dysmetria right	0.56	**0.75**	0.30	0.38	0.73
Finger nose dysmetria left	0.56	**0.77**	0.32	0.36	0.74
Finger nose tremor right	0.50	**0.70**	0.17	0.24	0.65
Finger nose tremor left	0.49	**0.66**	0.15	0.21	0.62
Finger finger right	0.51	**0.70**	0.14	0.15	0.64
Finger finger left	0.54	**0.63**	0.23	0.21	0.63
Dysdiadochokinesis right	0.47	**0.63**	0.37	0.27	0.62
Dysdiadochokinesis left	0.45	**0.59**	0.34	0.17	0.58
Archimedes	0.51	**0.59**	0.29	0.30	0.61
Dysarthria					
Speech fluency	0.31	0.29	**0.87**	0.36	0.38
Speech clarity	0.26	0.22	**0.87**	0.41	0.33
Oculomotor					
Nystagmus	0.34	0.29	0.23	**0.47**	0.37
Pursuit	0.27	0.22	0.44	**0.57**	0.32
Saccade	0.22	0.25	0.29	**0.52**	0.31

Table 8.3: ICARS validity.

Property	Posture and gait	Kinetic	Dysarthria	Oculomotor	Total
Inter-scale correlations					
Posture / Gait	1.00	0.72	0.30	0.36	0.90
Kinetic	0.72	1.00	0.26	0.32	0.93
Dysarthria	0.30	0.26	1.00	0.39	0.41
Oculomotor	0.36	0.32	0.39	1.00	0.47
Total	0.90	0.93	0.41	0.47	1.00
Other correlations					
Disease duration	0.35	0.39	0.17	0.14	0.40
Age	-0.02	-0.05	-0.18	-0.13	-0.06
Barthel ADL	-0.77	-0.64	-0.36	-0.31	-0.76
Disease stage					
Stage I mean	8.98	13.64	1.67	1.74	26.03
Stage II mean	13.34	18.17	1.49	1.85	34.61
Stage III mean	20.84	25.65	2.70	2.39	51.58
ANOVA P value	<0.0001	<0.0001	<0.0001	0.1	<0.0001
SF-36 (PF)	-0.39	-0.37	-0.41	-0.22	-0.43

Table 8.4: Responsiveness of ICARS. n=24.

Property	Posture and gait	Kinetic	Dysarthria	Oculomotor	Total
Time 1: mean score (SD)	14.38 (6.18)	19.29 (9.19)	1.50 (1.50)	2.33 (1.76)	37.50 (14.24)
Time 2: mean score (SD)	15.78 (7.52)	21.09 (9.06)	2.48 (1.56)	1.52 (1.90)	40.87 (15.56)
Mean change (SD)	1.41	1.80	0.98	-0.81	3.37
Mean interval in years (SD)	4.2 (1.7)	4.2 (1.7)	4.2 (1.7)	4.2 (1.7)	4.2 (1.7)
Effect size	0.23	0.20	0.65	-0.46	0.24
Standardised response mean	0.40	0.42	0.64	-0.51	0.57

8.3.1 Scaling assumptions

Corrected item-total correlations for subscales demonstrated that most items correlated with their own subscale more highly than with other subscales (item-own correlations mean 0.71, range 0.47–0.87, item-other correlations mean 0.33, range 0.05–0.67; Tables 8.1 and 8.2). However, one item (sitting quality) was more highly correlated with the kinetic subscale than its own posture/gait score. In addition, moderate correlations were observed between walking and overall kinetic score and lower limb dysmetria and tremor with the posture/gait subscale. All items were moderately or highly correlated to total ICARS score (mean 0.61, range 0.31–0.80), although this was more apparent for items from the posture/gait and kinetic subscales.

Exploratory factor analysis identified five latent variables each with eigenvalues of greater than 1.0 that together accounted for 73.6% of the total variance (Figure 8.2 and Table 8.5). These factors coincided with the ICARS subscales confirming items from posture and gait, speech and oculomotor scales grouped into three separate factors. However, kinetic functions appear to divide into two separate factors accounting for upper and lower limb function respectively (Table 8.6).

8.3.2 Targeting

Observed scores were well distributed for posture/gait, kinetic and total ICARS although mean scores were consistently below scale midpoint (Table 8.1). Floor and ceiling effects were low for posture/gait, kinetic and total ICARS score but large floor effects were seen for both dysarthria (35.5%) and oculomotor subscales (22%). Skewness statistics ranged between 0.34–0.70.

8.3.3 Reliability

Internal consistency, test-retest and inter-rater reliability measures were high for total ICARS score together with posture/gait and kinetic subscales (Table 8.1). However, dysarthria and oculomotor subscales did not meet required psychometric criteria for reliability with the oculomotor subscale failing all three criteria and

dysarthria failing one criterion (inter-rata reliability).

8.3.4   Validity

Inter-correlations between subscales ranged from 0.26 (kinetic and dysarthria) to 0.72 (posture/gait and kinetic) suggesting all but dysarthria were measuring related but different constructs consistent with the ICARS measurement model (Table 8.3).

Crude correlations between ICARS and disease duration were low/moderate (r=0.4) probably reflecting clinical heterogeneity and variability within the patients studied; for instance while mean (SD) ICARS score for patients within five years of disease onset was 32 (17) points compared to 46 (20) points for those with disease duration of 15 years or greater, we observed a wide range of scores within five years of disease onset (range 1–82 points). However, more sophisticated analysis combining prospective and cross-sectional data demonstrated a significant relationship between ICARS score and disease duration, compatible with a progressive disease course. Disease duration was a significant covariate affecting total ICARS score with a parameter estimate of 1.7 (95% CI 0.9–2.6) points on the ICARS scale per year of disease duration (Figure 8.1). In addition, the presence of extracerebellar features sufficient suggest a diagnosis of "probable multiple system atrophy" (sporadic patients only) had a significant effect (10.7 points per year, 95% CI 1.9– 19.5).

In addition, ICARS was significantly associated with measures of ambulation (ANOVA $P < 0.0001$, mean score stage I=26.03, stage II=34.61, stage III=51.58), indicators of disability (Barthel ADL, r=-0.76, $P < 0.0001$) and self-reported measures of physical functioning (SF-36 PF domain score, r=-0.43, $P < 0.01$). No relationship was observed between ICARS score and age.

8.3.5   Responsiveness

Although few patients were examined prospectively (n=24), these data demonstrated that scores for total ICARS score together with posture/gait, kinetic and dysarthria subscales increased during the study period (mean 4.2, range 2.0–8.0

years, SD 2, Table 8.4). However, oculomotor scores decreased potentially indicating an improvement although we suggest that this reflects the observed poor reliability of the oculomotor subscale. Effect sizes were small and ranged between -0.46 and 0.65 suggesting limited or moderate responsiveness. Transition questions did not predict change in ICARS score (ANOVA P 0.9).

8.4 Discussion

This is a large systematic study of ICARS in a population-based sample of patients with late-onset cerebellar ataxia including detailed psychometric analysis of total and subscale scores together with correlates to other disease outcome measures. In addition we have used a combination of longitudinal and cross-sectional data to examine the potential usefulness of ICARS in longitudinal and treatment trials.

As with previous studies,[16] the total ICARS score satisfied fundamental psychometric criteria with adequate scaling assumptions, targeting and reliability. In addition, we have demonstrated the validity of ICARS with clear relationships to disease duration, ambulatory stage, disability and self-reported measures of physical functioning. All items were correlated with total ICARS score suggesting that item-responses were measuring a single construct. We found ICARS total score to be significantly higher in patients with multiple system atrophy — ICARS increased by an additional 10.7 points per year, 95% CI 1.9– 19.5) compared to patients without multiple system atrophy.

Previous authors have noted item redundancy within ICARS scoring,[113] in which a rating in an item determines the rating in other items. Such dependency may result in contradictory scores: a walking status of "impossible, even with support" must result in a gait speed of "Walking no longer possible" and a standing capacity of "task impossible" must result "impossible" or "immediate falling" for other standing items. Contradictory ratings for walking status were not seen and only 2/215 (0.93%) of assessments were associated with a false rating for standing capacities. Our three investigators were highly experienced and this may explain the low false rating rate for our data compared to previous series in which up to a third of assessments had contradictory scores.[113] While redundancy in ICARS can result in contradictory and false scoring, we conclude that such problems can

be partially overcome by training and experience.

ICARS subscales did not satisfy required psychometric criteria demonstrating similar problems to previous published series.[16,113] In particular, oculomotor scores demonstrated poor internal consistency together with poor test-retest and inter-rata reliability suggesting that significant random error was associated with scoring this subscale. Similar problems with inter-rata reliability were seen with dysarthria scoring suggesting that, unlike posture/gait and kinetic scores, assessment of items within oculomotor and dysarthria subscales were subject to much inter-observer variation. These data question the reliability, use and reporting of these subscales. However, factorial analysis demonstrated ICARS to be determined by five different latent factors that corresponded to ICARS subscales, with kinetic subscale divided into upper and lower limb functions. Our factorial analysis results are similar to previous work in multiple system atrophy[140] but are at odds with analysis in patients with proven inherited spinocerebellar ataxia in which four latent traits were identified that did not coincide with ICARS scoring.[113] Such differences highlight the clinical heterogeneity in ataxic disorders with patients who commonly demonstrate variable degrees of cerebellar and extra-cerebellar dysfunction including pyramidal, sensory, and extra-pyramidal abnormalities.

Documenting natural history, identifying prognostic factors and determining the effects of therapeutic interventions require a scale to accurately and reliably measure the severity of ataxia and its components. Total ICARS score is a reliable and valid measure of severity in chronic progressive cerebellar ataxia but our data suggests a need for a new ataxia rating scale with more reliable items quantifying oculomotor and speech disorder in particular, although both speech and oculomotor function are likely to be intrinsically more difficult to quantify reliably. In addition, reducing item dependency within ICARS would result in a shorter, more practical scale with potentially fewer contradictory and false results. A new ataxia rating scale has been developed (scale for the assessment and rating of ataxia — SARA) which is shorter, more practical and avoids obvious item redundancy.[112,164] However, further work is necessary to validate this scale in a wide range of ataxic disorders.
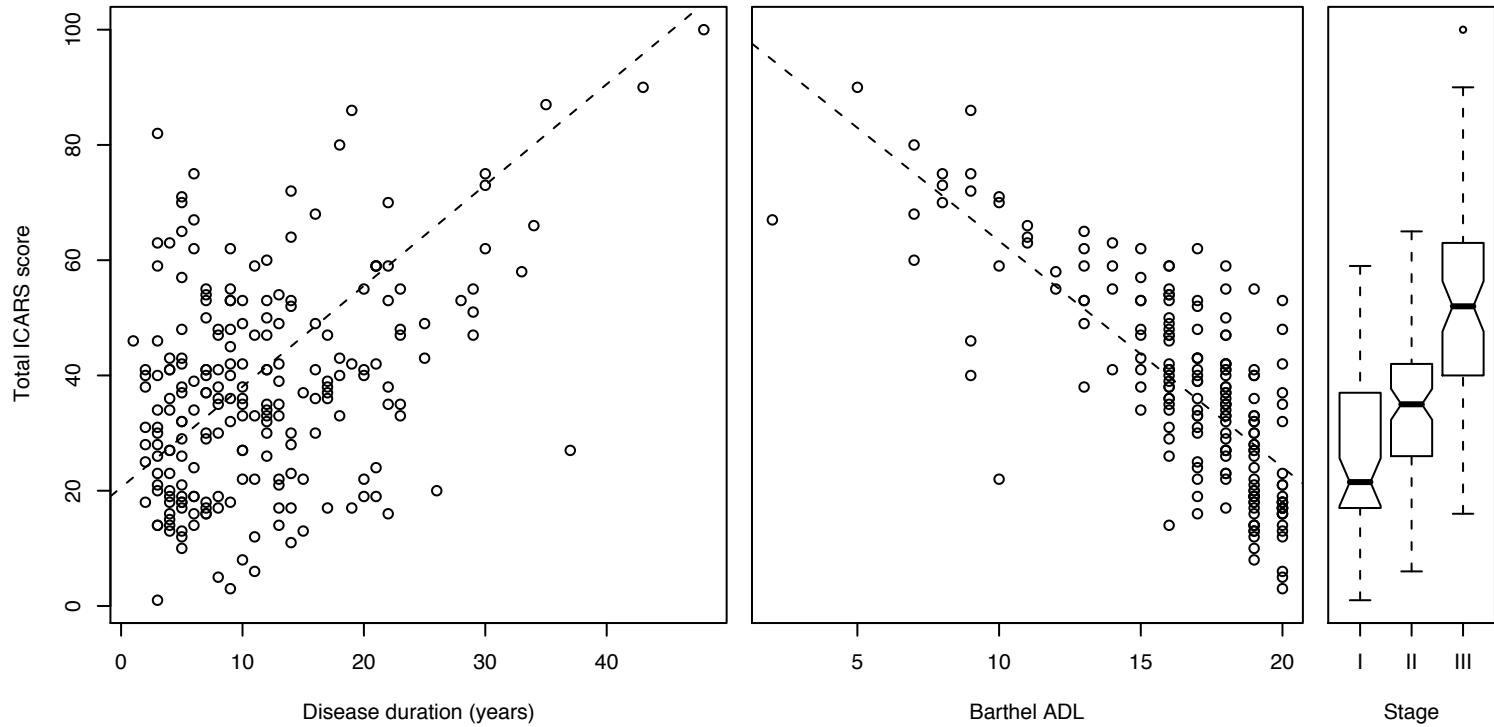
Figure 8.1: Relationship between ICARS score, disease duration, Barthel ADL and ambulatory support. (I:disease onset, II: support required, III: wheelchair).

Factor	Eigenvalues	Prop	Cumu	Par.Analysis	Pred.eig	OC	Acc.factor	AF
1	11.037	0.44149	0.44	1.60	2.659			(< AF)
2	2.548	0.10194	0.54	1.51	2.034		$7.9e+00$	
3	1.946	0.07784	0.62	1.44	1.580		$1.7e-01$	
4	1.509	0.06036	0.68	1.36	1.433		$2.9e-01$	
5	1.366	0.05463	0.74	1.30	1.079	(< OC)	$-2.0e-01$	
6	1.025	0.04101	0.78	1.25	0.766		$4.2e-02$	
7	0.727	0.02906	0.81	1.20	0.733		$2.7e-01$	
8	0.693	0.02772	0.83	1.15	0.661		$-3.7e-02$	
9	0.623	0.02491	0.86	1.11	0.581		$-6.6e-03$	
10	0.546	0.02184	0.88	1.06	0.502		$-2.8e-05$	
11	0.469	0.01876	0.90	1.01	0.471		$4.6e-02$	
12	0.438	0.01752	0.92	0.97	0.436		$-4.2e-03$	
13	0.403	0.01612	0.93	0.91	0.367		$-3.0e-02$	
14	0.338	0.01350	0.95	0.89	0.295		$-3.0e-03$	
15	0.269	0.01076	0.96	0.85	0.234		$1.1e-02$	
16	0.212	0.00847	0.97	0.81	0.208		$3.2e-02$	
17	0.186	0.00744	0.97	0.77	0.183		$9.2e-04$	
18	0.161	0.00645	0.98	0.73	0.145		$-1.1e-02$	
19	0.126	0.00503	0.98	0.69	0.121		$1.3e-02$	
20	0.103	0.00412	0.99	0.65	0.117		$1.6e-02$	
21	0.096	0.00384	0.99	0.62	0.092		$-1.7e-02$	
22	0.072	0.00289	1.00	0.57	0.074		$5.1e-03$	
23	0.053	0.00214	1.00	0.53	0.071		$6.6e-03$	
24	0.041	0.00166	1.00	0.49			$-1.7e-02$	
25	0.012	0.00048	1.00	0.42				

Table 8.5: Factorial analysis of the ICARS dataset: eigenvalues and related parameters of sequential factors. Prop: proportion of variance accounted, Cumu: cumulative proportion. Par.analysis: parallel analysis. Pred.eig: Predicted eigenvalue. OC: Optimal coordinates. AF: Acceleration factor.
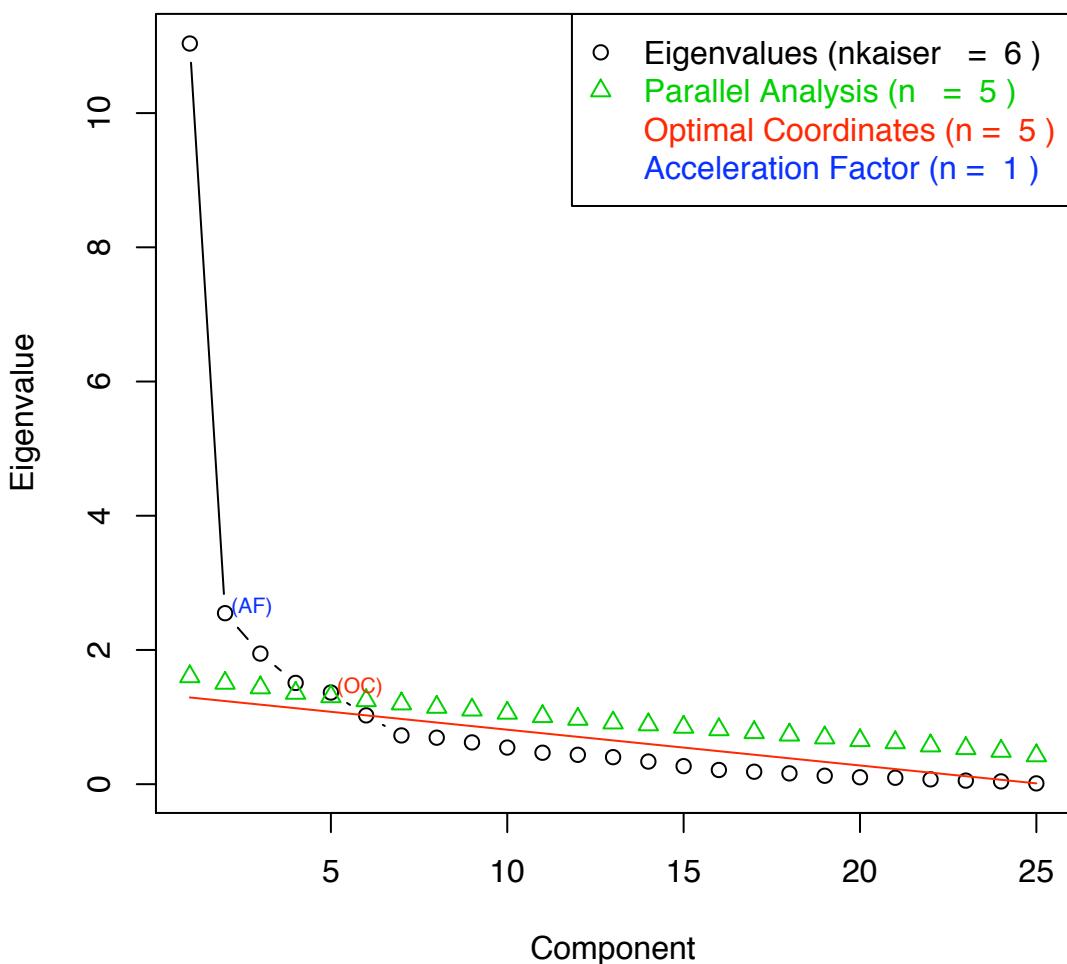
Figure 8.2: Scree plot demonstrating factorial analysis of ICARS dataset.

Item	PA1	PA2	PA3	PA4	PA5
Posture and gait					
Walking	**0.74**	0.31	0.26	-0.30	0.13
Gait	**0.60**	0.19	0.28	-0.25	0.09
Standing	**0.81**	0.22	0.22	-0.24	0.15
Feet spread	**0.68**	0.26	0.15	-0.15	0.09
Body sway eyes open	**0.79**	-0.09	0.35	-0.23	0.11
Body sway eyes closed	**0.73**	-0.15	0.27	-0.26	0.14
Sitting quality	**0.41**	-0.00	0.39	-0.34	0.10
Kinetic					
Knee shin dysmetria right	0.30	0.02	0.29	**-0.84**	0.09
Knee shin dysmetria left	0.26	0.05	0.32	**-0.84**	0.07
Knee shin tremor left	0.27	0.06	0.26	**-0.84**	0.09
Knee shin tremor right	0.29	0.03	0.23	**-0.86**	0.11
Finger nose dysmetria right	0.20	0.15	**0.80**	-0.21	0.27
Finger nose dysmetria left	0.20	0.17	**0.80**	-0.22	0.24
Finger nose tremor right	0.21	0.00	**0.82**	-0.15	0.10
Finger nose tremor left	0.21	-0.01	**0.81**	-0.12	0.09
Finger finger right	0.26	0.04	**0.62**	-0.33	0.01
Finger finger left	0.33	0.11	**0.52**	-0.26	0.05
Dysdiadochokinesis right	0.16	**0.46**	**0.51**	-0.29	-0.00
Dysdiadochokinesis left	0.18	**0.44**	**0.53**	-0.23	-0.10
Archimedes	0.27	0.22	**0.48**	-0.22	0.15
Dysarthria					
Speech fluency	0.14	**0.80**	0.12	0.01	0.27
Speech clarity	0.10	**0.81**	0.05	0.03	0.36
Oculomotor					
Nystagmus	0.22	0.12	0.16	-0.07	**0.45**
Pursuit	0.12	0.20	0.08	-0.00	**0.80**
Saccade	0.04	0.11	0.09	-0.13	**0.64**

Table 8.6: Factorial analysis of the ICARS dataset: each item is listed together with loadings associated with each calculated factor.

Table 8.7: Cluster analysis using ICLUST (VSS) algorithm.

| Cluster	C12	C21	C22
C12			
Knee shin tremor right	0.93	0.63	0.21
Knee shin dysmetria right	0.92	0.66	0.21
Knee shin dysmetria left	0.92	0.66	0.21
Knee shin tremor left	0.92	0.63	0.21
C21			
Finger nose dysmetria right	0.50	0.77	0.41
Finger nose dysmetria left	0.52	0.77	0.41
Walking	0.59	0.76	0.43
Body sway eyes open	0.54	0.75	0.22
Standing	0.54	0.74	0.41
Finger nose tremor right	0.45	0.71	0.23
Finger nose tremor left	0.42	0.69	0.21
Finger finger right	0.54	0.68	0.17
Gait	0.50	0.66	0.32
Body sway eyes closed	0.53	0.66	0.19
Finger finger left	0.49	0.66	0.25
Sitting quality	0.54	0.63	0.21
Archimedes	0.43	0.63	0.35
Dysdiadochokinesis right	0.46	0.62	0.37
Dysdiadochokinesis left	0.40	0.61	0.29
Feet spread	0.39	0.59	0.35
C22			
Speech clarity	0.09	0.29	0.65
Pursuit	0.14	0.28	0.64
Speech fluency	0.14	0.35	0.59
Saccade	0.21	0.24	0.50
Nystagmus	0.21	0.35	0.44

172
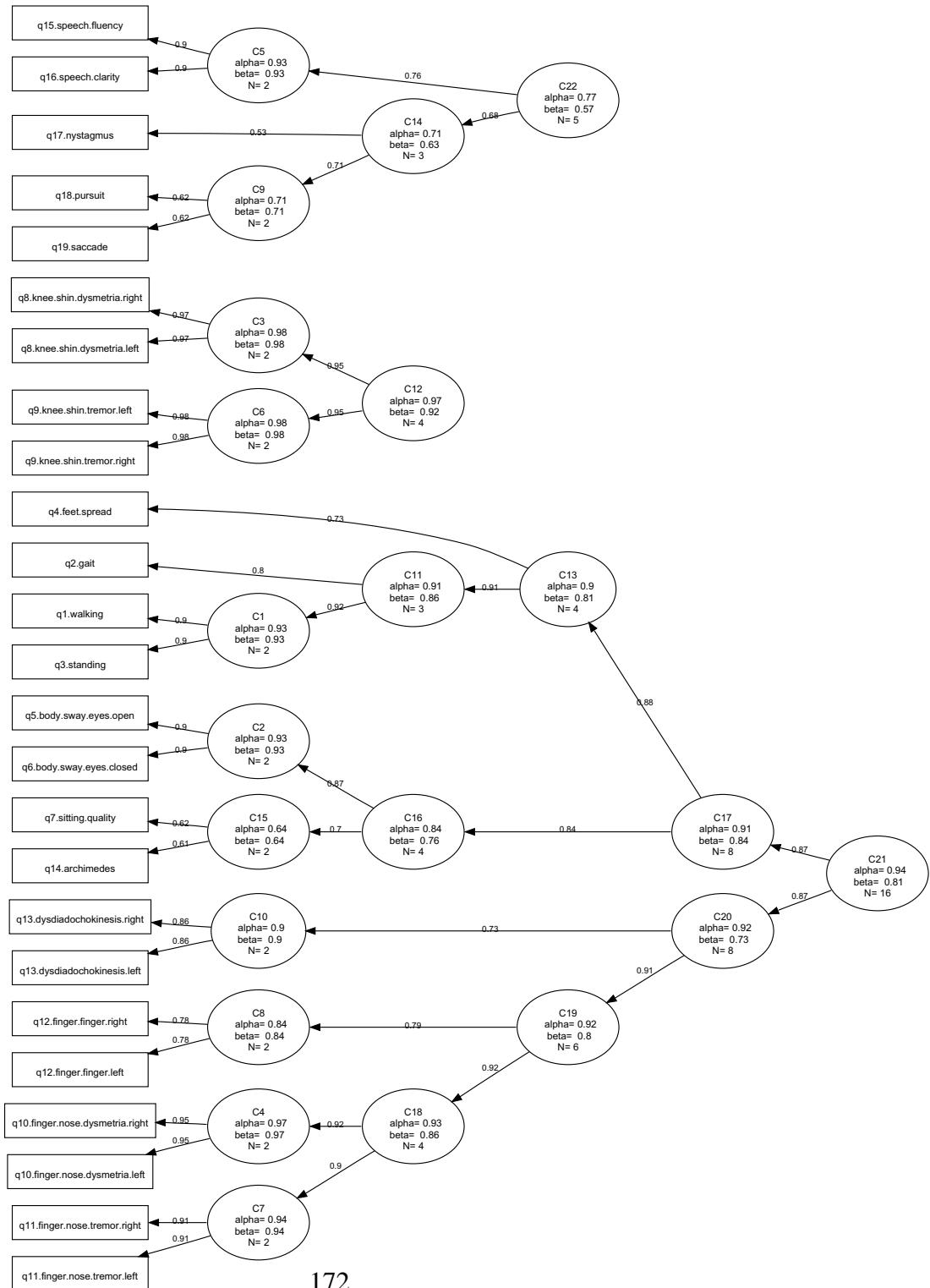
ICLUST

Figure 8.3: Cluster analysis of the ICARS items.

Chronic progressive cerebellar ataxia: A diagnostic strategy

9.1 Introduction

For many patients, especially those with an acute or sub-acute presentation of ataxia, initial investigations will readily identify an acquired cause (Table 9.1) such as chronic alcoholism, MS, remote malignancy (paraneoplastic cerebellar degeneration), vitamin deficiency, toxins or hypothyroidism.[1] Adult patients with a more progressive disease course of more than one year, particularly if associated with few discriminatory signs on neuroimaging, commonly present the most challenging clinical scenario. They require careful initial and subsequent clinical assessment of frequently complex clinical features which may change over time. This necessitates a practical diagnostic and management strategy, focusing on the early identification of potentially reversible causes and demands a logical approach to more specialised investigations (Table 9.2).

The most important discriminating factors in the history and examination of this group of patients with late onset cerebellar ataxia (LOCA) are family history, age of onset, rate and pattern of development of symptoms, a comprehensive drug and alcohol history, past medical history and the presence of other associated symptoms and signs.

9.1.1 Is there a family history?

A dominant family history is the single most important factor predicting the chance of successfully diagnosing a genetic cause of cerebellar ataxia. Analysis of the common spinocerebellar mutations results in a positive identification in 39–64% of dominant and 11-38% of non-dominant families, but only 1–19% of sporadic late-onset cases.[62,77,103,120,137]

The inherited ataxias are a broad heterogeneous group, and can manifest in childhood, adolescence or adulthood with widely variable clinical features, even within the same family. They may be inherited in an autosomal recessive, autosomal dominant (ADCA), X-linked or mitochondrial inheritance pattern, but prevalence estimates are limited and sensitive to founder effects resulting in variable frequencies of the different subtypes both geographically and ethnically. SCA1, SCA2 and SCA3 are the commonest cause of ADCA in Caucasian families, but

SCA3, SCA6 and DRPLA are more common in Asian populations (Chapter 3).

Which genetic tests?

NHS laboratories across the UK commonly perform SCA1, SCA2, SCA3, SCA6 and usually SCA7 in response to a generic "SCA screen" request. Other investigations such as SCA12, SCA17, DRPLA, and Friedreich's are available but usually must be specifically requested. Research laboratories may offer additional tests (Table 1.1) if the clinical circumstances are appropriate. The choice of diagnostic tests should be guided by local knowledge of the common ataxia families, an insight into the prevalence of common SCA subtypes (Chapters 1.2.2 and 3) within the ethnic group, and the presence of suggestive extracerebellar features (Table 9.3). However, phenotypic variability and overlap make clinical diagnosis difficult, and in most cases, screening for a range of diseases is necessary.

If there is a strong dominant family history, it is appropriate to screen for SCA1, SCA2, SCA3, SCA6 and SCA7 as part of first-line investigations. An important clue to the presence of a dominantly inherited trinucleotide repeat (TNR) disorder is anticipation, resulting in increasing severity and earlier age of onset through generations. However, even in sporadic cases, a routine screen is recommended since the presence of a dominant family history may be hidden by reduced penetrance (e.g., SCA17), marked anticipation (most notable in SCA7) or false paternity.

In sporadic cases, or if there is a history of consanguinity or affected siblings, testing for Friedreich's ataxia (FA) is essential. FA is the most common recessive cause of spinocerebellar ataxia, and traditionally this clinical diagnosis was limited to patients with an onset below the age of 25 with progressive ataxia, absent lower-limb reflexes and skeletal abnormalities, often associated with additional non-neurological symptoms such as cardiomyopathy and diabetes mellitus. Since the identification of the expanded intronic TNR (GAA) in the X25 gene (94% of patients),[15] it is now known that the clinical spectrum is broader than that defined by classical criteria, and includes patients with disease onset over the age of 25 with retained tendon reflexes. The remaining 6% of patients are compound heterozygotes with an expanded repeat on one allele, and a point mutation on the

other. FA is thought to be due to mitochondrial dysfunction; the gene encodes frataxin, a mitochondrial protein. Even in those patients without the characteristic phenotype, up to 5.2% of patients with sporadic ataxia may have FA and in those below the age of 40 this rises to 21%.[83,120] Other recessive disorders are listed in Table 9.4.

SCA1 is highly variable but a pancerebellar syndrome is usually described, with prominent ataxia of gait, limb, speech and eye movements. SCA2 is associated with marked ocular saccadic slowing. SCA3 is the most common subtype and has a widely variable phenotype. SCA6 is commonly described as a late-onset pure ataxic syndrome. Pigmentary maculopathy and retinopathy is associated with SCA7, but this may be preceded by ataxia by up to 20 years. There is much controversy regarding SCA8 and testing is not offered routinely since there is low penetrance and expanded repeats are also found in unaffected controls.

A history of psychiatric illness, chorea or dementia should prompt testing for dentatorubral pallidoluysian atrophy (DRPLA), SCA17 and Huntington's disease (HD). DRPLA is a rare autosomal dominant, clinically heterogeneous neurodegenerative disorder, most commonly reported in Japan and rare in Caucasian populations. However, a pure gait ataxia can precede the other manifestations by up to ten years making diagnosis challenging in the early stages of disease.[168]

Discrete episodes of ataxia are associated with the dominantly inherited episodic ataxias, caused by mutations in genes encoding voltage-dependent potassium (e.g., EA1) and calcium (e.g., EA2) channels. Episodes may last minutes in EA1 and hours to days in EA2. Interictal myokymia may be evident clinically and electromyographically in EA1, and some cases of EA2 can have a more progressive course similar to SCA6, to which it is allelic. Genetic testing is not widely available, and since EA2 may be responsive to acetazolamide, a therapeutic trial is warranted if the diagnosis is suspected clinically.

Fragile-X tremor/ataxia syndrome (FXTAS) was first described in 2001 in five elderly men carrying premutation range (55-200) triplet repeats in the FMR1 gene and characterised by a progressive action tremor associated with executive frontal deficits and generalised brain atrophy.[46] Initially thought to affect only men, it has subsequently been described in women albeit in a less severe form.[45] FMR1 premutation may account for 3.6–4.2%[12,147] of cases of sporadic ataxia in male

patients older than 50 years. FXTAS should be considered in elderly men, especially in families with grandchildren with Fragile-X or reported learning difficulties.

9.1.2 Age of onset and disease progression

In young adults (<40 years), there are a wide range of important, potentially reversible or treatable diagnostic possibilities that should not be missed (Table 9.4). Fortunately, these diagnoses are normally suspected because of the presence of characteristic extracerebellar features. While an early onset is normally associated with autosomal recessive disorders, it does not preclude the presence of a dominantly inherited disorder and they should be considered in both sporadic and familial cases.

The term "idiopathic" late-onset cerebellar ataxia[48] is a diagnosis of exclusion. However, there is considerable overlap with other neurodegenerative disorders and within five years 29–33% of cases will meet diagnostic criteria for possible or probable multiple system atrophy (MSA).[1,35] The main features of MSA comprise autonomic failure, parkinsonism, cerebellar ataxia and pyramidal signs in any combination, with two major subtypes distinguished: MSA-P (80%) and MSA-C (20%) with parkinsonian or cerebellar features dominating respectively,[160] but ultimate confirmation of diagnosis is pathological. Patients with MSA have a poor prognosis and accumulate greater disability, remaining ambulant for a median of six years, and surviving only 7–9 years. This contrasts to those with a pure cerebellar syndrome whose median survival is over 20 years.[35,64,158] In patients over the age of 50, a rapidly progressive disease course should prompt re-evaluation for MSA.

9.1.3 Is imaging helpful?

Magnetic resonance imaging is essential in the diagnostic work-up of patients presenting with late-onset cerebellar ataxia. The most important benefit is the exclusion of an acquired cause, but it can also provide clues to other causes of sporadic and familial ataxia. There are three clear patterns of radiological abnormality:

(a) spinal atrophy, (b) cortical cerebellar atrophy (CCA) and (c) olivopontocerebellar atrophy (OPCA) .

FA is characteristically associated with cervical spinal cord atrophy. CCA is found in the pure cerebellar syndromes whereas OPCA is found in those with prominent extracerebellar features. There is considerable overlap between all the SCAs and imaging cannot be used for diagnostic purposes alone.

In MSA, cranial MR imaging may show non-specific OPCA, as well as putamen, caudate and basal ganglia atrophy. Signal hyperintensities in the pons and middle cerebellar peduncles may be seen on T2-weighted images to give rise to "the hot cross bun sign" but such changes are also found in some patients with proven SCA.[14] The presence of widespread brainstem, caudate and putamen atrophy in patients presenting with cerebellar ataxia should raise the suspicion of MSA and predict a guarded prognosis.

9.1.4 What about immunological ataxia?

In subacute disease, up to 5% of cases may be associated with anti-neuronal antibodies (Table 9.5) and their presence should initiate a search for an occult neoplasm.[143] Paraneoplastic cerebellar degeneration may present months or even years before the appearance of the underlying tumour, but its significance in chronic disease is unclear.

There remains considerable controversy regarding the presence and significance of auto-antibodies in chronic progressive cerebellar ataxia. Antibodies to glutamic acid decarboxylase (GAD) are well described in patients with type I diabetes mellitus and Stiff-person syndrome, but it has been suggested that anti-GAD antibodies may play a pathogenic role in cerebellar ataxia[54] and even be responsive to immunosuppressive therapy.[71] Controversially, anti-gliaden antibodies have been implicated in the pathogenesis of some sporadic cases of cerebellar ataxia in patients without gluten enteropathy.[43] The presence of such antibodies may reflect a high prevalence of auto-immunity within this population but more research is needed before any definitive conclusions can be made regarding the pathogenic role of these antibodies in sporadic ataxia.

9.2   Management

Early and accurate diagnosis is invaluable in guiding treatment, and providing patient counselling and support. However, in up to 80% of cases, even after extensive investigation, no definitive diagnosis is made. The diagnostic label "idiopathic cerebellar ataxia" is unsatisfactory for both clinician and patient and in this group, longitudinal follow-up is essential to monitor progress and identify new symptoms and signs that may point to a previously neglected diagnosis. In symptomatic ataxia, management must be guided by the underlying cause, but all patients and their families need ongoing support. Local and national patient support organisations such as Ataxia UK (`http://www.ataxia.org.uk/`) can provide patient information leaflets, telephone advice lines and facilitate the creation of local patient groups.

Patients will also benefit from multidisciplinary care. In patients with FA, orthopaedic input may be required for skeletal deformities and early referral to a cardiologist is essential for management of cardiomyopathy. In all forms of spinocerebellar ataxia, patients may benefit from physiotherapy to reduce spasticity, improve mobility and to provide walking aids. Speech and language assessment is essential for those with communication and/or swallowing difficulties. Urinary difficulties commonly occur as a result of spasticity or autonomic failure, and have a considerable impact on quality of life for both the patient and their carer. Desmopressin spray may help nocturnal polyuria, anticholinergics such as oxybutynin may reduce detrusor instability and urgency, and intermittent or permanent urinary catheterisation may be required if there is incomplete bladder emptying.

In up to a third of patients with possible or probable MSA, symptoms of bradykinesia may respond to levodopa but its effect may decline within years, and use may be limited by autonomic and dyskinetic side-effects.[162] Autonomic failure is frequently difficult to manage, but if disabling patients should avoid aggravating factors such as large meals, straining at toilet, alcohol and drugs, and are sometimes helped by the use of elastic stockings, head-up tilt of the bed at night, increased salt intake and fludrocortisone.

The diagnosis of an inherited condition requires careful counselling for both

patient and family, and referral to clinical genetics is usually appropriate. At present, there are no disease modifying therapies available for the inherited ataxias.

9.3 Conclusions

Adult-onset progressive cerebellar ataxia frequently poses diagnostic difficulties and while a proven genetic aetiology may be identified in half of all dominant families, the identification of a defined molecular diagnosis will occur in only 1 in 10 sporadic cases. Genetic investigation of sporadic disease should include SCA1, SCA2, SCA3, SCA6, SCA7 and Friedreich's ataxia with the application of additional genetic tests in familial disease guided by local knowledge of ataxia families and the presence of extracerebellar features. Patients should be followed up for diagnostic, treatment and supportive purposes, ideally in a specialist ataxia clinic.

Acute (hours to days)
    Intoxication (alcohol, lithium, barbiturates)
    Acute viral cerebellitis
    Post-infection syndrome
    Vascular (e.g., cerebellar infarction, haemorrhage)
    Infectious (e.g., cerebellar abscess, Whipple's)

Chronic (months to years)
    Intoxication (phenytoin toxicity)
    Paraneoplastic cerebellar syndrome
    "Gluten ataxia"
    Vitamin E deficiency (inherited or acquired)
    Hypothyroidism
    Tabes dorsalis
    Creutzfeld-Jacob disease
    Rubella panencephalitis
    Previous vascular lesion or demyelination
    Congenital lesion
    Inherited ataxias
    "Idiopathic" degenerative ataxias

Subacute (days to weeks)
    Intoxication (mercury, solvents, petrol, glue, cytotoxic agents)
    Alcoholic cerebellar degeneration
    Nutritional / malabsorption (Vitamin B_1, vitamin B_{12})
    Posterior fossa tumour (e.g., cerebellar glioma, metastases)
    Multiple sclerosis
    Hydrocephalus
    Foramen magnum compression
    AIDS-related multi-focal leukoencephalopathy
    Miller-Fisher syndrome
    Lyme disease

Episodic ataxia
    Intoxication
    Multiple sclerosis
    Transient ischaemic attacks
    Foramen magnum compression
    Intermittent hydrocephalus (e.g., cysticercosis, colloid cyst)
    Dominant episodic ataxia (e.g., EA1,EA2 etc.)
    Inherited metabolic ataxias

Table 9.1: Aetiology of cerebellar ataxia. Adapted from [165].

First-line investigations
    Magnetic resonance (MR) imaging of brain
    Chest radiography
    Electrocardiogram
    Vitamin B_1, B_{12}
    Thyroid function tests
    Serum VDRL
Second-line investigations
    Lumbar puncture (inc. oligoclonal bands, VDRL)
    Genetic investigations — see Table 9.3
    Anti-neuronal antibodies — see Table 9.5
    Nerve conduction studies and electromyography
Investigations with specific indications
    Serum copper, caeruloplasmin, 24 hour urinary copper
    Blood film acanthocytes
    Serum lipids, immunoglobulins
    Vitamin E levels
    Phytanic acid levels
    Very long chain fatty acids
    Serum gonadotrophins
    Serum hexosaminidase A
    α-fetoprotein
    Serum/CSF lactate
    Muscle biopsy
    Organic acids, ammonia, pyruvate
    Anti-gliaden antibodies

Table 9.2: Diagnostic strategy in late-onset cerebellar ataxia.

Indication	Possible diagnoses
Recommended routine screen	SCA1, SCA2, SCA3, SCA6, SCA7, FRDA
Pure ataxia	SCA6†
Slow ocular saccades	SCA1, SCA2†, SCA3, SCA7,
Ophthalmoplegia	SCA1, SCA2, SCA3
Pigmentary maculopathy / retinopathy	SCA7†, abetalipoproteinaemia
Cognitive impairment	DRPLA†, SCA17†, HD
Chorea	DRPLA†, SCA17, HD
FA phenotype	FRDA†, vitamin E deficiency, abetalipoproteinaemia, AT
Cataract	Mitchondrial, cerebrotendinous xanthomatosis
Oculomotor apraxia	AT, ataxia with oculomotor apraxia type 1+2
Epilepsy	DRPLA†, SCA10, SCA17, HD, Wilson's disease, mitochondrial, prion disease
Myokymia	SCA3, EA1
Myoclonus	DRPLA, SCA2, SCA3
Peripheral neuropathy	SCA1, SCA2, SCA3, SCA4†, SCA6, SCA12, SCA18†, SCA22, SCA25†
Pyramidal signs	SCA1, SCA2, SCA3†, SCA7, SCA12
Extrapyramidal signs	SCA1, SCA2, SCA3, SCA12, SCA17, SCA21
Dystonia	SCA3, SCA17

Table 9.3: Genetic investigation of adult-onset cerebellar ataxia. †Feature highly suggestive of diagnosis.

Disorder	Gene locus	Diagnostic features
Autosomal recessive disorders		
Friedreich's ataxia	X25-FRDA1 9q13-q21	Hyporeflexia Pyramidal signs Cardiomyopathy
Ataxia telangiectasia	11q22.3	Elevated α-fetoprotein Reduced serum immunoglobulins Telangiectasia, dystonia Predisposition to malignancy
Wilson's disease	13q14.3-q21.1	Reduced caeruloplasmin Elevated 24hr urine copper Kayser-Fleischer ring Hepatosplenomegaly Abnormal basal ganglia on MR
Abetalipoproteinaemia (Acanthocytosis)	4q22-q24	Blood film for acanthocytes Serum cholesterol very low Serum beta lipoprotein absent. Pigmentary degeneration of the retina
Inherited vitamin E deficiency	8q13.1-q13.3	Reduced vitamin E levels
Refsum's disease (HMSN IV)	10pter-p11.2, 6q22-q24	Elevated phytanic acid levels Retinitis pigmentosa Polyneuropathy, sensorineural deafness Ichthyosis
Adrenoleukodystrophy / Adrenomyeloneuropathy	Xq28	Very long chain fatty acids Men (X-linked) Abnormal MRI brain
GM2 gangliosidoses	(multiple)	Reduced serum hexosaminidase A Supranuclear gaze palsy Dystonia
Cerebrotendinous xanthomatosis (Cholestanolysis)	2q33-qter	Elevated serum cholestanol Tendon xanthomata Dementia, cataract Peripheral neuropathy
Hypogonadotrophic hypogonadism (Holmes syndrome)		Secondary sexual characteristics Loss of libido / infertility
Mitochondrial and metabolic disorders		Elevated serum / CSF lactate Elevated serum ammonia, pyruvate Muscle biopsy, organic acids Additional neurological sequelae (e.g., stroke, myoclonic epilepsy)

Table 9.4: Additional diagnostic possibilities in young adults.

Antibody	Antigen	Typical tumour associated
Anti-Yo	cdr62,32 (purkinje cytoplasmic)	Gynaecological
		Breast
Anti-Hu	HuD (neuronal nuclear)	Small cell lung cancer (75-80%)
		Neuroblastoma
Anti-Ri	Nova1,2 (neuronal nuclear)	Breast
		Small cell lung cancer
Anti-Tr	(purkinje cytoplasmic)	Hodgkin's Lymphoma
Anti-VGCC	VGCC	Small cell lung cancer (>80%)
Anti-GAD	GAD	None
Anti-Ma1	Ma1,2,3 (neuronal nucleolar)	Various
Anti-Ma2	Ma2 (neuronal nucleolar)	Testis

Table 9.5: Antibodies to neuronal antigens in cerebellar syndromes. Adapted from [143, 134]. (VGCC–voltage-gated calcium channel antibodies)
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CHAPTER 10

Conclusions

10.1   Genetic causes of ataxia

The population-based epidemiological survey of late-onset cerebellar ataxia (LOCA) in South East Wales provides a contemporary minimum prevalence of 11.33 per 100,000 (95% CI 9.55–13.34) and has identified SCA6, dentatorubral pallidoluysian atrophy (DRPLA) and Friedreich's ataxia (FA) to be important genetic causes of ataxia within this region. There have been few similar population-based studies of genetic ataxia since most authors have examined clinic-based cohorts or have performed retrospective analysis of patients referred for laboratory testing and as such, inherently over-represent familial cases. Within sporadic patients, our data are broadly similar to previous UK reports with most cases being unexplained and SCA6 and FA identified as the most important pathogenic mutations.[72] Such data provides support for a rational diagnostic approach to patients presenting with LOCA (Chapter 9).

While the ethnic and geographic variability in SCA expansions remains unexplained, it has previously been suggested that new expansion may occur from high-normal alleles and lead to an association between the prevalence of high-normal alleles and disease prevalence.[137] Our data demonstrate a significant difference between Welsh and Japanese control chromosomes at all loci (Table 3.4) and in a pattern that mirrors the relative importance of different expansions when Asian and Caucasian series are compared. However, we have not demonstrated a significant or systematic relationship between high-normal repeat prevalence and disease prevalence between different Caucasian series, suggesting other factors, such as founder effects and ascertainment bias are more important.

There has been little previous investigation to determine genetic susceptibility factors in sporadic ataxia. Our work demonstrates that high-normal repeats are not a risk factor for the development of sporadic ataxia but that more study is required into environmental and genetic influences in sporadic and familial ataxia.

10.2   DRPLA

DRPLA is considered rare in Caucasian series. We have shown that DRPLA is a important cause of LOCA in South Wales, and although three of the four families

may have a common founder, at least one family did not share the same haplotype suggesting the expansion was not inherited from the same common ancestor. Our work demonstrates the broad clinical heterogeneity of DRPLA and suggest that it should be considered in the differential diagnosis of a wide spectrum of neurological disease especially if there is an autosomal dominant family history of dementia or movement disorders. In addition, previous work has neglected to document the marked psychiatric manifestations apparent from our families.

Further work is necessary to more completely define clinical phenotype in Caucasian series. While Chapter 6 is a systematic attempt to review all published cases, there are several inherent flaws in reporting such data. Most series have widely variable methodological approaches and without standardisation, differences between series may simply reflect such methodological differences rather than true phenotypic heterogeneity. We have obtained ethics approval to ascertain cases of DRPLA from across the United Kingdom (UK) and suggest a detailed and systematic national review of patients with DRPLA will provide a definitive account of the clinico-genetic characteristics of DRPLA in the UK. In particular, there are very little data reporting the psychiatric, radiological and epileptic phenotypes in DRPLA. We have received a small number of anecdotal notifications from UK neurologists already, including another family from South Wales (Dr. Khalid Hamandi, personal communication). In addition, it would be useful to perform a systematic review of patients with a Huntington's disease (HD)-like phenotype negative for HD on molecular testing and evaluate the significance of DRPLA within that population.

10.3 Clinical characteristics and natural history of LOCA

Data from the population-based sample of patients documents the considerable burden that LOCA imposes on patients, families and carers as well as local health and social services. In addition, patients commonly demonstrate significant disease progression with time, becoming decreasingly ambulant, increasingly dependent and suffer an increasing burden of morbidity and mortality. Furthermore

we have shown sporadic LOCA is clinically heterogeneous, with evidence of a subset of patients with defined extra-cerebellar symptoms and signs who, despite having a shorter disease duration, are less ambulant, more disabled and have a significantly worse prognosis. There is need for further detailed longitudinal study of patients LOCA with regular follow-up, systematic clinical evaluations and subsequent post-mortem confirmation of pathological diagnosis. Determination of mortality rates and causes of death in LOCA would be helpful in providing counselling and support for patients and their carers. It is possible to register patients with the "NHS General Register Office" who monitor death notifications and provide researchers access to death certification information and therefore obtain prospective notifications of deaths within a specified cohort. Our work with the use of NHS-identifiers and core NHS demographic databases (including the NHS Strategic Tracing Service and the NHS Administrative Register, see Chapter 2.3.4) highlights the potential use of such data in longitudinal follow-up of patients, reducing losses in follow-up when patients move house or general practitioner (GP).

We found an overall significant excess of patients with a reported history of auto-immune disease compared to previously published reports for the UK population and compared to familial cases. We have advised caution in the interpretation of these data (Section 7.4) but such data provide exciting and compelling clues to possible pathology in sporadic ataxia. An identified excess of auto-immunity in patients with sporadic ataxia may suggest a hitherto unrecognised auto-immune process in a proportion of patients. There remains controversy surrounding the positive identification and significance of a range of antibodies in patients with ataxia (for example anti-gliaden antibodies, anti-GAD antibodies)[43,54] and while our data suggests some patients with sporadic ataxia may have an immune-mediated cause, it is conceivable that the identification of an excess of a range of auto-antibodies is to be expected. Further work will be necessary to determine whether there is an excess frequency of positive auto-antibodies in sporadic cerebellar ataxia, and to establish whether they are directly pathogenic or merely a marker of increased auto-immunity generally.

10.4   Measurement of ataxia severity

Our work on International Cooperative Ataxia Rating Scale (ICARS) suggests that total ICARS score satisfied fundamental psychometric criteria with adequate scaling assumptions, targeting and reliability. However, more detailed analysis highlights important deficiencies ICARS subscales, with particular problems with the reliability of assessments of speech and ocular ataxia. Although both these functions are likely to be intrinsically more difficult to quantify reliably, our data suggests a need for a new ataxia rating scale. In addition, reducing item dependency within ICARS would result in a shorter, more practical scale with potentially fewer contradictory and false results. A new ataxia rating scale has been developed (scale for the assessment and rating of ataxia — SARA) which is shorter, more practical and avoids obvious item redundancy.[112,164] However, further work is necessary to validate this scale in a wide range of ataxic disorders.

10.5   The Ataxia Register and future opportunities

Many patients recruited during the study of LOCA in South Wales had been lost to ongoing neurological secondary or tertiary care (unpublished data). Our research highlights a need for a focused and rational diagnostic evaluation together with ongoing longitudinal evaluation of patients with LOCA. Ataxia UK (`http://www.ataxia.org.uk`) is developing a "nationwide network of Accredited Ataxia Centres". Such a centre in South Wales would provide "integrated services" for patients with cerebellar ataxia and "links to research programmes". Together with a central ataxia register, such a centralised resource would integrate demographic, clinical, radiological, serum and genetic data and provide a detailed, and systematic resource for future local and collaborative projects.

Papers and presentations

A.1 Papers

A.1.1 Progressive late-onset cerebellar ataxia

Wardle M, Robertson NP (2007) "Progressive late-onset cerebellar ataxia" ACNR 7;6-12. Commissioned review article[154] (see `http://www.acnr.co.uk/may_june/ACNR_MJ07_progressive.pdf`)

A.1.2 Dentatorubral pallidoluysian atrophy in South Wales

Wardle M, Majounie E, Williams NM, Rosser AE, Morris HR, Robertson NP (2007) "Dentatorubral pallidoluysian atrophy in South Wales" J Neurol Neurosurg Psych (Published Online First: 26 October 2007. `doi:10.1136/jnnp.2007.128074`).[152]

A.1.3 The genetic aetiology of chronic progressive cerebellar ataxia: a population-based study

Wardle M, Majounie E, Muzaimi M, Williams NM, Morris HR, Robertson NP (2007) "The genetic background of chronic progressive cerebellar ataxia: a population-based study" J Neurol (in press).[151]

A.1.4 Case control analysis of repeat expansion size in ataxia

Majounie E, Wardle M, Muzaimi M, Cross WC, Robertson NP, Williams NM, Morris HR (2007) "Case control analysis of repeat expansion size in ataxia." Neurosci Lett 429, 28–32.[75]

A.1.5 Clinical characteristics and natural history of late-onset cerebellar ataxia

Wardle M, Muzaimi MB, Majounie E, Williams NM, Morris HR, Robertson NP (2008) "Clinical characteristics and natural history of late-onset cerebellar ataxia". J Neurol Neurosurg Psych (in submission).

A.2 Presentations and published abstracts

A.2.1 Late-onset cerebellar ataxia: natural history and prognosis

Presented at ABN, Dublin, 2008. J Neurol Neurosurg Psychiatry (in press).

A.2.2 DRPLA in South Wales

Wardle M, Majounie E, Williams NM, Morris H, Robertson NP (2007) "DR-PLA in South Wales" J Neurol Neurosurg Psychiatry 78, 1014–1038 `http://jnnp.bmj.com/cgi/content/full/78/9/1014`. Winner of the *"Sir Charles Symonds Best Platform Presentation"* at the ABN Spring Scientific Meeting Homerton College, Cambridge, UK, 11–13 April 2007[153]

A.2.3 Clinical features of idiopathic late-onset cerebellar ataxia in South Wales

Wardle M, Robertson NP. Presentation at SWENA, 2005 (prize-winning).

A.2.4 The clinical and genetic characteristics of DRPLA in Europe and North America

Wardle M, Majounie E, Williams NM, Rosser AE, Morris HR, Robertson NP. Presentation at SWENA, 2007 (prize-winning)

Investigator booklet

CARDIFF UNIVERSITY: Patient ID: <u>**Axxxx**</u>
CEREBELLAR ATAXIA IN SOUTH
WALES   Date:
FRONT SHEET

CEREBELLAR ATAXIA IN SOUTH WALES

DATE OF VISIT: <u>()</u>   **PLACE: "at home"**

<u>**Mr(s) Firstnames Lastname**</u>   **Dr GP Name**
Address1   **Surgery name (Wxxxxx)**
Address2   **Surgery address**
Address3   Postcode   **Surgery address**
Tel: Telephone   **Surgery address Surgery postcode**

          Cons:

DOB: dob   (Age at visit:)   **NHS number:**

INVESTIGATOR: **Dr. Wardle** / ~~**Dr. Muzaimi / Dr. Thomas**~~

PRE-VISIT CHECKLIST:
❑ **Patient pack**
❑ **Patient labels**
❑ **Route-planning**
❑ **Phlebotomy equipment and safe-storage unit**
❑ **Video recording equipment**
❑ **Secretary informed of visit appointment**

VISIT CHECKLIST:
❑ **Information sheet(s) given**
❑ **Consent forms completed**
❑ **Step monitor given (if appropriate)**   **START DATE/TIME:**

POST-VISIT CHECKLIST:
❑ **Step monitor retrieved (if appropriate)**   **END DATE/TIME:**
❑ **Results of investigations recorded**
❑ **Visit data entered onto computer**
❑ **Letter dictated**
❑ **Letter sent to GP**
❑ **Letter sent to consultant**
❑ **Video edited and recorded onto database**

Notes:

PT_01_FRONT-2006-01-30.doc (1/1)   Investigator: _____

CARDIFF UNIVERSITY:
CEREBELLAR ATAXIA IN
SOUTH WALES
CONSENT FORM

Patient ID: «patientID» («dob»)

Date: «dateOfVisit»

CONSENT FORM FOR PARTICIPATION IN A STUDY OF LATE-ONSET CEREBELLAR ATAXIA IN SOUTH WALES

Please read the following carefully. If you have any questions, then do not hesitate to ask. You may decide to agree to all, some or none of the following components of the research project.

1. **I agree to participate in the above study.** Y/N

2. **I have read the attached information sheet on the above project** and been given a copy to keep. I have had the opportunity to ask questions about the project and I understand why the research is being done and any forseeable risks involved. Y/N

3. **I agree to give a sample of blood for research in the above project.** I understand how the sample will be collected, that giving a sample for this research is voluntary and that I am free to withdraw my approval for the use of the sample at any time without giving a reason and without my medical treatment or my legal rights being affected. This sample will be used to study inherited material (DNA) and the chemical make-up of the body (plasma/serum). Y/N

4. **I would like to be informed of research results** that might indicate that a test for my condition could be developed which might be of use to me or my family. Y/N

5. If I have had a lumbar puncture test, as part of my routine clinical care, **I agree that surplus cerebro-spinal fluid can be used for further chemical analysis for research purposes.** Y/N

6. **I give permission for my medical records to be looked at confidentially** by members of the medical research team who would not normally be involved with my clinical care. Y/N

7. **I give permission for a videotape examination, in which I am personally identifiable, to be stored** as part of my clinical record and to be used for teaching purposes, shown to doctors and health care workers. Y/N

8. **I understand that I will not benefit financially** if this research leads to the development of new treatments or new tests. Y/N

9. **I know how to contact the research team if I need to.** Y/N

10. **I agree that the DNA, plasma, and spinal fluid samples that I have given can be looked after and stored** for use in future projects, as described in the information sheet. I understand that this research may be carried out by individuals other than the original researchers and that this may include commercial companies. Y/N

11. **I agree that my own doctor (GP and/or hospital) can be informed** of the clinical assessment that takes place as part of this study and that this can form part of my medical records. Y/N

PT_02_CONSENT_FULL-2006-03-14.doc (1/1)

CARDIFF UNIVERSITY:
CEREBELLAR ATAXIA IN
SOUTH WALES
CONSENT FORM

Patient ID: «patientID» («dob»)

Date: «dateOfVisit»

12. **I agree that my clinical details can be stored in a clinical research database** on the NHS hospital computer network and understand that a separate anonymised research database, at Cardiff University will be used to store research results. You may ask for your personal information to be removed from this database at any time, in accordance with the Data Protection Act 1998.

Y/N

13. **I agree that information** held by the NHS and records maintained by the General Register Office **may be used to keep in touch with me** and follow up my health status.

Y/N

14. **I am happy to be contacted** by telephone or letter for future research projects.

Y/N

The overall results of the study will be publicised through scientific journals and by contact with patient support groups.

Thank you for your participation in this study.

Name of patient «firstname» «lastname»   Date   «dateOfVisit»

Signature ....

Name of witness ....   Date ....   Signature ....

Name of researcher ....   Date ....   Signature ....

PT_02_CONSENT_FULL-2006-03-14.doc (2/2)

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School of Medicine
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Department of Neurology, Ophthalmology and Audiological Medicine
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CARDIFF UNIVERSITY

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Patient Information Sheet

Study title: "A STUDY INTO LATE ONSET ATAXIA"

We would like to invite you to consider participating into this research study. Before you decide it is important for you to understand why the research is being done and what it will involve. Please take your time to decide whether you wish or do not wish to take part, after reading the following information carefully and discuss it with your friends, relatives and your GP if you wish. Please do not hesitate to ask us if there is anything that is not clear or if you would like more information.

What is ataxia?

Ataxia means clumsiness or loss of coordination. Ataxia may affect the hands, arms or legs, the body, speech and eye movements. In general, the first symptom that a person with ataxia develops is difficulty with walking, where he or she walks as if drunk. Ataxia has no barrier, in that it may affect anyone regardless of their age, sex or race. It also affects people in different manners and to different extents. There are a number of different causes of ataxia, and for this reason it is important that a person with ataxia seeks medical assistance. However, it is quite common too that no clear cause can be pinned down, even after many tests have been done. Knowing the possible causes of ataxia helps doctors and researchers find the appropriate treatment. Sometimes ataxia is due to an illness that is acquired during life, for example, a vitamin or hormone imbalance. In others, ataxia may be due to a change in our genetic make-up, with or without any family history. For some causes of ataxia, there are specific treatments but for a large number of people in whom the cause is not identified, there is no effective treatment.

What is this study about?

In the past years, medical researchers have been gathering more information about causes of ataxia. As a result, in addition to the existing tests available to us, we now have a range of genetic tests that would allow identification of new causes of ataxia. In order to achieve this, we are collaborating with doctors in the Institute of Medical Genetics in Cardiff and Institute of Molecular Medicine in Oxford to see if it is worthwhile to test all patients who have ataxia, where no obvious cause has been found. In addition, we aim to establish a register of patients with this condition in South Wales in the form of clinical and disability information, and a stored collection of blood samples. We would also look into the impact of ataxia on a person's daily life, and this is important for us to help you live successfully with ataxia.

PT_03_INFO_MAIN-2006-03-13.doc (1/1)

Your participation

It is up to you to decide whether or not to take part. If you do decide to take part, you will be given this information sheet to keep and be asked to sign a consent form. If you agree to join this study, a doctor would come and see you at your convenience. The doctor would go over your case history, look into your medical records, examine you carefully, make clinical assessments and take a sample of blood.

You can choose whether you wish to hear about any positive results and we would be pleased to discuss these with you and any issues that may arise. It is important to bear in mind that, irrespective of the test result, no specific treatment will arise from the test. In addition, it might not be possible to give definitive advice about whether other members of your family might be susceptible to the same condition.

If you consent to take part in this study, any information that is collected from you will be stored securely and will be, and remains confidential. You can withdraw from the study at any stage, without needing to give us a reason and this will not interfere with or prejudice you for any usual treatment you would normally receive. Any information about you, which leaves the hospital/surgery, will have your name and address removed so that you cannot be recognised from it.

If you are harmed by taking part in this research project, there are no special compensation arrangements. If you are harmed due to someone's negligence, then you may have grounds for a legal action but you may have to pay for it. Regardless of this, if you wish to complain about any aspect of the way you have been approached or treated during the course of this study, the normal NHS complaints mechanisms may be available to you.

Sometimes during the course of a research project, new information becomes available about a similar investigation that is being studied. If this happens, your research doctor will tell you about it and discuss with you whether to continue in the study. If you decide to continue in the study, you will be asked to sign an updated consent form. As there is no specific cure or treatment for ataxia to date, it is hoped that the information we get from this study may help us learn more about late onset ataxia and understand the nature of this condition better. If you decide not to participate, this will not interfere with, or prejudice you for any usual care would normally receive.

Thank you for your time and attention.

Find out more about this and some useful information on ataxia at Ataxia UK:
www.ataxia.org.uk (Helpline ☎ 0845 644 0606) and the National Ataxia Foundation
website: www.ataxia.org

Research Team : **Dr. M Wardle, Dr N Robertson**
Direct Line   : **029 20743454**
Secretary   : **029 20743798**
Email   : **wardle@cardiff.ac.uk**

PT_03_INFO_MAIN-2006-03-13.doc (2/2)

CARDIFF UNIVERSITY:
CEREBELLAR ATAXIA IN SOUTH
WALES
HISTORY

Patient ID: **PatientID**

Date: **DATEOFVISIT**

General notes history [H.General]

PT_05_HIST-2005-07-25.doc (1/11)   Investigator: _____

CARDIFF UNIVERSITY: Patient ID: **PatientID**
CEREBELLAR ATAXIA IN SOUTH
WALES   Date: **DATEOFVISIT**
HISTORY

Walking Disturbance   [H.Walk.x]

1. Do you have any walking difficulty?   *Age at onset:*
    1. Yes
    2. No
    3. Uncertain
    4. Other

2. How fast would you consider the symptom has progressed since its first onset?
    1. Slow   : over at least 5 years or more
    2. Fairly rapid : over less than 5 years but more than 1 year
    3. Rapid   : over 1 year or less
    4. Episodic   : intermittent episode with a symptom-free period
    5. Uncertain   : none of the above

Is there a history of intermittent or episodic ataxia?   Yes/No/Uncertain/Other

3. What is your current walking status?
    1. Walk without support
    2. Walk with support
    3. Unable to walk
    4. Uncertain
    Note: (If wheelchair-bound, to establish disease duration prior to dependency)

Age first needed unilateral support in some circumstances:	(4)
Age needed unilateral support most of the time:	(5)
Age first needed bilateral support in some circumstances:	(6)
Age needed bilateral support most of the time:	(7)
Age first needed wheelchair in some circumstances:	(8)
Age needed wheelchair most of the time:	(9)

10. In the last month, have you had any episodes of falling (with both knees reaching the ground) when walking?
    1. Yes
    2. No
    3. Uncertain
    4. Other

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| | CARDIFF UNIVERSITY: CEREBELLAR ATAXIA IN SOUTH WALES HISTORY | Patient ID: **PatientID** Date: **DATEOFVISIT** |

Incoordination / Tremor   [H.Limb]

1. Do you notice any clumsiness of your arms and/or legs?   *Age at onset*
    1. Yes
    2. No
    3. Uncertain
    4. Other

2. Do you notice any tremor of your arms and/or legs?   Age at onset:
    1. Yes
    2. No
    3. Uncertain
    4. Other

3. Do you notice any tremor of your head?   Age at onset:
    1. Yes
    2. No
    3. Uncertain
    4. Other

Speech Difficulty   [H.Speech]

1. Do you have any difficulty with your speech?   Age at onset:
    1. Yes
    2. No
    3. Uncertain
    4. Other

2. Have you or others noticed any change in your voice or speech?   Age:
    1. Yes
    2. No
    3. Uncertain
    4. Other

3. Do you use any communication aid?   Age at onset:
    1. Yes
    2. No
    3. Uncertain
    Other

Swallowing Difficulty   [H.Swallow]

1. Do you have problem with your swallowing?   Age at onset:
    1. Yes
    2. No
    3. Uncertain
    4. Other

CARDIFF UNIVERSITY:
CEREBELLAR ATAXIA IN SOUTH
WALES
HISTORY

Patient ID: **PatientID**

Date: **DATEOFVISIT**

2. Do you avoid certain foods? Age at onset:
   1. Yes
   2. No
   3. Uncertain
   4. Other

3. Does your food need special preparation? Age at onset:
   1. Yes
   2. No
   3. Uncertain
   4. Other

4. In the last month, have you had any episodes of coughing when eating?
   Age at onset:
   1. Yes
   2. No
   3. Uncertain
   4. Other

Visual Disturbance   [H.Vision]

1. Do you have problem with your vision? Age at onset:
   1. Yes
   2. No
   3. Uncertain
   4. Other
   Note:(Establish nature of disturbance: including double vision, blurring, night blindness, etc)

Motor / Sensory Disturbance   [H.Limb]

1. Have you any weakness affecting certain parts of your body?   Age at onset?
   1. Yes
   2. No
   3. Uncertain
   4. Other

2. If yes, please state the site(s) involved:
   1. Face
   2. Right upper limb
   3. Left upper limb
   4. Right lower limb
   5. Left lower limb

3. Have you any numbness or tingling sensation? Age at onset:
   1. Yes
   2. No
   3. Uncertain
   4. Other

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CARDIFF UNIVERSITY:	**Patient ID:**	**PatientID**
CEREBELLAR ATAXIA IN SOUTH		
WALES	**Date:**	**DATEOFVISIT**
HISTORY		

4. If yes, please state the site(s) involved:
    1. Face
    2. Right upper limb
    3. Left upper limb
    4. Right lower limb
    5. Left lower limb
    6. Trunk

Other Neurological Disturbance   [H.Other]

1. In the past month, have you had a fit or loss of consciousness? Age onset:
    1. Yes
    2. No
    3. Uncertain
    4. Other

2. Do you have any problem with your memory?   Age at onset:
    1. Yes
    2. No
    3. Uncertain
    4. Other

3. Do you have any problem with your hearing?   Age at onset:
    1. Yes
    2. No
    3. Uncertain
    4. Other

4. Are you using a hearing aid?   Age at onset:
    1. Yes
    2. No
    3. Uncertain
    4. Other

Sphincter Disturbance   [H.Sphincter]

1. Have you any problem with urinary urgency?   Age at onset:
    1. Yes
    2. No
    3. Uncertain
    5. Other

2. Have you any problem with urinary frequency?   Age at onset:
    1. Yes
    2. No
    3. Uncertain
    4. Other

CARDIFF UNIVERSITY:	**Patient ID:**	**PatientID**
CEREBELLAR ATAXIA IN SOUTH		
WALES	**Date:**	**DATEOFVISIT**
HISTORY		

3. Have you any problem with hesitancy?   Age at onset:
    1. Yes
    2. No
    3. Uncertain
    4. Other

4. Do you suffer from urinary incontinence?   Age at onset:
    1. Yes
    2. No
    3. Uncertain
    4. Other

5. Do you suffer from faecal incontinence?   Age at onset:
    1. Yes
    2. No
    3. Uncertain
    4. Other

6. Do you have an in-dwelling urinary catheter?   Age at onset:
    1. Yes
    2. No
    3. Uncertain
    4. Other

7. Do you require an intermittent urinary catheter?   Age at onset:
    1. Yes
    2. No
    3. Uncertain
    4. Other

8. Do you suffer from erectile dysfunction?   Age at onset:
    1. Yes
    2. No
    3. Uncertain
    4. Other

CARDIFF UNIVERSITY: CEREBELLAR ATAXIA IN SOUTH WALES HISTORY	Patient ID:	**PatientID**
	Date:	**DATEOFVISIT**

Alcohol intake   [H.Alcohol]

1. Do you drink?
    1. Yes
    2. No

2. If yes, please indicate number of units per week**:
    1. **Guide: 1 unit is equivalent to the following:*
        a. *½ pint of ordinary strength beer, lager or cider*
        b. *1 small glass of wine or sherry*
        c. *1 single measure of spirits or aperitifs*

    Notes:

3. If patient used to be a heavy drinker, what was the usual number of units per week during that time?

4. If patient used to be a heavy drinker, from and to what age did the heavy drinking occur?

Smoking history   [H.Smoking]

1. Do you smoke?   (Y/N)

2. How many cigarettes are smoked per day currently?

3. How many pack-years smoked in the past?

CARDIFF UNIVERSITY:		**Patient ID:**	**PatientID**
CEREBELLAR ATAXIA IN SOUTH WALES		**Date:**	**DATEOFVISIT**
HISTORY			

Drug History [H.Drugs]

1. Do you have any known allergy?   (List allergies)
   1. Yes
   2. No
   3. Uncertain
   4. Other

2. Have you ever used or exposed to any illicit or recreational drugs?   (list)
   1. Yes
   2. No
   3. Uncertain
   4. Other

3. List of current or past medications (include from+to ages, if appropriate)

CARDIFF UNIVERSITY: Patient ID: **PatientID**
CEREBELLAR ATAXIA IN SOUTH
WALES   Date: **DATEOFVISIT**
HISTORY

Past medical history

1. List of past medical problems

Ask specifically about:
Diabetes mellitus, hypertension, IHD, stroke, epilepsy, pernicious anaemia, thyroid disturbance, rheumatic fever, birth-related, delayed milestones, orthopaedic and other surgical history.

CARDIFF UNIVERSITY:
CEREBELLAR ATAXIA IN SOUTH
WALES
HISTORY

Patient ID: **PatientID**

Date: **DATEOFVISIT**

Systemic Review

CVS/RS:
1. Do you suffer from any of the following symptoms:
   1. Chest pain   6. Oedema
   2. Palpitation   7. Wheeze
   3. PND   8. Cough
   4. Orthopnoea   9. Expectorant
   5. Dyspnoea   10. Other

2. Detail(s) of symptom(s): (including age at onset)

GIT:
1. Do you suffer from any of the following symptoms:
   1. Weight loss   5. Abdo bloating
   2. Indigestion   6. Altered bowel habit
   3. Vomiting   7. Other
   4. Abdo pain

2. Detail(s) of symptom(s): (Including age at onset)

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CARDIFF UNIVERSITY: Patient ID: **PatientID**
CEREBELLAR ATAXIA IN SOUTH
WALES   Date: **DATEOFVISIT**
HISTORY

Family History   (draw pedigree, and include history of gait disturbance, ataxia, proven genetic problems, auto-immune disease, and institutionalisation)

[Hist.Family]

1. FH ataxia	☐	2. FH gait disturbance	☐
3. FH learning difficulties	☐	4. FH mental illness	☐
5. FH epilepsy	☐		

PT_05_HIST-2005-07-25.doc (11/11)   Investigator: _____

CARDIFF UNIVERSITY: **Patient ID:**   «patientID»
CEREBELLAR ATAXIA IN
SOUTH WALES   **Date:**   «dateOfVisit»
NEURO EXAMINATION

General [N.General.x]

1. Gait ataxia	☐	2. Truncal ataxia	☐	3. Non-ambulant	☐
4. Head tremor	☐	5. Ataxia dysarthria	☐	6. Anosmia	☐
7. Sway EO	☐	8. Sway EC	☐		

9. Corneal reflex absent	☐	10. Abn facial sensation	☐
11. UMN facial weakness	☐	12. LMW facial weakness	☐
13. Deafness	☐	14. Abn palatal sensation	☐
15. Abn palatal movements	☐	16. Bovine cough	☐
17. Hoarse voice	☐	18. Nasal speech	☐
19. Shoulder shrug weak	☐	20. SCM weak	☐
21. Tongue wasting	☐	22. Tongue spastic	☐
23. Tongue deviation	☐	24. Brisk jaw jerk	☐

25. Facial or tongue myokymia   ☐

26. Details (if necessary) _____

Eye movements [N.EOM.x]

1. Broken pursuit	☐	2. Abn saccades	☐	3. INO	☐
4. Supranuclear palsy	☐	5. Ophthalmoplegia	☐	6. Strabismus	☐
7. Nystagmus	☐				

8. Gaze-evoked horizontal nystagmus	☐
9. Downbeat nystagmus	☐
10. Upbeat nystagmus	☐
11. Nystagmus in primary position	☐
12. Rotational nystagmus	☐
13. Complex nystagmus	☐

14. Other _____

Eyes - [N.EYE.x]

1. Maculopathy	☐	2. Optic atrophy	☐
3. Retinopathy	☐	4. Retinitis pigmentosa	☐
5. Cataract	☐	6. Visual field defect	☐
7. Chemosis	☐	8. Proptosis	☐
9. Lid lag	☐	10. Ptosis	☐
11. Pupillary abn	☐		

12. Other _____

CARDIFF UNIVERSITY: Patient ID: **«patientID»**
CEREBELLAR ATAXIA IN
SOUTH WALES   **Date:**   **«dateOfVisit»**
NEURO EXAMINATION

12. VA right   6/6 ☐ 6/12 ☐ 6/24 ☐ 6/60 ☐
                    Finger count ☐ Hand movement ☐
                    NPL ☐
13. VA left   6/6 ☐ 6/12 ☐ 6/24 ☐ 6/60 ☐
                    Finger count ☐ Hand movement ☐
                    NPL ☐
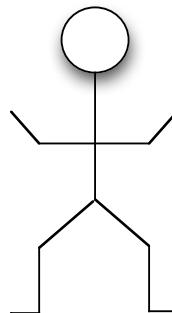
14. Other _____

Limb [N.Limb.x]

1. Normal tone	☐	2. Clonus	☐	3. Hypotonia	☐
4. Rigidity	☐	5. Spasticity	☐	6. Resting tremor	☐
7. Postural tremor	☐	8. Bradykinesia	☐	9. Dystonia	☐
10. Chorea	☐	11. Myoclonus	☐		

12. Wasting	☐	13. Fasciculation	☐	14. Myokymia	☐

11. Intention tremor	☐	12. Limb dysmetria	☐
13 Dysdiadochokinesis	☐	14. Dysrhythmogenesis	☐
15.Rebound	☐		

Reflexes [N.DTR.x]

	Right		Left
Biceps	1.		2.
Triceps	3.		4.
Supinator	5.		6.
Knee	7.		8.
Ankle	9.		10.
Plantars			

CARDIFF UNIVERSITY: **Patient ID:**   «patientID»
CEREBELLAR ATAXIA IN
SOUTH WALES   **Date:**   «dateOfVisit»
NEURO EXAMINATION

Power [N.Power.x]   (MRC grade 0-5, or '-' if not assessed)

	Right	Left
Sh ab	1.	2.
Sh ad	3.	4.
El flx	5.	6.
El ext	7.	8.
Wr flx	9.	10.
Wr ext	11.	12.
Finger flx	13.	14.
Finger ext	15.	16.
Finger ab	17.	18.
Hip flx	19.	20.
Hip ext	21.	22.
Knee flx	23.	24.
Knee ext	25.	26.
Ank dorsiflx	27.	28.
Ank plantarflx	29.	30.

Sensation [N.SENS.x]

1. Abnormal vibration   ☐   2. joint position   ☐
3. Abnormal pinprick   ☐   4. temperature   ☐

5. Details   _____

PT_06_EXAM_CNS-2006-02-20.doc (3/3)   Investigator: _____

CARDIFF UNIVERSITY:
CEREBELLAR ATAXIA IN SOUTH
WALES
MMSE

Patient ID: **PatientID**

Date: **DATEOFVISIT**
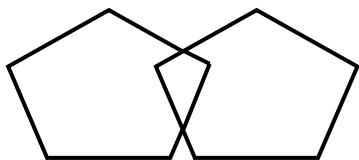
MINI MENTAL STATE EXAMINATION (MMSE)

RANGE OF SCORE

Question	0	1	2	3	4	5
What is the day, date, month, year and season?	[0	1	2	3	4	5]
Where are we? (House.#, Street, Town, County, Country)	[0	1	2	3	4	5]
Name 3 objects: one second to say each one (Ask patient for all three you have told them. 1 point for each correct answer. Repeat until patient has learnt all 3; < 6 tries)	[0	1	2	3]		
Serial 7s. 1 point for each correct subtraction (Stop after 5 answers) Alternative: spell WORLD backwards	[0	1	2	3	4	5]
Ask for 3 objects repeated above (1 point for each correct)	[0	1	2	3]		
Name: a pen and a watch	[0	1	2]			
Repeat the following: **"No ifs, ands or buts"**	[0	1]				
Follow a 3-stage command: *"Take this sheet of paper in your right hand, fold it in half, and put it on the floor"*	[0	1	2	3]		
Repeat and obey the following:	[0	1]				

"CLOSE YOUR EYES"

Write a sentence of your choice	[0	1]

_____

Copy a design	[0	1]

TOTAL SCORE: _____/30

CARDIFF UNIVERSITY: **Patient ID:**   **PatientID**
CEREBELLAR ATAXIA IN
SOUTH WALES   **Date:**   **DATEOFVISIT**
GENERAL EXAMINATION

General examination [E.Gen.x]

1 Spider naevi   ☐   2 Jaundice   ☐   3 Palmar erythema   ☐
4 Xanthelasma   ☐   5 Dry skin   ☐   6 Telangiectasia   ☐
7 Pigmentation   ☐   8 Dermatitis herpetiformis   ☐
9 Photosensitivity ☐   10. Lymphadenopathy   ☐

11 Weight: _____   12 Height : _____

13 Other findings: ☐

14 Details: _____

_____

Nails: [E.Nail.x]
1 Clubbing   ☐   2 Pitting   ☐   3 Leuconychia   ☐
4 Tar staining   ☐

Hair: [E.Hair.x]
1 Hair loss   ☐   2 Brittle   ☐   3 Tight curls ☐
4 Low hairline   ☐

Skeletal: [E.Skel.x]
1 Kyphosis   ☐   2 Scoliosis   ☐   3 Limb deformities ☐
4 Pes cavus   ☐   5. Pes planus ☐   6 Xanthoma ☐
7. Other foot deformity ☐
        8. Details _____

Cardiovascular examination [E.CVS.x]

1. Central cyanosis ☐   2. Periph cyanosis   ☐   3. ↑JVP   ☐

4. Resting pulse: _____   / min
5. Regular   ☐   6. Regularly regular ☐   7. Irreg irreg ☐

Lying/sitting: 8 systolic BP _____ mmHg   9. diastolic _____ mmHg

Standing: 10 systolic BP _____ mmHg   11. diastolic _____mmHg

12. Systolic murmur ☐   13. Diastolic murmur ☐
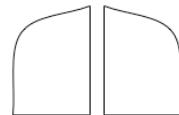
CARDIFF UNIVERSITY: Patient ID: **PatientID**
CEREBELLAR ATAXIA IN
SOUTH WALES   Date: **DATEOFVISIT**
GENERAL EXAMINATION

Respiratory examination [E.RS.x]

1 Hyperinflated   ☐   2 Wheeze   ☐
3 Crepitation   ☐

Abdominal examination [E.Abd.x]

1. Hepatomegaly   ☐   2. Splenomegaly   ☐
3. Enlarged kidneys ☐   4. Other masses   ☐

5. Other information _____

6. Free fluid   ☐   7. Bowel sounds abnormal   ☐

CARDIFF UNIVERSITY:
CEREBELLAR ATAXIA IN SOUTH
WALES
ICARS

Patient ID: <u>1113</u>

Date:

I. POSTURE AND GAIT

(I) 1: WALKING CAPACITY

Task: Walking naturally (unsupported) for 10m 1st including a half-turn near a wall, about 1.5m; followed by tandem walking. Episodic use of wall for support is allowed during natural walking only. Walking naturally (with support) for 10m including a half-turn, near a wall, about 1.5m. No tandem walking. Support refers to use of stick(s), rolator, stroller, or even accompanying person. If impossible, see score.

I.1 Walking capacities	Tick(✔)
0 = Normal	
1 = Almost normal, but unable to do tandem walking	
2 = Walking without support, but clearly abnormal and irregular	
3 = Walking without support, but with considerable staggering;difficulties with half-turn	
4 = Walking with autonomous support no longer possible;uses as well episodic support	
5 = Walking with support: one stick	
6 = Walking with support: two sticks or rolator/stroller	
7 = Walking with support: only with an accompanying person	
8 = Walking impossible even with support (wheelchair)	

(I) 2 GAIT SPEED

Task: As above during 10m walk, observed only among preceding score 0-3.

Preceding score 4-8 automatically receives score 4.

I.2 Gait speed	Tick(✔)
0 = Normal	
1 = Slightly reduced	
2 = Markedly reduced	
3 = Extremely slow	
4 = Walking with autonomous support no longer possible	

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(I) 3: STANDING CAPACITIES, EYES OPEN

Task: 1ST to stand on one foot for >10sec. If impossible, try 2nd.
2nd to stand with feet in tandem position. If impossible, try 3rd.
3rd to stand with feet together. If impossible, try 4th.
4th to stand in natural position, i.e. ask patient to find a standing
position that he or she finds comfortable. If impossible, see score.

I.3 Standing capacities	Tick(✔)
0 = Normal (Able with 1st)	
1 = Able with 2rd but not with 1st	
2 = Able with 3rd but not with 2nd	
3 = Able with 4th without support, with no or moderate sway	
4 = Able with 4th without support, with marked sway and corrections	
5 = Able with 4th only with strong one arm support	
6 = Tasks impossible, even with strong 2 arms support	

(I) 4: NATURAL POSITION, EYES OPEN

Task: Stand (or sit) in natural position as described before. Examiner to
measure the distance between medial malleoli, Xcm.

I.4. Natural position, eyes open	Tick(✔)
0 = Normal (X <10cm)	
1 = Slightly enlarged (X >10cm)	
2 = Clearly enlarged (25cm > X > 35cm)	
3 = Severely enlarged (X > 35cm)	
4 = Task impossible	

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(I) 5: BODY SWAY WITH FEET TOGETHER: EYES OPEN

Task: Stand with feet together and eyes open.

I.5 Feet together, body sway, eyes open	Tick(✔)
0 = Normal	
1 = Slight oscillations	
2 = Moderate oscillations (<10cm at the level of head)	
3 = Severe oscillations (>10cm at the level of head)	
4 = Immediate falling	

(I) 6: BODY SWAY WITH FEET TOGETHER: EYES CLOSED

Task: Stand with feet together and eyes closed.

I.6 Feet together, body sway, eyes closed	Tick(✔)
0 = Normal	
1 = Slight oscillations	
2 = Moderate oscillations (<10cm at the level of head)	
3 = Severe oscillations (>10cm at the level of head)	
4 = Immediate falling	

(I) 7: QUALITY OF SITTING POSITION

Task: Thighs together, arms folded, sitting on a hard surface, unsupported.

I.7 Sitting position quality	Tick(✔)
0 = normal	
1 = slight trunk oscillations	
2 = moderate trunk and leg oscillations	
3 = severe trunk and leg oscillations	
4 = task impossible	

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II. KINETIC FUNCTIONS

(II) 8: KNEE-TIBIA DECOMPOSITION AND INTENTION TREMOR

Task: Raise one leg and place heel on the knee; then slide heel down the
anterior tibial surface of the resting leg towards the ankle; on arriving
at ankle joint, leg is raised again in the air to a height of ~40cm and
to repeat the same movement at least 3 times or more.
To repeat task on the other leg.

8. Heel knee test I	Right (✔)	Left (✔)
0 = Normal		
1 = Heel lowered in continuous axis;decomposition in several phases; without real jerks or abnormally slow		
2 = Heel lowered jerkily in continuous axis		
3 = Heel lowered jerkily with lateral movements		
4 = Heel lowered jerkily with extremely strong lateral movements; or task impossible		

(II) 9 ACTION (POSTURAL) TREMOR ON HEEL-KNEE TEST

Task: As described in preceding test. Tremor is that of heel on the knee
when patient holds the heel on the knee for few seconds before
lowering down the anterior tibial surface.

9. Heel knee test II	Right (✔)	Left (✔)
0 = No trouble		
1 = Tremor stopping immediately when heel reaches the knee		
2 = Tremor stopping in < 10sec after reaching the knee		
3 = Tremor continuing > 10sec after reaching the knee		
4 = Uninterrupted tremor or task impossible		

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(II) 10: FINGER NOSE DECOMPOSITION AND DYSMETRIA

Task: In sitting position, hands rested on thighs before start of test.
3 movements must be performed for each limb.

10. Finger nose test I	Right (✔)	Left (✔)
0 = No trouble		
1 = Oscillating movement; no decomposition		
2 = Segmented movement in 2 phases ± moderate dysmetria in reaching target		
3 = Segmented movement in > 2 phases ± considerable dysmetria in reaching target		
4 = Dysmetria preventing patient from reaching target		

(II) 11: FINGER NOSE - INTENTION TREMOR

Task: Position and condition as before. Tremor is that appearing during
ballistic phase of movement. Test for each limb.

11 Finger nose test II	Right (✔)	Left (✔)
0 = No trouble		
1 = Simple swerve of movement		
2 = Mild tremor, estimated amplitude < 10cm		
3 = Moderate tremor, estimated amplitude between 10cm and 40cm		
4 = Severe tremor, estimated amplitude > 40cm		

(II) 12: FINGER-FINGER:

Task: In sitting position; To maintain medially 2 index finger pointing at
each other, at the level of thorax, at a distance about 1cm apart.

12 Finger-finger test	Right (✔)	Left (✔)
0 = Normal		
1 = Mild instability		
2 = Moderate oscillations of finger, estimated amplitude < 10cm		
3 = Considerable oscillations of finger, estimated amplitude between 10cm and 40cm		
4 = Jerky movements > 40cm of amplitude		

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(II) 13: PRONATION SUPINATION ALTERNATING MOVEMENTS

Task: In sitting position; To raise forearm vertically and make alternative
movements of the hand; Moved and assessed each hand separately.
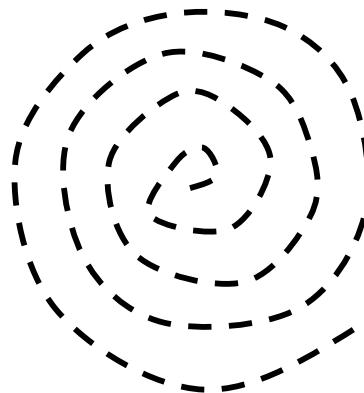
13 Alternate test	Right (✓)	Left (✓)
0 = Normal		
1 = Slightly irregular with detectable clumsiness and slowed		
2 = Clearly irregular and slowed, but without sway of elbow		
3 = Extremely irregular, slowed, severe clumsiness and sway of elbow		
4 = Task impossible		

(II) 14: ARCHIMEDES SPIRAL

Task: In sitting position in front of table or hard surface. Using the same
pen and the dominant hand, to draw on a pre-drawn pattern on a fixed
sheet of paper. No timing requirement.

14 Archimedes's draw	Tick(✓)
Score 0	
Score 1	
Score 2	
Score 3	
Score 4	

(Compare drawing with Archimedes score)
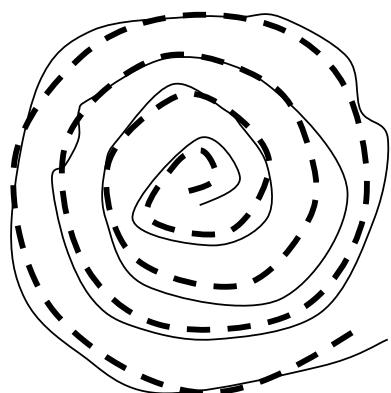
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WALES
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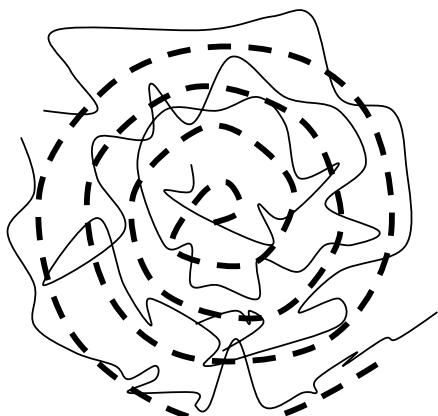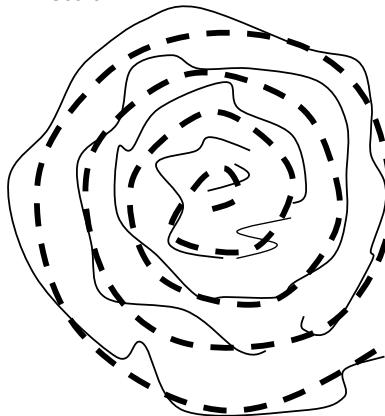
Date:

(II) 14: Guide to score of patient's drawing

Score 0: normal
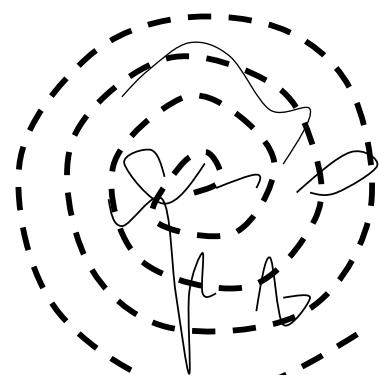
Score: 1   Score: 2

Score: 3   Score: 4

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III. SPEECH DISORDERS

(III) 15: FLUENCY OF SPEECH

Task: The patient is asked to repeat several times a standard sentence, always the same, for instance: "A mischievous spectacle in Czechoslovakia".

15 Fluency of speech	Tick(✓)
0 = Normal	
1 = Mild modification of fluency	
2 = Moderate modification of fluency	
3 = Considerable slow and dysarthric speech	
4 = No speech	

(III) 16: CLARITY OF SPEECH

C6/1 Clarity of speech	Tick(✓)
0 = Normal	
1 = Suggestion of slurring	
2 = Definite slurring, most words understandable	
3 = Severe slurring, speech not understandable	
4 = No speech	

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IV: OCULOMOTOR DISORDERS

(IV) 17: GAZE EVOKED NYSTAGMUS

Task: To look at examiner's finger held laterally. Horizontal movement is mainly assessed, but may be others: oblique, rotarory, or vertical.

17 Gaze-evoked nystagmus	Tick(✓)
0 = Normal	
1 = Transient	
2 = Persistent but moderate	
3 = Persistent and severe	

(IV) 18: ABNORMALITIES OF OCULAR PURSUIT

Task: To follow slow lateral movement of examiner's finger.

D7/2 Pursuit	Tick(✓)
0 = Normal	
1 = Slightly saccadic	
2 = Clearly saccadic	

(IV) 19: DYSMETRIA OF OCULAR SACCADE

Task: Examiner's 2 fingers placed laterally at each temporal field of patient, right and left. Patient's eyes in the primary position. To look laterally at the finger held on the right and on the left. The average overshoot or undershoot of the 2 sides is then estimated.

D7/3 Saccade	Tick(✓)
0 = Absent	
1 = Bilateral clear overshoot or undershoot of saccade	

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ALOCA: ADL BARTHEL INDEX   **EXAMINATION ID:**

PATIENT ID: PatientID….   NAME: TITLE FIRSTNAME LASTNAME   DATE:DATEOFVISIT

Dressing   :   **[0   1   2]**

Dressing	Tick(✔)
0 = Dependent	
1 = Need helps with some aspects	
2 = Independent	

Grooming   :   **[0   1]**

Grooming	Tick(✔)
0 = Needs help	
1 = Independent (hair/face/teeth/shaving)	

Bathing   :   **[0   1]**

Bathing	Tick(✔)
0 = Dependent	
1 = Independent	

Toilet use   :   **[0   1   2]**

Toilet use	Tick(✔)
0 = Dependent	
1 = Needs some help	
2 = Independent (on/off, wiping, dress)	

Bowel   :   **[0   1   2]**

Bowel	Tick(✔)
0 = Incontinent	
1 = Occasional accident	
2 = Continent	

Date of review : …………………………   Review by   : ……………………………

1

ALOCA: ADL BARTHEL INDEX   **EXAMINATION ID:**

PATIENT ID: PatientID….   NAME: TITLE FIRSTNAME LASTNAME   DATE:DATEOFVISIT

Bladder   :   [0   1   2]

Bladder	Tick(✔)
0 = Incontinent or catheterised	
1 = Occasional accident	
2 = Continent	

Feeding   :   [0   1   2]

Feeding	Tick(✔)
0 = Unable/dependent	
1 = Needs help (e.g. food cutting)	
2 = Independent	

Transfer   :   [0   1   2   3]

Transfer	Tick(✔)
0 = Unable	
1 = Major help (1 or 2 people,physical)	
2 = Minor help (verbal, physical)	
3 = Independent	

Mobility   :   [0   1   2   3]

Mobility	Tick(✔)
0 = Immobile	
1 = Dependent on assistance of person	
2 = Some limitations (e.g. corners, steps)	
3 = Independent	

Date of review : ……………………………   *Review by   :……………………………….*

2

ALOCA: ADL BARTHEL INDEX	EXAMINATION ID:

PATIENT ID: PatientID....   NAME: TITLE FIRSTNAME LASTNAME   DATE:DATEOFVISIT

Stairs   :   [0   1   2]

Stairs	Tick(✔)
0 = Unable	
1 = Needs help	
2 = Independent (up and down)	

Total score :   [1   2   3   4   5]

Total score	Tick(✔)
1. Very severe disability (0 - 4)	
2. Severe disability (5 - 9)	
3. Moderate disability (10 - 14)	
4. Mild disability (15 - 19)	
5. Independent (20)	

Date of review : ……………………………   *Review by   :………………………………*

3

CARDIFF UNIVERSITY:
CEREBELLAR ATAXIA IN
SOUTH WALES
"SF36 V2"

Patient ID: **PatientID**

Date: **DATEOFVISIT**

SF36 VERSION 2

OVERALL HEALTH

The following questions ask for your views about your health and how you feel about life in general. If you are unsure about how to answer any question, try and think about your overall health and give the best answer you can. Do not spend too much time answering, as your immediate response is likely to be the most accurate.

---

1. In general, would you say your health is:

(Please tick **one** box)

Excellent ☐

Very good ☐

Good ☐

Fair ☐

Poor ☐

---

2. Compared to 3 months ago, how would you rate your health in general now?

(Please tick **one** box)

Much better than 3 months ago ☐

Somewhat better than 3 months ago ☐

About the same ☐

Somewhat worse now than 3 months ago ☐

Much worse now than 3 months ago ☐

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Patient ID: **PatientID**

Date: **DATEOFVISIT**

3. The following questions are about activities you might do during a typical day. Does your health limit you in these activities? If so, how much?

(Please tick **one** box on each line)

		Yes, limited a lot	Yes, limited a little	No, not limited at all
a)	**Vigorous activities,** such as running, lifting heavy objects, participating in strenuous sports	☐	☐	☐
b)	**Moderate activities,** such as moving a table, pushing a vacuum, bowling or playing golf	☐	☐	☐
c)	Lifting or carrying groceries	☐	☐	☐
d)	Climbing **several** flights of stairs	☐	☐	☐
e)	Climbing **one** flight of stairs	☐	☐	☐
f)	Bending kneeling or stooping	☐	☐	☐
g)	Walking **more than a mile**	☐	☐	☐
h)	Walking **half a mile**	☐	☐	☐
i)	Walking **100 yards**	☐	☐	☐
j)	Bathing and dressing yourself	☐	☐	☐

4. During the past 2 weeks, how much time have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

(Please tick **one** box) on each line

		All of the time	Most of the time	Some of the time	A little of the time	None of the time
a)	Cut down on the **amount of time** you spent on work or other activities	☐	☐	☐	☐	☐
b)	**Accomplished less** than you would like	☐	☐	☐	☐	☐
c)	Were limited in the **kind** of work or other activities	☐	☐	☐	☐	☐
d)	Had difficulty performing the work or other activities (eg it took more effort)	☐	☐	☐	☐	☐

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CARDIFF UNIVERSITY: CEREBELLAR ATAXIA IN SOUTH WALES "SF36 V2"

Patient ID: **PatientID**

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5. During the <u>past 2 weeks</u>, how much time have you had any of the following problems with your work or other regular daily activities <u>as a result of any emotional problems</u> (such as feeling depressed or anxious)?

(Please tick **one** box) on each line	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a) Cut down on the **amount of time** you spent on work or other activities	☐	☐	☐	☐	☐
b) **Accomplished less** than you would like	☐	☐	☐	☐	☐
c) Didn't do work or other activities as **carefully** as usual	☐	☐	☐	☐	☐

6. During the <u>past 2 weeks</u>, to what extent have your physical health or emotional problems interfered with your normal social activities with family, neighbours or groups?

(Please tick **one** box)

Not at all ☐

Slightly ☐

Moderately ☐

Quite a bit ☐

Extremely ☐

7. How much bodily pain have you had during the <u>past 2 weeks</u> ?

(Please tick **one** box)

None ☐

Very mild ☐

Mild ☐

Moderate ☐

Severe ☐

Very severe ☐

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"SF36 V2"

Patient ID: **PatientID**

Date: **DATEOFVISIT**

8. During the past 2 weeks, how much did pain interfere with your normal work (including both outside the home and housework)?

(Please tick **one** box)

Not at all ☐

Slightly ☐

Moderately ☐

Quite a bit ☐

Extremely ☐

---

9. These questions are about how you feel and how things have been with you during the past 2 weeks. For each question please give one answer that comes closest to the way you have been feeling.

(Please tick **one** box) on each line

How much time during the last 2 weeks:	All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	None of the time
a) Did you feel full of life?	☐	☐	☐	☐	☐	☐
b) Have you been a very nervous person?	☐	☐	☐	☐	☐	☐
c) Have you felt so down in the dumps that nothing would cheer you up?	☐	☐	☐	☐	☐	☐
d) Have you felt calm and peaceful?	☐	☐	☐	☐	☐	☐
e) Did you have a lot of energy?	☐	☐	☐	☐	☐	☐
f) Have you felt downhearted and low?	☐	☐	☐	☐	☐	☐
g) Did you feel worn out?	☐	☐	☐	☐	☐	☐
h) Have you been a happy person?	☐	☐	☐	☐	☐	☐
i) Did you feel tired?	☐	☐	☐	☐	☐	☐

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SOUTH WALES
"SF36 V2"

Patient ID:　**PatientID**

Date:　　**DATEOFVISIT**

10. During the past 2 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting friends, relatives etc.).

(Please tick **one** box)

All of the time ☐

Most of the time ☐

Some of the time ☐

A little of the time ☐

None of the time ☐

---

11. How TRUE or FALSE is each of the following statements for you?

(Please tick **one** box on each line)

	Definitely true	Mostly true	Not sure	Mostly false	Definitely false
a) I seem to get ill more easily than other people	☐	☐	☐	☐	☐
b) I am as healthy as anybody I know	☐	☐	☐	☐	☐
c) I expect my health to get worse	☐	☐	☐	☐	☐
d) My health is excellent	☐	☐	☐	☐	☐

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CARDIFF UNIVERSITY: CEREBELLAR ATAXIA IN SOUTH WALES FAIS - IMPACT SCALE	Patient ID:	**PatientID**
	Date:	**DATEOFVISIT**

Adapted from the "Long form" version of the FAIS (8 SCALES 117 ITEMS)

<u>**1. Symptoms (31 ITEMS):**</u>

1.1 BODY MOVEMENT (19 ITEMS)

People like you who have cerebellar ataxia are bothered by different problems. The following questions ask about problems you may have been bothered by <u>during the past 2 weeks</u>.

As a result of your cerebellar ataxia, how much in the past two weeks have you been bothered by:	Not at all bothered	A little bothered	Mod-erately bothered	Quite a bit bothered	Extremely bothered
a. Loss of balance?	1	2	3	4	5
b. Loss of balance when standing?	1	2	3	4	5
c. Loss of balance when transferring?	1	2	3	4	5
d. Lack of co-ordination?	1	2	3	4	5
e. Being clumsy?	1	2	3	4	5
f. Requiring more planning to do things?	1	2	3	4	5
g. Weakness in muscles?	1	2	3	4	5
h. Lack of control over your body?	1	2	3	4	5
i. Having to concentrate on doing things?	1	2	3	4	5
j. Heavy legs?	1	2	3	4	5
k. Not able to control and use your hands?	1	2	3	4	5
l. Restless legs?	1	2	3	4	5
m. Difficulty with repetitive movement?	1	2	3	4	5
n. Spasms?	1	2	3	4	5
o. Lack of strength in arms?	1	2	3	4	5
p. Lack of movement in your fingers?	1	2	3	4	5
q. Shaky hands?	1	2	3	4	5
r. Shaky legs?	1	2	3	4	5
s. Shaky head?	1	2	3	4	5

1.2 SPEECH AND SWALLOWING (12 ITEMS)

People like you who have cerebellar ataxia are bothered by different problems. The following questions ask about problems you may have been bothered by <u>during the past 2 weeks</u>.

As a result of your cerebellar ataxia, how much in the past two weeks have you been bothered by:	Not at all bothered	A little bothered	Moderately bothered	Quite a bit bothered	Extremely bothered
a. Being self-conscious about your voice?	1	2	3	4	5
b. Being asked to repeat yourself when talking?	1	2	3	4	5
c. Slurred speech?	1	2	3	4	5
d. Slow speech?	1	2	3	4	5
e. Talking on the telephone?	1	2	3	4	5
f. Choking when swallowing or drinking?	1	2	3	4	5
g. Effort needed to talk?	1	2	3	4	5
h. Being nervous talking to strangers?	1	2	3	4	5
i. Not talking as much or avoiding talking where possible?	1	2	3	4	5
j. Not being able to say certain words?	1	2	3	4	5
k. Choking for no reason?	1	2	3	4	5
l. Avoiding speaking to others?	1	2	3	4	5

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	Date:	**DATEOFVISIT**

2. Activities (51 ITEMS):

2.1 UPPER LIMB FUNCTIONING (16 ITEMS)

The following section asks about activities, which you might do during a typical day. During the <u>past 2 weeks</u>, has cerebellar ataxia limited your ability to carry out your usual daily activities? Please indicate whether the ataxia problem <u>LIMITS</u> you not at all, a little, moderately, quite a bit or extremely in these activities by circling the appropriate number (Please circle 5 if you are unable to do the activity).

As a result of your cerebellar ataxia, how much have you been limited in your ability over the past two weeks to carry out the following daily activities?	Not at all limited	A little limited	Moderately limited	Quite a bit limited	Extremely limited
a. Doing intricate things?	1	2	3	4	5
b. Writing?	1	2	3	4	5
c. Pick things up from the floor?	1	2	3	4	5
d. Cutting up food when eating?	1	2	3	4	5
e. Opening a bottle?	1	2	3	4	5
f. Holding a pen?	1	2	3	4	5
g. Holding things?	1	2	3	4	5
h. Opening the door?	1	2	3	4	5
i. Typing?	1	2	3	4	5
j. Gripping things?	1	2	3	4	5
k. Eating food?	1	2	3	4	5
l. Turning pages in books?	1	2	3	4	5
m. Using the telephone?	1	2	3	4	5
n. Pressing buttons?	1	2	3	4	5
o. Using the computer?	1	2	3	4	5
p. Brushing your teeth?	1	2	3	4	5

2.2 ADL (16 ITEMS)

The following section asks about activities, which you might do during a typical day. During the <u>past 2 weeks</u>, has cerebellar ataxia limited your ability to carry out your usual daily activities? Please indicate whether the cerebellar ataxia problem <u>LIMITS</u> you not at all, a little, moderately, quite a bit or extremely in these activities by circling the appropriate number (Please circle 5 if you are unable to do the activity).

As a result of your cerebellar ataxia, how much have you been limited in your ability over the past two weeks to carry out the following daily activities?	Not at all limited	A little limited	Moderately limited	Quite a bit limited	Extremely limited
a. Standing?	1	2	3	4	5
b. Sitting in a chair without back and sides?	1	2	3	4	5
c. Getting in and out of shower and/or bath?	1	2	3	4	5
d. More difficulty in doing things?	1	2	3	4	5
e. Taking longer to do things?	1	2	3	4	5
f. Getting into or out of a chair?	1	2	3	4	5
g. Being slow to do things?	1	2	3	4	5
h. Putting on your socks or shoes?	1	2	3	4	5
i. Requiring more effort to do things?	1	2	3	4	5
j. Getting in and out of a car?	1	2	3	4	5
k. Getting on or off the toilet seat?	1	2	3	4	5
l. Getting into or out of bed?	1	2	3	4	5
m. Getting dressed or undressed?	1	2	3	4	5
n. Sitting up in bed?	1	2	3	4	5
o. Washing yourself in the shower/bath	1	2	3	4	5
p. Sitting in a chair with back and sides?	1	2	3	4	5

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2.3 LOWER LIMB FUNCTIONING (19 ITEMS)

The next series of questions ask about how the cerebellar ataxia has affected your walking. The following questions ask about problems you may have been bothered by <u>during the past 2 weeks</u>.

If you cannot walk at all, please tick this box ☐ **and go to section 6.**

As a result of your cerebellar ataxia, how much in the past two weeks have you been bothered by:	Not at all bothered	A little bothered	Moderately bothered	Quite a bit bothered	Extremely bothered
a. Tripping over or stumbling when walking?	1	2	3	4	5
b. Falling over when walking?	1	2	3	4	5
c. Walking not being steady?	1	2	3	4	5
d. Having to hang on to something when walking?	1	2	3	4	5
e. Walking being jerky?	1	2	3	4	5
f. Swaying when walking?	1	2	3	4	5
g. Bumping into things when walking?	1	2	3	4	5
h. Needing someone else to walk with you?	1	2	3	4	5
i. Having to concentrate on your walking?	1	2	3	4	5
j. Difficulty going up or down stairs?	1	2	3	4	5
k. Being unable to walk long distances?	1	2	3	4	5
l. Needing to know in advance where you are walking?	1	2	3	4	5
m. Difficulty walking on a slippery or uneven surface?	1	2	3	4	5
n. Feeling scared of falling over when walking?	1	2	3	4	5
o. Losing your confidence to walk?	1	2	3	4	5
p. Being clumsy when walking?	1	2	3	4	5
q. Difficulty moving legs?	1	2	3	4	5
r. Being slow when walking?	1	2	3	4	5
s. Walking not being stable?	1	2	3	4	5
t. Legs giving up on you?	1	2	3	4	5
u. Stiff legs?	1	2	3	4	5

4. Social Functioning (13 ITEMS):

4.1 Isolation (13 ITEMS)

The next series of questions ask about how the cerebellar ataxia has affected you in social situations. The following questions ask about problems you may have been bothered by <u>during the past 2 weeks</u>.

As a result of your cerebellar ataxia, how much in the past two weeks have you been bothered by:	Not at all bothered	A little bothered	Moderately bothered	Quite a bit bothered	Extremely bothered
a. Difficulties going out?	1	2	3	4	5
b. Not being able to visit other people's homes?	1	2	3	4	5
c. Difficulties going to pubs and restaurants?	1	2	3	4	5
d. Giving up on leisure activities?	1	2	3	4	5
e. Difficulty socialising?	1	2	3	4	5
f. Not being able to meet other people?	1	2	3	4	5
g. Lost confidence to go places?	1	2	3	4	5
h. Difficulty making new friends?	1	2	3	4	5
i. Interacting with other people?	1	2	3	4	5
j. Not being invited out?	1	2	3	4	5
k. Losing friends?	1	2	3	4	5

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5. Psychological Functioning (22 ITEMS):

5.1 MOOD (11 ITEMS)

The next series of questions ask about how the cerebellar ataxia has affected your feelings. The following questions ask about problems you may have been bothered by <u>during the past 2 weeks</u>.

As a result of your cerebellar ataxia, how much in the past two weeks have you been bothered by:	Not at all bothered	A little bothered	Moderately bothered	Quite a bit bothered	Extremely bothered
a. Feeling frustrated?	1	2	3	4	5
b. Feeling anxious about the future?	1	2	3	4	5
c. Feeling annoyed?	1	2	3	4	5
d. Feeling fed up?	1	2	3	4	5
e. Feeling down?	1	2	3	4	5
f. Feeling irritable?	1	2	3	4	5
g. Feeling angry?	1	2	3	4	5
h. Feeling depressed?	1	2	3	4	5
i. Feeling upset?	1	2	3	4	5
j. Feeling frightened or scared?	1	2	3	4	5
k. Feeling tearful?	1	2	3	4	5

5.2 SELF-PERCEPTIONS (11 ITEMS)

The next series of questions ask about how the cerebellar ataxia has affected your feelings. The following questions ask about problems you may have been bothered by <u>during the past 2 weeks</u>.

As a result of your cerebellar ataxia, how much in the past two weeks have you been bothered by:	Not at all bothered	A little bothered	Moderately bothered	Quite a bit bothered	Extremely bothered
a. Self-conscious about your appearance?	1	2	3	4	5
b. Feeling cut off?	1	2	3	4	5
c. Losing your confidence?	1	2	3	4	5
d. Feeling like you are on your own?	1	2	3	4	5
e. Feeling embarassed?	1	2	3	4	5
f. Being more introverted?	1	2	3	4	5
g. Lack of self-esteem?	1	2	3	4	5
h. Feeling withdrawn?	1	2	3	4	5
i. Being quieter?	1	2	3	4	5
j. Not wanting to be noticed?	1	2	3	4	5
k. Being shy?	1	2	3	4	5

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CARDIFF UNIVERSITY:
CEREBELLAR ATAXIA IN
SOUTH WALES
Transition questions

Patient ID: «patientID»

Date: 28-Feb-06

We are interesting in finding out how your ataxia has changed since we saw you last (according to our records, we saw you on the «dateOfVisit»).

Please answer all the questions below.

Tick the box that applies to you.   For example:

No change
✓

1. Overall, how do you think things have generally changed?

Much Worse	Moderately worse	A little worse	No change	A little better	Moderately better	Much better

2. Many people with ataxia have difficulty with their walking. Do you think your walking has changed since we saw you last?

Much Worse	Moderately worse	A little worse	No change	A little better	Moderately better	Much better

3. Many people with ataxia have difficulty or clumsiness using their arms. Do you think your clumsiness has changed since we saw you last?

Much Worse	Moderately worse	A little worse	No change	A little better	Moderately better	Much better

4. Many people with ataxia have difficulty with slurred speech. Do you think your speech has changed since we saw you last?

Much Worse	Moderately worse	A little worse	No change	A little better	Moderately better	Much better

5. Many people with ataxia have difficulty with their vision. Do you think your vision has changed since we saw you last?

Much Worse	Moderately worse	A little worse	No Change	A little better	Moderately better	Much better

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CARDIFF UNIVERSITY: **Patient ID:**   <u>«patientID»</u>
CEREBELLAR ATAXIA IN
SOUTH WALES   **Date:**   **28-Feb-06**
Transition questions

If there is anything further you want us to know, then please use this space

Many thanks

Mark Wardle

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