GENETIC AND CLINICAL PROFILE OF THE SPINOCEREBELLAR ATAXIAS FOLLOWED IN THE CALGARY MOVEMENT DISORDERS CLINIC

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SCOTT W. KRAFT
GENETIC AND CLINICAL PROFILE OF THE SPINOCEREBELLAR ATAXIAS
FOLLOWED IN THE CALGARY MOVEMENT DISORDERS CLINIC

By

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ABSTRACT

The adult onset spinocerebellar ataxias are a genetically and clinically heterogeneous group of neurodegenerative disorders. The relative frequencies of these disorders vary within different ethnic groups and geographical locations. We sought to identify the relative frequencies of these disorders in the Calgary Movement Disorders Clinic, as well as to determine the proportion of patients that have a positive family history and to determine the diagnostic utility of genetic testing in individuals with and without family members with similar symptoms.

A retrospective chart review of individuals given a clinical diagnosis of adult onset spinocerebellar ataxia in the Calgary Movement Disorders Clinic was carried out. Testing for SCA types 1, 2, 3, 6, 7, and 8 as well as Friedreich's Ataxia and the fragile X premutation tremor/ataxia syndrome was performed on at least one member of each family.

A total of 69 patients in 60 families presented with an adult onset progressive ataxic disorder. Twenty-one (35.0%) of the families had a pedigree suggestive of an autosomal dominant disorder. An apparent autosomal recessive pattern of inheritance was present in 3.3%. A positive but undefined family history was noted in 15.0%. Sporadic disease appeared to be present in 43.3%. Two patients (3.3%) were adopted. The most commonly found mutation in the autosomal dominant families was SCA3 (5 families – 23.8%). This was followed by SCA2 (3 families – 14.3%) and SCA6 (2 families – 9.5%). The SCA1 and SCA8 expansions were only identified in 1 family.
(4.8%) each. Although the family history was suggestive of a dominant disorder, one patient was found to have Friedreich's Ataxia. A patient in one of the two autosomal recessive appearing families tested positive for Friedreich's ataxia. One individual (11.1%) with a positive but undefined family history tested positive for SCA6. A single sporadic patient had a positive test which was SCA3. Neither of the two adopted patients had a positive test. DRPLA testing was performed on 21 of the families and no positive tests were found. No expansions of the fragile X mental retardation gene were found.

A positive test result was found in 61.9% of autosomal dominant pedigrees, 50% of autosomal recessive pedigrees, and 11.1% of patients with positive but undefined family histories. Of the sporadic patients only 1 of 26 (3.8%) was found to have a positive genetic test.

SCA3 is the most common mutation found in our clinic patients followed by SCA2 and SCA6. A positive test result is uncommon in individuals without any family history of a similar disorder. The fragile X tremor/ataxia syndrome was not identified in our SCA patient population.
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LIST OF ABBREVIATIONS

SCA – Spinocerebellar ataxia

FA - Friedreich's Ataxia

ADCA – Autosomal dominant cerebellar ataxia

MSA – Multiple system atrophy

DRPLA – Dentatorubral-pallidoluysian atrophy

FMR1 – Fragile X mental retardation gene 1

CT – Computed tomography

MRI – Magnetic resonance imaging

DNA – Deoxyribonucleic acid

RNA – Ribonucleic acid

HLA – Human leukocyte antigen

PET – Positron emission tomography

Nucleotides: A = adenine, G = guanine, T = thymine and C = cytosine
CHAPTER I – INTRODUCTION

1.1 Background of Study

The spinocerebellar ataxias are a large group of neurological disorders which may be hereditary or sporadic. The core clinical features of gait and limb ataxia are manifestations of degeneration of the cerebellum and its connections. Other neurological systems are variably involved producing features such as extraocular movement abnormalities, pyramidal tract dysfunction, sensory loss, bulbar dysfunction, and movement disorders such as parkinsonism, dystonia and tremor.¹

As is the case with most genetic disorders, the relative frequencies of the SCAs varies within different populations. Published information regarding the distribution of the SCAs in a Canadian population is not currently available. The diagnostic utility of genetic testing of SCA patients in Canada has not been described.

The fragile X premutation tremor/ataxia syndrome is a recently described disorder found in some patients carrying premutation range expansions of the fragile X mental retardation gene 1 (FMR1).² The diagnostic utility of testing for this disorder in patients presenting with SCA has not yet been established.
1.2 **Purpose of Study**

The main objective of this study was to examine the clinical epidemiology of SCA in patients referred to the University of Calgary Movement Disorders and Neurogenetics Clinics. The diagnostic utility of genetic testing for the SCAs and the FMR1 premutation was to be determined.
CHAPTER II – LITERATURE REVIEW

2.1 **Autosomal Dominant Spinocerebellar Ataxias**

Prior to the identification of different genotypes for the dominantly inherited spinocerebellar ataxias, these disorders were classified according to a scheme suggested by Harding.\(^3\) In this system, the autosomal dominant cerebellar ataxias (ADCA) were separated clinically into 3 types. In addition to cerebellar ataxia, ADCA I patients have variable degrees of dementia, supranuclear ophthalmoplegia, optic atrophy, and extrapyramidal features. Patients classified as having ADCA Type II develop pigmentary retinal degeneration which may precede the development of the ataxia. Other characteristics of ADCA II include supranuclear ophthalmoplegia in 50% as well as dementia and extrapyramidal features in some of the affected individuals. ADCA Type III is a relatively pure cerebellar syndrome. The additional features found in the other two types are absent.

The Human Genome Organisation Gene Nomenclature Committee lists 23 approved gene names for the autosomal dominant spinocerebellar ataxias (Accessed August 8, 2003 at http://www.gene.ucl.ac.uk/nomenclature/). Of these, SCA 9, 15, 19, and 22 are listed as reserved although the Online Mendelian Inheritance in Man website describes references for SCA15 and SCA19 (Accessed August 8, 2003 at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=OMIM). Recently a locus has been described for SCA22.\(^4\) No information or reference is provided for SCA23. There is no
listing for SCA20. Table 1 gives a comparison of Harding’s classification and the currently identified spinocerebellar ataxias. Dentatorubral-pallidoluysian atrophy is another autosomal dominant disorder that has ataxia as part of its symptomology. 

| Table 1. Genetically Defined SCAs Grouped by Harding’s Classification |
|---------------------------------|-----------------|
| ADCA I  | SCA1, SCA2, SCA3, SCA4, SCA8, SCA12, SCA17, SCA18, SCA19, SCA21 |
| ADCA II | SCA7            |

In the SCAs where a genetic defect has been identified the abnormality has so far always involved expansion of unstable repeat sequences of deoxyribonucleic acid (DNA). The most common of the expansions are of triplet CAG (cytosine/adenine/guanine) sequences which encode polyglutamine within the protein. This is the case for SCA types 1, 2, 3, 6, 7, and 17. Unstable nucleotide repeat sequences have been found to be responsible for a variety of other degenerative neurological disorders including, in chronological order of discovery, fragile X syndrome, myotonic dystrophy, Kennedy spinal and bulbar muscular atrophy, and Huntington disease.

With the exception of SCA6, all of the polyglutamine expansion disorders exhibit a feature called anticipation. Anticipation refers to a decrease in the age of onset of symptoms that occurs in successive generations. The molecular basis for anticipation is that further expansion in the number of trinucleotide repeats may occur during transmission from one generation to the next as larger numbers of repeats have some correlation with age of onset.
The specific mechanism by which the CAG expansions cause disease is not fully understood. Studies of animal models and tissue cultures have suggested that the expanded polyglutamine tracts result in a toxic gain of function.\textsuperscript{20,21}

Expansion of trinucleotide repeats in non-encoding regions of a gene may also lead to disease. Examples of this include SCA8, SCA12, Friedreich’s ataxia, fragile-X syndrome, and myotonic dystrophy.\textsuperscript{12,15,22-24} In the case of SCA10 the expansion is of an ATTCT (adenine/thymine/thymine/cytosine/thymine) pentanucleotide repeat.\textsuperscript{25} The pathologic repeat numbers in these disorders are generally much larger than those that occur because of expansions in the encoding regions.

Genetic testing is possible for SCA1, SCA2, SCA3, SCA6, SCA7, SCA8, SCA10, SCA12, SCA17, FA, and DRPLA. Genetic testing for SCA10, SCA12 and SCA17 is not currently performed in the Alberta Children’s Hospital in Calgary.

2.1.1 SCA1

The initial linkage of a spinocerebellar ataxia to the human leukocyte antigen (HLA) locus on chromosome 6 was made by Jackson et al in 1977.\textsuperscript{26} Moller et al. (1978) and Nino et al. (1980) confirmed this through the study of other families.\textsuperscript{27,28} Morton et al (1980) reviewed the linkage of SCA to HLA on chromosome 6 that had been found in 13 kindreds and proposed the label “SCA1” for families with this linkage.\textsuperscript{29} More specific localization on chromosome 6 followed but it was not until 1993 that the genetic
abnormality was found to be a trinucleotide repeat disorder when Orr and colleagues found an expanded number of CAG repeat units in individuals with SCA1. Following this finding of the polyglutamine sequence, Banfi et al (1994) then proceeded to identify the gene and name it ataxin-1. Servadio et al. (1995) looked at the expression of ataxin-1 in normal and affected individuals and found that the protein was expressed in the brain of both groups of individuals including in the nucleus and cytoplasm of Purkinje cells. The normal function of the protein is currently unknown but the work of Yue et al. (2001) suggested that it may be involved in ribonucleic acid (RNA) metabolism.

Anticipation has been noted in SCA1 families. Chung et al 1993 found that in 63% of paternal transmissions there was an increase in repeat number, whereas 69% of maternal transmissions showed either no change or a decrease in repeat number. In addition they noted that 98% of unexpanded alleles had an interruption in the CAG repeat while the repeat was continuous in all of the expanded alleles. This suggested that the loss of the interruption may predispose to the expansion. The importance of the interruptions was further clarified by Matsuyama et al (1999). They reported that the presence of CAT (cytosine/adenine/thymine) trinucleotide interruptions resulted in a later age of onset. Further information from Zuhlke et al (2002) revealed that the presence of a CAT interruption in an intermediate sized allele prevented the development of the SCA1 phenotype whereas its absence would produce the usual disease state.
The normal range of CAG repeats is 6 to 36 whereas affected individuals have 44 to 81 repeats. Alleles in the 36 to 44 range may not result in symptoms if interrupted by a CAT sequence.\textsuperscript{31, 35, 36}

The clinical features found in individuals with SCA1 are variable with some features only appearing late in the disease. Ranum et al (1994) described the clinical features found within 9 large SCA1 kindreds.\textsuperscript{37} Gait and limb ataxia, dysarthria, and dysfunction of cranial nerves IX, X, and XII were found in all SCA1 individuals. Other features that were variably present included oculomotor deficits (nystagmus, slow saccades, or ophthalmoplegia), motor weakness and amyotrophy, proprioceptive loss, and pyramidal tract signs. Late in the disease dystonic posturing and other involuntary movements such as chorea may appear.

The average age of onset of symptoms is around age 30, but SCA1 has been described to manifest in childhood. Those that develop symptoms before 13 years of age progress very rapidly. Death at 10 to 30 years after symptom onset is the more typical course that is seen in adult onset cases. Respiratory failure related to bulbar dysfunction is the main cause of death.\textsuperscript{38}
2.1.2 SCA 2

Analysis of a large Cuban family with an autosomal dominant spinocerebellar ataxia initially described by Orzoco in 1990 failed to show linkage to chromosome 6p as demonstrated with SCA1. Further testing enabled assignment of SCA2 to chromosome 12q23-24.1. Trottier et al (1995) used a monoclonal antibody that detected polyglutamine expansions and found that a SCA2 patient, but not his normal relative, had a protein with an expansion. This suggested that SCA2 was also a trinucleotide repeat disorder and identification of the causative gene was accomplished in 1996.

The normal range of CAG repeats is 14 to 31 with more than 95% of normals having 22 or 23 repeats. Disease causing alleles have 36 to 64 repeats with most falling between 37 and 39. An allele size of 32 to 35 may or may not produce the disease phenotype. An infant has been described as having an expansion greater than 200.

The phenotype of SCA2 is highly variable. The clinical features of the original large Cuban kindred as described by Orozco et al in 1990 included gait ataxia, dysarthria, dysmetria, and adiadochokinesia. Additional features of cramps, tremor, slowed/limited saccadic eye movements, hypotonia, and abnormal reflexes were present in over 50% of the patients. The age of onset in this group was between 2 and 65 years with a mean of 31.7 years.

In the initial clinical descriptions of SCA2 the patients did not have any parkinsonian features. More recent reports have described families in which
individuals with levodopa responsive parkinsonism are found to carry the SCA2 expanded CAG allele. These patients all had family histories suggestive of an autosomal dominantly inherited form of parkinsonism. The family described by Furtado et al (2002) lacked any physical examination features suggestive of cerebellar involvement. Positron emission tomography (PET) scanning of 2 affected family members revealed changes which were similar to that found in idiopathic Parkinson’s disease as well as in inherited parkinsonism. Shan et al (2001) had previously reported similar PET findings in two patients with familial parkinsonism who tested positive for the SCA2 mutation.

Three categories of presenting features were noted in the family reported by Gwin-Hardy et al (2000). There were individuals with typical levodopa responsive parkinsonism, others had a parkinsonism and ataxic combination, and some appeared to have progressive supranuclear palsy.

### 2.1.3 SCA 3

A family originating in the Portuguese Azores was found to have an autosomal dominant ataxia by Nakano, Dawson and Spence in 1972. These individuals were the descendants of a William Machado. Other families of Azorean descent with dominantly inherited neurodegenerative disorders were then described. Rosenberg referred to this disorder as Joseph Disease as the original ancestor was Antonio Jose (Joseph) Bastiana.

After travelling to the Azores, Coutinho and Andrade suggested that all of these families shared a common genetic disorder even though there were phenotypic
This lead to the naming of the disorder as Machado-Joseph Disease. In that paper they divided the disorder into 3 syndromes. Type I comprised 15% of cases and patients had pyramidal and extrapyramidal findings, progressive external ophthalmoplegia and minor cerebellar deficits. In Type II (38% of cases) there were cerebellar and pyramidal deficits, without extrapyramidal signs with or without progressive external ophthalmoplegia. Forty-seven percent (47%) of the patients were classified as Type III and their findings included distal symmetrical muscle atrophy with cerebellar findings with or without progressive external ophthalmoplegia and pyramidal signs. A fourth type of presentation consisting of parkinsonism and peripheral neuropathy has also been described and may be more common in individuals of African ancestry. 55-57

Takiyama et al reported in 1993 that Machado-Joseph disease mapped to 14q24.3-q32. 58 In investigating a dominantly inherited ataxia in France, Stevanin et al discovered that the locus mapped to 14q24.3-qter but could not determine at that time if it was the same gene that was responsible for Machado-Joseph disease. 59

A CAG repeat was found to be responsible for the disorder by Kawaguchi et al in 1994. 9 In 1995 Schols et al established that SCA3 and Machado-Joseph Disease shared the same genetic etiology when they tested 38 German families with an autosomal dominant ataxia for the Machado Joseph CAG repeat. 60
Normal individuals have 12 to 43 repeats whereas affected individuals have 56 to
86.9, 61-64 No intermediate allele lengths have been described. Age of onset has been
found to correlate with CAG repeat number.63-65

2.1.4 SCA4

The initial report of an autosomal dominant SCA family of Scandinavian origin
living in Utah that mapped to chromosome 16 was made by Gardner and colleagues in
1994 in an abstract at the American Academy of Neurology Meeting.66 Further details
were later provided in a publication in 1996 with a more specific localization made to
16q22.1.67 The median age of onset was 39.3 years (range 19 to 59) and anticipation
seemed to exist. To be deemed affected, an individual had to have gait or limb ataxia. A
sensory neuropathy was invariably present. Dysarthria was present in half. Babinski
signs were found in 20%. Oculomotor signs were uncommon with only 15% of the
patients manifesting this abnormality.

A second family with an autosomal dominantly inherited ataxia has been mapped
to chromosome 16q.68 The clinical features of the 28 affected individuals in this family
were significantly different from the Utah family. The age of onset was older averaging
55.9 years (range 45 to 72). Dysarthria was more common (92.6%). The most striking
difference was that sensory loss was not a feature and reflexes were all normal or near
normal.
Given that anticipation has been reported as a feature of this disorder, SCA4 may also turn out to be a trinucleotide repeat disorder and the phenotypic differences between the two families may be explained by differing repeat numbers. Alternatively, these differences may occur because the two families have separate genetic defects.

2.1.5 SCA5

A form of spinocerebellar ataxia found in the descendants of Abraham Lincoln’s paternal grandparents has been linked to chromosome 11.69 This kindred contained 170 members over 10 generations with 56 of them being affected. This form of SCA appeared to have a more benign course than the previously described ones. The symptoms were largely restricted to the cerebellum and progressed slowly over decades. Bulbar paralysis was not found in adult onset cases but was seen in two of the juvenile onset patients. Disease onset was usually in the third or fourth decade with a range of 10 to 68 years. Anticipation appeared to be present.

A second family with similar clinical features and linkage to the SCA5 locus has also been described in France.70

2.1.6 SCA6

The discovery of SCA6 did not follow the usual method of linkage analysis followed by gene identification that the other SCAs had done. Zuchenko et al (1997)
found that a CAG repeat existed within the human alpha 1A voltage-dependent calcium channel subunit. They then tested ataxia patients and normal controls and found 8 unrelated patients with a late onset ataxic syndrome. Further analysis of family members of these individuals confirmed that an expanded CAG repeat within the alpha 1A voltage-dependent calcium channel subunit was associated with ataxia.

The normal range of repeats is 5 to 20 while affected individuals have 21 to 25 which is shorter than the expansion found in other CAG repeat disorders. No intermediate repeat lengths have been described.

The clinical features of SCA6 consist of a predominantly cerebellar syndrome. While Ishikawa et al (1997) did not find non-cerebellar system involvement, Schöls et al (1998) reported the presence of mild degrees of external ophthalmoplegia, spasticity, and peripheral neuropathy, especially if symptoms are present for more than 5 years. Onset of symptoms has been found to range from 20 to 71 years.

One individual with both SCA6 and retinitis pigmentosa has been described. Retinal degeneration had only previously been found in association with SCA7. In this case the retinal problem was not thought to be a manifestation of SCA6 as the parents of the patient were first cousins and two of his three male cousins, whose parents were also first cousins, also had the retinitis pigmentosa but had no evidence of ataxia.
The specific means by which the expansion of the polyglutamine repeat of the alpha 1A voltage-dependent calcium channel subunit results in ataxia is not completely understood. Ishikawa et al (1999) reported that this gene is most intensely expressed in the Purkinje cells of normal individuals.\textsuperscript{73} When they examined the brains of SCA6 patients they found that there were many oval or rod-shaped aggregates in the cytoplasm of Purkinje cells which were not found elsewhere. This suggested to the authors of this paper that the mechanism of neurodegeneration in SCA6 is associated with cytoplasmic aggregations of the mutant alpha 1A voltage-dependent calcium channel subunit protein.

Unlike the other SCAs true anticipation has not been found to be a feature of SCA6. While repeat number has correlated with age of onset among different families and earlier onset has been found in the children of affected individuals, actual expansion of the number of repeats in subsequent generations has not been demonstrated.\textsuperscript{10, 18, 19, 74}

Other types of mutations of the alpha 1A voltage-dependent calcium channel subunit gene can also produce disease but the phenotype can be quite different. Ophoff et al (1996) found missense mutations in people with familial hemiplegic migraine and mutations which disrupt the reading frame were found in patients with episodic ataxia type 2.\textsuperscript{75} There has also been some evidence that this gene may be involved in idiopathic generalized epilepsy. Chioza et al. (2001) found that a single nucleotide polymorphism within the gene showed significant association with the disease.\textsuperscript{76}
2.1.7 SCA7

The only entity that currently falls within Harding's classification of ADCA II is SCA7. The distinguishing feature of this disorder is the presence of a pigmentary retinal degeneration, first described by Fromet and colleagues in 1937.\(^77\)

The median age of onset of the 47 patients with SCA7 studied by Giunti et al (1999) was 32 years with a range of 1 to 76. Correlation was found between the age of onset and the number of repeats. Two phenotypic categories were observed. For those with less than 49 CAG repeats the clinical course consisted of a fairly pure cerebellar ataxia for many years with a more benign progression. Patients with 49 or more repeats had a cerebellar ataxia with additional neurological signs such as fasciculations and extrapyramidal features along with a more rapid progression. Macular degeneration was present in 89% of the patients. Other common features included supranuclear ophthalmoplegia (69%), increased reflexes (92%), Babinski (31%), dysphagia (55%) and dysarthria (100%).\(^78\)

Benomar et al (1995) mapped the gene for this disorder to 3p21.1-p12 and Gouw et al (1995) and Holmberg et al. (1995) to 3p21.1-p14.\(^79\)-\(^81\) In the Benomar et al paper, analysis was performed on four different families from geographically diverse regions with all of them mapping to the same chromosomal region. While a specific gene was not identified, Trotter et al (1995) demonstrated that SCA7 appeared to be the result of a polyglutamine expansion.\(^41\) This was confirmed by Lindblad et al. in 1996.\(^82\) The gene was finally discovered in 1997 by David et al and named ataxin-7.\(^8\) The normal function
of ataxin-7 is not known. No other genetic locus has been found for families with the combination of ataxia and pigmentary retinal degeneration.

Gouw et al (1995) and Holmberg et al. (1995) had previously noted anticipation in the families that they studied.\textsuperscript{80, 81} David et al. (1996) found that anticipation was more prominent with paternal rather than maternal transmission and this was confirmed in their 1997 paper describing the CAG expansion.\textsuperscript{83}

The SCA7 allele was found to be highly unstable with normal repeat numbers ranging from 4 to 35 and mutant alleles having anywhere from 38 to around 200 repeats.\textsuperscript{8}\textsuperscript{84} Intermediate repeat numbers ranging from 28 to 35 were reported in families of SCA7 patients but were rare in the general population. This intermediate range was not associated with symptoms but was prone to expansion in future generations.\textsuperscript{78}

\subsection*{2.1.8 SCA8}

Koob et al (1999) reported that a non-coding CTG expansion on chromosome 13q21 resulted in SCA8.\textsuperscript{22} Onset of symptoms in this family ranged from 18 to 65 years with a mean of 39 years. Common initial symptoms were dysarthria, mild aspiration, and gait instability. Other clinical features included nystagmus, limb ataxia, spasticity and decreased vibration sense. Stevanin et al. (2000) looked for the CTG repeat expansion in 188 French controls with no family history of neurologic disorders and 250 European index patients with different forms of ataxia.\textsuperscript{85} While they found expansions in 8 of 148
autosomal dominant cerebellar ataxia families, expansions were also seen in an apparently sporadic ataxia patient, in a patient with neuropathologically confirmed Lafora disease, in a patient with familial essential tremor, as well as in three control patients aged 57, 62, and 64 years.

The findings of Koob et al (1999) came under further scrutiny as other researchers found large sized alleles in apparently normal individuals. Worth et al. (2000) found five expanded alleles in their control population as well as a large number of repeats in the 92-year-old asymptomatic mother of an affected patient. Vincent et al. (2000) observed that more than 100 repeats could be found in 1.25% of patients with various psychiatric disorders and 0.7% of healthy controls but none were present in individuals affected by or with a family history of SCA. Silveira et al. (2000) failed to find expansions greater than 100 in any normal controls.

In contrast to other triplet repeat diseases, expanded alleles found in affected SCA8 individuals can have either a pure uninterrupted CTG repeat tract or an allele with 1 or more CCG, CTA, CTC, CCA, or CTT trinucleotide interruptions. The repeat number in sperm may undergo contractions which may underlie the reduced penetrance associated with paternal transmission.

In examining the SCA8 expansion in an 81 member SCA8 expansion positive family, Day et al (2000) found that all of the 21 affected family members inherited the
expansion from their mothers and contraction in sperm was again observed. The CTG repeat was consistently longer in affected than in unaffected individuals.\textsuperscript{90}

Controversy remains about the role of the SCA8 expansion in producing disease.

### 2.1.9 SCA10

Grewal et al. (1998) described a Mexican American family which did not carry the SCA types 1, 2, 3, 6, or 7 mutations and did not link to the sites described for SCA4 and SCA5.\textsuperscript{91} They later reported linkage of the ataxia to chromosome 22q13 and labelled this as SCA10.\textsuperscript{92} They noticed the phenomena of anticipation which suggested that this might also be a trinucleotide repeat disorder. Instead of the usual trinucleotide repeat, Matsuura et al (2000) found a pentanucleotide repeat in an intron of the SCA10 gene.\textsuperscript{93} Normal individuals were found to have 10 to 22 ATTCT repeats and affected individuals had 800 to 4500.

The age of onset of symptoms ranges from 12 to 48 years. Like the other SCAs a progressive ataxia has been the core clinical feature but SCA10 patients have also had the additional characteristic of seizures in 20% to 100%. Generalized seizures were the most common but some individuals developed complex partial seizures. The seizures generally began after the onset of ataxia.\textsuperscript{91-94} Mild pyramidal signs, behavioural disturbances, and peripheral neuropathy occurred in some patients and systemic disorders
such as hepatic failure, anemia, and/or thrombocytopenia have been recorded in one family.\textsuperscript{94}

Anticipation has been seen in families with SCA10.\textsuperscript{91,92}

Testing of 123 French families with autosomal dominant cerebellar ataxias failed to find any SCA10 mutations.\textsuperscript{95} A search for the SCA10 mutation in 67 white American, 40 French-Canadian, 6 Italian, 17 Japanese, and 39 Spanish families with ADCA also failed to find a positive test. Testing of 250 sporadic ataxic patients of white American or Spanish descent also did not find any patients with the SCA10 mutation.\textsuperscript{96} As SCA10 has not yet been described in non-Mexican populations diagnostic testing is not being performed at the University of Calgary Molecular Genetics Laboratory.

\textbf{2.1.10 SCA11}

Worth et al (1999) described a family with a pure cerebellar syndrome with linkage to 15q14-q21.3.\textsuperscript{97} The mean age of onset of symptoms was 24.7 years with a range of 15 to 43 years. These individuals had a relatively benign disease with a normal appearing life expectancy. Extraocular movement abnormalities were limited to jerky pursuit and horizontal nystagmus and all individuals had mild hyperreflexia but no other neurological exam abnormalities.
2.1.11 SCA12

Holmes et al (1999) described a large German pedigree in which they identified an expanded CAG repeat on chromosome 5q31-q33. The repeat occurred within the 5' promoter region for a brain-specific regulatory subunit of the protein phosphatase PP2A. Age of onset ranged from 8 to 55 years. The most common presentation was of upper extremity tremor in the fourth decade. The disease then progressed slowly to include head tremor, gait and limb ataxia, hyperreflexia, paucity of movement, abnormal eye movements, and, in the oldest subjects, dementia. Further analysis of this family by O'Hearn et al. (2001) revealed that action tremor of the head and arms distinguished SCA12 from the other SCAs. Cholfin et al. (2001) failed to find the SCA12 mutation in any of the 180 kindreds that they screened. Fujigasaki et al. (2001) found that only one of 145 autosomal dominant SCA families carried the SCA12 mutation. In 77 Indian families Srivastava et al. (2001) found five that were SCA12 positive. Hand tremor again was the initial presenting symptom in affected individuals.

2.1.12 SCA13

A childhood onset autosomal dominant cerebellar ataxia associated with mental retardation linked to chromosome 19q13.3-q13.4 was described by Herman-Bert et al (2000). SCA13 is not addressed further in this paper as it is a disorder of childhood onset and this study involved only patients with adult onset of symptoms.
2.1.13 SCA14

Yamashita et al (2000) reported a three generation Japanese family with a SCA that linked to 19q13.4-qter.\textsuperscript{103} Mean age of onset was 27.7 years with a range of 12 to 42 years. All individuals had a cerebellar ataxia but the presenting features differed according to age of onset. Those with onset age 39 or greater presented with cerebellar ataxia while those with a younger onset (less than 27 years) first showed intermittent axial myoclonus which was then followed by the development of ataxia.

A second SCA family with linkage to 19q13.4-qter was described by Brkanac et al. (2002).\textsuperscript{104} This family was of English and Dutch descent. This family had a pure cerebellar ataxia. The myoclonus noted by Yamashita et al (2000) was not noted in this family.

Identification of the gene responsible for SCA14 has not yet been made. Given that there are phenotypic differences and a specific localization has not yet been made, the possibility exists that these two families do not share the same genetic defect.
2.1.14 SCA15

Storey et al. (2001) excluded linkage to the previously described SCAs in an Australian kindred with a relatively pure cerebellar ataxia.\(^\text{105}\) The most distinctive clinical feature in this family was an exceptionally slow rate of progression with three of the individuals maintaining a very mild degree of gait ataxia despite having symptoms for 30 or more years. A specific chromosomal locus for this family has not yet been described in the literature.

2.1.15 SCA16

Linkage analysis of a 4-generation Japanese ADCA family by Miyoshi et al. (2001) suggested that the locus was situated on 8q22.1-24.1.\(^\text{106}\) Mean age of onset was 39.6 years and the range was 20 to 66 years. The clinical features of the patients included a relatively pure cerebellar ataxia with head tremor.

2.1.16 SCA17

While screening 118 patients with various forms of neurological disease for expansions of CAG repeats of the TATA box binding protein gene on chromosome 6q27, Koide et al. (1999) identified a sporadic patient with the clinical features of ataxia and intellectual deterioration who had an expansion of this gene.\(^\text{11}\) The TATA box binding protein is the DNA-binding subunit of the RNA polymerase II transcription factor D which is required for the expression of protein-encoding genes. Zuhlke et al. (2001) used
a similar approach in looking for the expansion in 604 sporadic and familial cases with various forms of neurological syndromes and found four patients in two families with an autosomal dominant ataxia, dystonia, and intellectual decline. Nakamura et al. (2001) identified expanded CAG repeats in the same TATA-binding protein gene in 4 Japanese pedigrees. The age of onset ranged from 19 to 48 years, and symptoms included ataxia, bradykinesia, and dementia.

TATA-binding protein is known to be an important general transcription initiation factor but the specific mechanism by which the CAG expansion causes disease is not known.

2.1.17 SCA18

Brkanac et al (2002) identified a family with variable degrees of sensory loss, ataxia, pyramidal tract signs, and muscle weakness. Linkage was made to 7q22-q32 and they referred to this initially as sensory/motor neuropathy with ataxia (SMNA) but it has since been reclassified as SCA18.
2.1.18 SCA19

Schelhaas et al. (2001) excluded the other known SCA loci in a 4-generation Dutch family with a mild ataxia syndrome with cognitive impairment, poor performance on the Wisconsin Card Sorting Test, myoclonus, and a postural irregular tremor of low frequency. Verbeek et al. (2002) proceeded to map the disorder to chromosome 1p21-q21.

2.1.19 SCA21

The SCA21 label has been applied to a family first described by Devos et al (2001). The clinical features variably included cerebellar ataxia, limb ataxia and akinesia, dysarthria, dysgraphia, hyporeflexia, postural tremor, rigidity, resting tremor, cognitive impairment, and cerebellar atrophy. Extraocular movements were generally normal. The age of onset ranged from 6 to 30 years. Anticipation appeared to be a feature of the disorder. Vuillaume et al. (2002) mapped the locus for the disorder in this family to chromosome 7p21.3-p15.1.

2.1.20 SCA22

The most recently discovered SCA locus was described by Chung et al (2003). They found a four generation Chinese family with a dominantly inherited ataxia that linked to chromosome 1p21-q23. Affected members of this family had a cerebellar ataxia with associated dysarthria, nystagmus and hyporeflexia. Other neurological systems were not involved. The mean age of onset of symptoms was 40.5 years with a range of 35 to
46 years. The progression appeared to be very slow. Only 1 of the 9 affected individuals
needed assistance with walking 20 years after onset of symptoms.4
2.1.21 Summary of the ADCAs

The clinical features of the currently classified autosomal dominant cerebellar ataxias are summarized in table 2.

Table 2. Clinical Features of the Genetically Defined SCAs

<table>
<thead>
<tr>
<th>SCA</th>
<th>Clinical Features in Addition to Gait and Limb Ataxia</th>
</tr>
</thead>
<tbody>
<tr>
<td>SCA1</td>
<td>Oculomotor defects, muscle weakness, decreased vibration sense, pyramidal signs</td>
</tr>
<tr>
<td>SCA2</td>
<td>Slow saccades, hypotonia, Parkinsonism</td>
</tr>
<tr>
<td>SCA3</td>
<td>Type I – pyramidal and extrapyramidal findings, progressive external ophthalmoplegia and minor cerebellar deficits</td>
</tr>
<tr>
<td></td>
<td>Type II – cerebellar and pyramidal deficits, without extrapyramidal signs with or without progressive external ophthalmoplegia</td>
</tr>
<tr>
<td></td>
<td>Type III – distal symmetrical muscle atrophy with cerebellar findings with or without progressive external ophthalmoplegia and pyramidal signs</td>
</tr>
<tr>
<td></td>
<td>Type IV – parkinsonism and peripheral neuropathy</td>
</tr>
<tr>
<td>SCA4</td>
<td>2 families – one with sensory neuropathy and the other with dysarthria and no sensory neuropathy</td>
</tr>
<tr>
<td>SCA5</td>
<td>Predominantly cerebellar. Very slow progression</td>
</tr>
<tr>
<td>SCA6</td>
<td>Predominantly cerebellar</td>
</tr>
<tr>
<td>SCA7</td>
<td>Pigmentary retinopathy</td>
</tr>
<tr>
<td>SCA8</td>
<td>Spasticity and decreased vibration sense. The role of the SCA8 expansion is controversial</td>
</tr>
<tr>
<td>SCA9</td>
<td>No listing</td>
</tr>
<tr>
<td>SCA10</td>
<td>Predominantly cerebellar</td>
</tr>
<tr>
<td>SCA11</td>
<td>Early upper extremity tremor and late dementia</td>
</tr>
<tr>
<td>SCA12</td>
<td>Mental retardation</td>
</tr>
<tr>
<td>SCA13</td>
<td>Predominantly cerebellar but axial myoclonus if younger age of onset</td>
</tr>
<tr>
<td>SCA14</td>
<td>Predominantly cerebellar. Very slow progression</td>
</tr>
<tr>
<td>SCA15</td>
<td>Predominantly cerebellar with head tremor</td>
</tr>
<tr>
<td>SCA16</td>
<td>Intellectual deterioration</td>
</tr>
<tr>
<td>SCA17</td>
<td>Sensory loss, pyramidal tract signs, muscle weakness</td>
</tr>
<tr>
<td>SCA18</td>
<td>Mild ataxia with cognitive impairment, myoclonus, and a low frequency postural tremor</td>
</tr>
<tr>
<td>SCA19</td>
<td>No Listing</td>
</tr>
<tr>
<td>SCA20</td>
<td>Hyporeflexia, postural tremor, parkinsonism, cognitive impairment. Extraocular movements generally normal</td>
</tr>
<tr>
<td>SCA21</td>
<td>Predominantly cerebellar with hyporeflexia. Slow progression.</td>
</tr>
</tbody>
</table>
2.1.22 Dentatorubral-pallidoluysian atrophy

Naito and Oyanagi (1982) reported a syndrome of myoclonic epilepsy, dementia, ataxia, and choreoathetosis in five Japanese families. Onset was usually in the twenties with death occurring in the forties. The initial description of this disorder was probably made by Smith et al. (1958). Nagafuchi et al. (1994) localized the gene responsible for DRPLA to chromosome 12p. Koide et al. (1994) was able to demonstrate that a CAG repeat expansion was present in 22 individuals with DRPLA. They also noted that size of the CAG repeat expansion correlated with the age of onset of symptoms.

Farmer et al. (1989) described a five-generation family, with ancestors born in Haw River, North Carolina, that contained individuals who suffered from a progressive neurological disorder characterized by the development of ataxia, seizures, choreiform movements, and progressive dementia between 15 and 30 years of age with death occurring after 15 to 25 years of illness. Burke et al. (1994) later demonstrated that affected members of this family had the same trinucleotide repeat expansion found in DRPLA.

DRPLA is thought to be uncommon outside of the Japanese population.
2.2 **Autosomal Recessive Ataxias**

There are several autosomal recessive disorders that contain ataxia within the clinical description but only Friedreich’s ataxia and ataxia with vitamin E deficiency are thought to occasionally have onset of symptoms in adulthood and have ataxia as the most prominent feature. Examples of autosomal recessive ataxias with onset of symptoms in childhood include ataxia telangiectasia, ataxia with oculomotor apraxia, abetalipoproteinemia, the autosomal recessive spastic ataxia of Charlevoix-Saguenay, and Refsum’s disease.\(^\text{121}\)

### 2.2.1 Friedreich’s ataxia

The clinical features of Friedreich’s ataxia were outlined in the diagnostic criteria proposed by Harding (1981).\(^\text{122}\) The criteria included progressive ataxia of gait and limbs, absent reflexes in the legs, onset before age 25 years, dysarthria, decrease in position sense and/or vibration sense in lower limbs, and muscle weakness. Signs that were present after five years from onset were dysarthria, areflexia, pyramidal weakness of the legs, extensor plantar responses, and distal loss of joint position and vibration sense. Other frequent signs were scoliosis, pes cavus, cardiomyopathy of the hypertrophic non-obstructive type, optic atrophy, deafness, and glucose intolerance or diabetes.

While the clinical definition of Friedreich ataxia required onset earlier than 25 years of age, with the demonstration of the genetic defect it is now known that older ages of onset can occur.\(^\text{123-126}\) The oldest onset of symptoms published is 51 years.\(^\text{127}\)
Chamberlain et al. (1988) mapped the gene of Friedreich ataxia to chromosome 9. The specific genetic abnormality was discovered by Campuzano et al. (1996). They found that it was caused by an intronic GAA triplet repeat expansion. Ninety-four percent (94%) of patients with the classic form of the disease were found to be homozygous for this GAA expansion. Some of those that were not homozygous for the expansion have been found to be compound heterozygotes, carrying an expansion on one allele and a point mutation on the other.

2.2.2 Ataxia with vitamin E deficiency (AVED)

Harding et al. (1985) described a young woman with no measurable vitamin E level who had developed a progressive disorder consisting of ataxia, areflexia, and marked loss of proprioception at age 13. There was no evidence of fat malabsorption. She improved with vitamin E administration. Both of her parents and four brothers had low or low-normal serum vitamin E levels which was thought to represent the heterozygous carrier state.

Ben Hamida et al. (1993) localized the gene responsible for a Friedreich's ataxia like disease with low vitamin E levels to the proximal portion of 8q. Further mapping was performed by Doerflinger et al. (1995). Demonstration that ataxia with isolated vitamin E deficiency was caused by mutations in the alpha-tocopherol transfer protein was accomplished by Ouahchi et al. (1995).
2.3 The Fragile X Premutation Tremor/Ataxia Syndrome

Fragile X syndrome is caused by an expansion of CGG repeats greater than 200 in the fragile X mental retardation 1 gene (FMR1). Repeats falling within the range of 50 to 200 repeats are considered to be premutations and are at risk of further expansion in subsequent generations. The prevalence of the premutation is approximately 1 in 700 males and 1 in 250 females.

Recently, a syndrome consisting of tremor, cerebellar dysfunction, parkinsonism, and cognitive decline associated with the fragile X premutation has been described. The initial report consisted of case reports of five men over the age of 57 who were all grandfathers of children with fragile X syndrome. Several other reports have been published describing clinical, radiological, and pathological findings of other individuals with this disorder. Common neuroradiological findings have been found to include increased T2 signal intensity in the middle cerebellar peduncles and deep white matter of the cerebellum as well as diffuse cerebral and cerebellar atrophy. Neuropathological examination has revealed the presence of intranuclear inclusions in the neuronal and astrocytic nuclei of the cortex.

There has been one report of two females with the association of tremor and ataxia with the FMR1 premutation. While females carrying the full mutation have been though to have no clinical manifestations, 16% of women with the premutation develop premature menopause.
2.4 **Acquired Ataxias**

The hereditary ataxias must be separated from ataxic disorders that have non-genetic/acquired etiologies. Many of these conditions differ from the genetic ataxias by their time course. Multiple sclerosis is usually a relapsing remitting disorder and ataxia is often only one aspect of the disease. Ataxias caused by vascular insults are sudden and non-progressive. Tumours may have a progressive course but the duration of disease is usually much shorter than the degenerative disorders. Neuroimaging will often reveal the presence of such disorders. Toxic exposure may also produce damage to the cerebellum with the most common substance being ethanol which may be combined with a thiamine deficiency. Metabolic conditions such as hepatic encephalopathy, pontine and extrapontine myelinolysis related to hyponatremia, and hypothyroidism may have an associated ataxia. Some infectious conditions such as Acquired Immune Deficiency Syndrome and Creutzfeldt-Jakob Disease may have ataxia as part of the disease process but there are usually additional clinical features which leads one to suspect one of these disorders.\(^{143}\)

The cerebellum and its connections may also be damaged through immunological means. In addition to direct effects via cerebellar tumours, malignancy may also produce ataxia as part of a paraneoplastic syndrome. Again this is generally a much faster process than would generally be found with a genetic disorder. A number of autoantibodies have been described to be associated with a paraneoplastic ataxic disorder. The most common antibody found is anti-Yo which is found in association with ovarian, breast or other gynecological malignancies.\(^{144}\)
Gluten sensitivity has been suggested as a possible cause of sporadic ataxia. The presence of ataxia in individuals with adult celiac disease was first noted by Cooke and Thomas-Smith in 1966.\textsuperscript{145} Hadjivassiliou et al (2003) found that there was a significantly higher prevalence of antigliadin antibodies in sporadic SCA patients (54/132 (41\%)) than in normal controls (149/1200 (12\%)) or in those with a familial ataxia (8/59 (14\%)).\textsuperscript{146}

Anti glutamic acid decarboxylase antibodies (GAD) have a known association with stiff person syndrome but they have also been found in individuals with spinocerebellar ataxia.\textsuperscript{147-149} Abele et al (1999) reported a patient with progressive cerebellar ataxia, insulin-dependent diabetes mellitus, and GAD antibodies who responded to intravenous immunoglobulins.\textsuperscript{150}

The acquired ataxias are summarized in Table 3.
Table 3. Conditions Associated with Acquired Ataxia

<table>
<thead>
<tr>
<th>Auto-immune</th>
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</thead>
<tbody>
<tr>
<td>Multiple Sclerosis</td>
</tr>
<tr>
<td>Anti-GAD antibodies</td>
</tr>
<tr>
<td>Celiac disease</td>
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<tr>
<td>Post-infectious cerebellitis – e.g. varicella zoster</td>
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<table>
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<tr>
<th>Infectious</th>
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<tbody>
<tr>
<td>Creutzfeldt-Jakob disease</td>
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<tr>
<td>Lyme disease</td>
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<tr>
<td>Mycoplasma pneumoniae</td>
</tr>
<tr>
<td>Legionella pneumoniae</td>
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<tr>
<td>Toxoplasma gondii</td>
</tr>
<tr>
<td>Tuberculosis</td>
</tr>
<tr>
<td>Human immunodeficiency virus</td>
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<tr>
<td>Progressive multifocal encephalopathy</td>
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<table>
<thead>
<tr>
<th>Medications</th>
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</thead>
<tbody>
<tr>
<td>Anticonvulsants – Phenytoin, Carbamazepine, Barbiturates</td>
</tr>
<tr>
<td>Piperazine</td>
</tr>
<tr>
<td>5-fluorouracil</td>
</tr>
<tr>
<td>Cytosine arabinoside</td>
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<td>Lithium</td>
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<table>
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<tr>
<th>Toxic</th>
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<tbody>
<tr>
<td>Ethanol</td>
</tr>
<tr>
<td>Carbon tetrachloride</td>
</tr>
<tr>
<td>Toluene</td>
</tr>
<tr>
<td>Methyl mercury</td>
</tr>
<tr>
<td>Thallium</td>
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<tr>
<td>Ciguatera poisoning</td>
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<table>
<thead>
<tr>
<th>Nutritional</th>
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<tbody>
<tr>
<td>Vitamin E deficiency</td>
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<tr>
<td>Thiamine deficiency</td>
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<table>
<thead>
<tr>
<th>Metabolic</th>
</tr>
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<tbody>
<tr>
<td>Hepatic encephalopathy</td>
</tr>
<tr>
<td>Pontine and extrapontine myelinolysis related to hyponatremia</td>
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<tr>
<td>Hypothyroidism</td>
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<table>
<thead>
<tr>
<th>Neoplastic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary tumours</td>
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<tr>
<td>Metastatic tumours</td>
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<tr>
<td>Paraneoplastic</td>
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<table>
<thead>
<tr>
<th>Vascular</th>
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<tbody>
<tr>
<td>Cerebellar Infarction</td>
</tr>
<tr>
<td>Cerebellar Hemorrhage</td>
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<tr>
<td>Superficial Siderosis</td>
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</tbody>
</table>
2.5 **Multiple System Atrophy**

Multiple system atrophy (MSA) is a sporadic neurodegenerative disorder manifest by variable combinations of parkinsonism, cerebellar ataxia, autonomic insufficiency, and pyramidal dysfunction. The median age of onset is 55 years and the male to female ratio is 1.3:1. The course of the disease is quite rapid with 50% becoming disabled or wheelchair bound within 5 years. Median survival is 9.3 years from the onset of symptoms. Multiple system atrophy can be further subdivided into MSA-P if the parkinsonian features predominate and MSA-C if the cerebellar features predominate. The diagnostic criteria for MSA is summarized in Appendix 1. The etiology is unknown.\(^{151-153}\)

The term MSA currently encompasses disorders previously known as Shy Drager syndrome, striato-nigral degeneration, and olivopontocerebellar atrophy as all three disorders have been shown to share the same pathological feature of glial cytoplasmic inclusions.\(^{154}\)

2.6 **Distribution of the SCAs varies within different populations**

As with most genetic disorders the prevalence of an abnormal gene differs between ethnic groups as well as within geographically separated ethnic groups.

Moseley et al (1998) looked at the frequencies of SCA types 1, 2, 3, 6, 7, and Friedreich’s ataxia in 361 families with ataxia. Specific information about the ethnic
Recruitment of the patients was performed by the use of four of the authors' patients as well as via an announcement in the National Ataxia Foundation’s publication. Most had an adult onset but an unspecified number had onset before age 18. Patients with a clinical diagnosis of Friedreich’s ataxia were excluded. A dominant inheritance pattern was noted in 49.3%, 12.2% appeared recessive, 37.1% were apparently sporadic and 1.4% were unknown. SCA3 was the most common expansion in the dominant families accounting for 20.8% of the cases. SCA2 and SCA6 were found in 15.2% each. SCA1 was much less frequent at 5.6% and SCA7 was the least frequent at 4.5%. Even though patients with a clinical diagnosis of Friedreich’s ataxia were excluded, a homozygous GAA expansion was found in 11.4% of the recessive families and 5.2% of the apparent sporadic patients. In families with an apparent recessive inheritance pattern a SCA2 mutation was found in one family (2.3%) and a SCA6 mutation in two families (4.5%).

The frequencies of SCA 1, 2, 3, 6, and 7 in Australia was examined by Storey et al (2000). The Australian population is largely of Anglo-Celtic origin. A total of 88 pedigrees with at least two seemingly affected family members were tested. The 2 most common genes involved were SCA6 (17%) and SCA1 (16%). This was followed by SCA3 (12%). SCA2 (6%) and SCA7 (2%) were much less common. All tests were negative in 47%.

The distribution of SCA types 1, 2, 3, 6, and 7 in the Netherlands was studied by van de Warrenburg et al 2002. This was a review of the results of the laboratories in the Netherlands rather than a study of a clinically defined population so only relative
frequencies are available. SCA3 was the most frequent mutation (44.1%) followed by SCA6 (23.5%). The remainder was made up by SCA7 (11.7%), SCA2 (11.0%) and SCA1 (9.7%).

Given that 90% of the patients in the sample were of Portuguese – Azorean descent it is not surprising that 92% (48/52) of families in Southern Brazil with an autosomal dominant SCA were found to carry the SCA3 mutation. Testing for SCA1, 2, 6, 7, and 8 testing only resulted in the discovery of a single family (2%) with the SCA8 expansion. Six percent (6%) were undiagnosed. A second report involving patients from both Brazil and Portugal also found the majority to have SCA3 (63%) with only 3% having the SCA2 expansion, SCA8 – 2%, SCA6 - 1%, SCA7 - 1%, and DRPLA - 2%. A study of 74 families in Taiwan with dominantly inherited ataxia revealed SCA3 (47.3%) was the most common SCA. SCA6 and SCA2 each made up 10.8% followed by SCA1 (5.4%), and SCA7 (2.7%). One family (1.4%) was positive for DRPLA. No cases of SCA8 were identified. A diagnosis was not made in 21.6% of cases.

Testing for SCA types 1, 2, 3, 6, 7, and DRPLA in 26 patients with positive family histories in eastern India resulted in the finding that SCA2 was the most common (26.9%). SCA1 accounted for 19.2%, SCA3 – 11.5%, and SCA6 – 3.8%. No cases of SCA7 or DRPLA were found. All tests were negative in 38.5%. Another study from India also found SCA2 (25.6%) to be the most common mutation among the SCA
patients. Seven of these 42 families studied came from eastern India while the rest were from northern India.162

Two studies done in Japan demonstrate that the proportion of the different SCAs can vary significantly even within the same ethnic group because of geographic isolation. In the northernmost island of Japan (Hokkaido) the frequency of the SCAs in 117 families was as follows: SCA6 – 29%, SCA3 – 23.9%, SCA1 – 9.7%, SCA2 – 7.7%, and DRPLA – 2.6% All tests were negative in 27.1%.163 This contrasts with the numbers found in the Tohoku District on Honshu Island (117 families) where the most common was SCA1 (24.8%) followed closely by SCA3 (23.9%). SCA6 made up 10.3% of cases, SCA7 – 1.7%, SCA2 – 0.8%, and SCA8 – 0.8%. DRPLA accounted for 14.5% and 23.1% tested negative for all of these disorders.164

Cellini et al (2001) described testing of 32 autosomal dominant cerebellar ataxia families in central Italy and found that SCA2 was the most common (31%) followed by SCA1 (19%) and SCA3 (3%). There were no positive tests for SCA6, SCA7, or SCA12.165

Eighty-seven unrelated families in Spain were tested and SCA2 and SCA3 were the most common accounting for 15.3% each. The others types were much lower: SCA1 – 5.6%, SCA7 – 2.8% and SCA6 – 1.4%. One family (1.4%) with DRPLA was found and 58.3% tested negative for all mutations.166
In 85 Chinese kindreds with autosomal dominant spinocerebellar ataxia, SCA3 accounted for 48.23% whereas only 4.7% were positive for SCA1 and 5.88% for SCA2. No families were found to have SCA6, SCA7, or DRPLA. \(^{167}\)

Information about the distribution of the SCAs in the UK came from a review of the results of genetic testing laboratories. No clinical information was available and the family history information on the testing request form was not significant enough to classify mode of inheritance in 124/146 (84.9%) cases. It is possible that some of the patients were related but this could not easily be determined because of the methodology. The two most commonly identified mutations were SCA6 (5%) and SCA2 (4%). SCA1 and DRPLA were each found in 1.4% and SCA3 in 0.7%. \(^{168}\)

Of 47 kindreds with Harding’s ADCA I phenotype followed at the University of California, Los Angeles 23% tested positive for the SCA3 allele, 13% for SCA2, and 6% for SCA1. \(^{45}\)

In 77 German ataxia families SCA3 accounted for 42%, SCA6 for 22%, SCA2 for 10%, and SCA10 for 9%. The authors included eight families with family histories suggestive of sporadic disease in their analysis after discovering these individuals had a positive test. Other sporadic patients were not included. \(^{169}\)
2.7 SCA and Friedrich Testing in Sporadic Patients

The yield of SCA testing in apparently sporadic patients has been addressed in a number of reports.

Schöls et al (2000) looked at the incidence of positive test results for SCA types 1, 2, 3, 6, 7, 8, and 12 and Friedrich’s ataxia in 124 patients with an idiopathic sporadic ataxia and 20 individuals with a clinical diagnosis of multi-system atrophy. Patients with a congenital or non-progressive disease were excluded as well as those with a first or second degree relative with an unexplained gait disturbance. Those who had a typical Friedrich ataxia phenotype or with a secondary cause of ataxia were also excluded. All but 7 of the 124 were of German ancestry. A mutation was found in 23/124 (19%) of patients. Ten patients (8%) were homozygous for the GAA repeat expansion in Friedrich’s ataxia and all had onset of symptoms under age 40. SCA6 was the next most common with 9 patients (7%) having positive tests with age of onset all greater than age 40. Three (2%) were found to have SCA8 and 1 (1%) was positive for SCA2. A second report authored again by Schols described the results of genetic testing in sporadic adult-onset ataxia patients. It is not clear how many patients of the above described study were included in the second report’s sample. In this case an expanded SCA allele was found in 13%. The distribution was similar including 4% with FA, 6% with SCA6, 2% with SCA3, and 1% with SCA2.
Futamura et al (1998) tested 85 adult onset Japanese ataxia patients for SCA1, SCA2, SCA3, SCA6, and DRPLA and found that 22% had a positive test. Most of these individuals carried an expanded SCA6 allele (11/19). The sporadic SCA6 patients had a smaller CAG repeat and a later age of onset than those with SCA6 who had a positive family history.  

Testing of sporadic cases by Moseley et al (1998) yielded a positive result for SCA2 in two cases (1.5%), SCA3 in one patient (0.7%), SCA6 in two cases (1.5%), and SCA7 in one (0.7%) for an overall positive test proportion of 9.7%.  

Fourteen sporadic cases were tested for SCA1, 2, 3, 6, 7, and 8 in the south Brazil population. Only one (7%) was found to have an expansion and this occurred at the SCA8 locus.  

In the Taiwanese population only 2 of 49 (4.1%) sporadic SCA patients tested positive for SCA6. Testing of this group of patients for SCA types 1, 2, 3, 7, and 8 and DRPLA did not result in any positive tests.  

In investigating 60 sporadic patients for FA, SCA types 1, 2, 3, 6, and 7, and DRPLA, Pujana et al (1999) only found one individual with a positive test. This patient developed symptoms at age 30 and was found to be homozygous for the Friedreich's ataxia GAA repeat expansion. Also, testing of 15 familial cases without a clear dominant pattern of inheritance failed to have any positive results.
CHAPTER III – METHODS

3.1 Study Patient Population

Patients were identified by a search of the Movement Disorders Clinic patient registry for the diagnoses of spinocerebellar ataxia, Friedreich’s Ataxia (FA), and multisystem atrophy – olivopontocerebellar atrophy. The Movement Disorders Clinic is located at the Foothills Hospital in Calgary, Alberta and is part of the Faculty of Medicine, Department of Clinical Neurosciences at the University of Calgary. This specialized outpatient clinic was founded in 1984 and approximately 2000 patients are followed in the clinic. Four (4) neurologists who specialize in movement disorders are associated with the clinic (O. Suchowersky, S. Furtado, R. Ranawaya, R. Lee). Patients are seen at the clinic after being referred to one of the four movement disorder neurologists by general practitioners or other specialists. The geographical patient catchment area includes southern Alberta, south-western Saskatchewan, and south-eastern British Columbia. The majority of patients seen in the clinic live in the southern Alberta area.

The files of all patients seen in the Movement Disorders Clinic are stored within the clinic itself. All Movement Disorder Clinic patient files were perused to identify all patients with the diagnoses of interest for this study. All patients with a diagnosis of interest seen from January 1, 1996 to December 31, 2002 were included in this study. Only those patients with an onset of symptoms at age 18 or greater were included. Individuals were excluded if they had a diagnosis of a secondary ataxia from disorders...
such as multiple sclerosis, brain tumour, paraneoplastic syndrome, stroke, or alcoholism. Patients seen for presymptomatic genetic testing were also excluded.

3.2 Patient Assessments

As part of routine clinical assessments of patients referred to the clinic, all patients had complete medical histories including detailed family histories and physical examinations performed by one of the Movement Disorders Clinic neurologists – OS, SF, RR, RL. Assessments were not made as part of this study. This information was obtained retrospectively from the clinic notes.

3.3 Data Collection

A detailed clinical chart review was performed, and the abstracted information was recorded on a standardized data collection form. The following variables were collected: gender, age of symptom onset, age at last assessment, presenting complaint, family history, neuroimaging findings, and the presence or absence of dysarthria, nystagmus, saccadic smooth pursuit, hyperreflexia, hyporeflexia, Babinski, spasticity, sensory findings, limb ataxia, parkinsonism, dystonia, and autonomic symptoms. The aforementioned variables of interest were recorded as present if they were documented in the chart. If no information was documented, then the variables were recorded as absent. The results of available vitamin E levels, anti-GAD antibodies and anti-endomysial antibodies were also collected. Anti-endomysial antibody testing was used to screen for
celiac disease. All charts were reviewed by one investigator (Scott Kraft), a neurologist currently completing fellowship training in movement disorders at the clinic.

3.4 Genetic Testing

Genetic testing for SCA1, SCA2, SCA3, SCA6, SCA7, SCA8, the FMR1 expansion and Friedreich’s Ataxia was performed on at least one member of each family. All tests were performed in the Molecular Diagnostics Laboratory of the Alberta Children’s Hospital in Calgary, Alberta using standard testing methods involving polymerase chain reaction primers as previously published.6-10,22,24

DRPLA testing had been performed on some of the families. Testing was performed using previously published methods.116

3.5 Neuroimaging

Neuroimaging results were obtained by reviewing the final radiologist report included in the chart. The variables of interest that were abstracted from the report included the presence of cerebellar, cerebral, or brainstem atrophy. The reports of both computed tomography (CT) and magnetic resonance imaging (MRI) were included. For patients who had more than one examination all abnormalities mentioned were collected. Patient films were not directly examined by the study investigator (SK) during data collection.
3.6 **Assignment of Family History Categories**

Family history was divided into the following categories: autosomal dominant, autosomal recessive, positive but unknown, and adopted/unavailable. Autosomal dominant inheritance was assigned if at least two generations were affected and there was evidence of transmission from one generation to the next. The information about the pedigrees was often too limited making it difficult to determine if an X-linked disorder could be responsible. Autosomal recessive pedigrees were those that had affected siblings without other family history of a similar disorder or if there were other similarly affected family members (e.g. cousins) without evidence of parent-child transmission. Some pedigrees contained family members who could possibly have had similar symptoms but adequate clinical information was not available. Such cases were labelled as positive but unknown inheritance.

3.7 **Multiple System Atrophy Diagnostic Criteria**

The Consensus Criteria for multiple system atrophy was used (See Appendix 1).
3.8 **Statistical Analysis**

For comparisons of sporadic versus hereditary cases individuals with autosomal dominant, autosomal recessive, and positive but unknown pedigrees were grouped together and the adopted/unavailable cases were grouped with sporadic.

Gender, age of onset, mean duration of symptoms at last clinic visit, whether or not the presenting complaint was gait related, and the presence of dysarthria, nystagmus, saccadic smooth pursuit, hyperreflexia, hyporeflexia, Babinski, spasticity, sensory findings, limb ataxia, parkinsonism, dystonia, and autonomic symptoms were compared between sporadic and hereditary cases using Chi-square for categorical variables and Student’s t test for continuous variables. Differences were considered to be statistically significant if the two-tailed P values were less than 0.05.

All statistical analyses were performed using SAS for Windows (release 8.02; SAS Institute Inc., Cary, NC, 1999-2001).
CHAPTER IV – RESULTS

4.1 Patient Characteristics

4.1.1 Overall SCA Patient Characteristics

A total of 69 patients in 60 families were identified as having an adult onset spinocerebellar ataxia (Table 4). Thirty three (47.8%) of the study patients were male and 36 (52.1%) were female. The mean age of symptom onset was 46.5 years with a range of 18 to 85 years. The mean duration of disease symptoms at the last follow-up visit was 11.7 years with a range of 1 to 44 years.

Table 4. Characteristics of Study Patients

<table>
<thead>
<tr>
<th>Total Number of Patients</th>
<th>69 patients in 60 families</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>33 (47.8%)</td>
</tr>
<tr>
<td>Female</td>
<td>36 (52.1%)</td>
</tr>
<tr>
<td>Mean Age of Symptom Onset</td>
<td>46.5 (range = 18-85) ±16.8 SD</td>
</tr>
<tr>
<td>Mean Duration of Symptoms at last visit</td>
<td>11.7 years (range = 1-44) ± 8.9 SD</td>
</tr>
</tbody>
</table>

SD = Standard Deviation
4.1.2 Age Distribution

The distribution of the age of onset of symptoms is described in Table 5.

<table>
<thead>
<tr>
<th>Age of Onset (Years)</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Less than 20</td>
<td>2 (2.9)</td>
</tr>
<tr>
<td>20 to 29</td>
<td>12 (17.4)</td>
</tr>
<tr>
<td>30 to 39</td>
<td>12 (17.4)</td>
</tr>
<tr>
<td>40 to 49</td>
<td>10 (14.5)</td>
</tr>
<tr>
<td>50 to 59</td>
<td>16 (23.2)</td>
</tr>
<tr>
<td>60 to 69</td>
<td>12 (17.4)</td>
</tr>
<tr>
<td>&gt;= 70</td>
<td>5 (7.3)</td>
</tr>
</tbody>
</table>

4.1.3 Initial Symptom

The majority of patients (79.7%) described gait dysfunction as the initial symptom of their disease. A symptom due to an extraocular movement abnormality was the presenting feature in 7.3%, tremor in 4.4%, parkinsonism in 2.9%, dysarthria in 2.9%, dystonia in 1.5%, and chorea in 1.5% (Table 6).

<table>
<thead>
<tr>
<th>Initial Symptom</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gait Dysfunction</td>
<td>55 (79.7)</td>
</tr>
<tr>
<td>Extraocular movement abnormality</td>
<td>5 (7.3)</td>
</tr>
<tr>
<td>Tremor</td>
<td>3 (4.4)</td>
</tr>
<tr>
<td>Parkinsonism</td>
<td>2 (2.9)</td>
</tr>
<tr>
<td>Dysarthria</td>
<td>2 (2.9)</td>
</tr>
<tr>
<td>Dystonia</td>
<td>1 (1.5)</td>
</tr>
<tr>
<td>Chorea</td>
<td>1 (1.5)</td>
</tr>
</tbody>
</table>
4.1.4 Family History

A family history suggestive of an autosomal dominant disorder was present in 35.0% of the families. An apparent autosomal recessive pattern of inheritance was present in 3.3%. A positive but undefined family history was noted in 15.0%. Sporadic disease appeared to be present in 43.3%. Two patients (3.3%) were adopted and did not have family histories available (Table 7). The pedigrees of those with positive family histories are found in Appendix 2.

Table 7. Family History Category Among Study Families

<table>
<thead>
<tr>
<th>Family History</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autosomal Dominant</td>
<td>21 (35.0)</td>
</tr>
<tr>
<td>Autosomal Recessive</td>
<td>2 (3.3)</td>
</tr>
<tr>
<td>Sporadic</td>
<td>26 (43.3)</td>
</tr>
<tr>
<td>Positive but Undefined</td>
<td>9 (15.0)</td>
</tr>
<tr>
<td>Adopted</td>
<td>2 (3.3)</td>
</tr>
<tr>
<td>Total</td>
<td>60 (100)</td>
</tr>
</tbody>
</table>
4.2 Results of Genetic Testing

The results of genetic testing by family history classification are summarized in Table 8. DRPLA testing had been done on 21 of the families and all results were negative. No premutation or pathological range expansions of the FMR1 gene were found.

<table>
<thead>
<tr>
<th>Genetic Test</th>
<th>AD</th>
<th>AR</th>
<th>Undefined</th>
<th>Sporadic</th>
<th>Adopted</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>SCA1</td>
<td>1 (4.8)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1 (1.7)</td>
</tr>
<tr>
<td>SCA2</td>
<td>3 (14.3)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>3 (5.0)</td>
</tr>
<tr>
<td>SCA3</td>
<td>5 (23.8)</td>
<td>0</td>
<td>0</td>
<td>1 (3.8)</td>
<td>0</td>
<td>6 (10.0)</td>
</tr>
<tr>
<td>SCA6</td>
<td>2 (9.5)</td>
<td>0</td>
<td>1 (11.1)</td>
<td>0</td>
<td>0</td>
<td>3 (5.0)</td>
</tr>
<tr>
<td>SCA7</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>SCA8</td>
<td>1 (4.8)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1 (1.7)</td>
</tr>
<tr>
<td>FA</td>
<td>1 (4.8)</td>
<td>1 (50)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2 (3.3)</td>
</tr>
<tr>
<td>DRPLA</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>FMR1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>All Negative</td>
<td>8 (38.1)</td>
<td>1 (50)</td>
<td>8 (88.9)</td>
<td>25 (96.2)</td>
<td>2 (100)</td>
<td>44 (73.3)</td>
</tr>
<tr>
<td>Total</td>
<td>21 (100)</td>
<td>2 (100)</td>
<td>9 (100)</td>
<td>26 (100)</td>
<td>2 (100)</td>
<td>60 (100)</td>
</tr>
</tbody>
</table>

AD = Autosomal Dominant
AR = Autosomal Recessive

4.2.1 Genetic Test Results in Autosomal Dominant Families

The most commonly found mutation in the autosomal dominant families was SCA3 (5 families – 23.8%). This was followed by SCA2 (3 families – 14.3%) and SCA6 (2 families – 9.5%). The SCA1 and SCA8 expansions were only identified in 1 family (4.8%) each.
Although the family history was suggestive of a dominant disorder, one patient was found to have Friedreich's Ataxia. This pedigree is summarized in Figure 1.

![Pedigree Diagram](image)

Figure 1. Autosomal dominant appearing pedigree of patient diagnosed with Friedreich's ataxia. Circles indicate females, squares indicate males, diamonds indicate unknown sex, filled symbols represent affected individuals and unfilled symbols indicate unaffected individuals. The arrow indicates the index case.

4.2.2 Genetic Test Results in Autosomal Recessive Families

A patient in one of the two autosomal recessive appearing families tested positive for Friedreich's ataxia. This pedigree is summarized in Figure 2.
Figure 2. Autosomal recessive appearing pedigree of patient diagnosed with Friedreich’s ataxia. Circles indicate females, squares indicate males, filled symbols represent affected individuals and unfilled symbols indicate unaffected individuals. The arrow indicates the index case.
4.2.3 Genetic Test Results in Undefined Families

One individual (11.1%) with a positive but undefined family history tested positive for SCA6. One of his eight sisters were similarly affected by an ataxia and another sister may have had balance problems. This patient’s mother died at age 89 with no gait abnormality and his father died at age 85 and had walked with a cane for a long time because of a supposed World War II injury leading to a stroke. If the potential gait abnormality of the father is ignored then the pedigree could be interpreted as recessive but if it is deemed significant then a dominant inheritance is suggested. This pedigree is described in Figure 3.

![Pedigree diagram](image)

**Figure 3.** Pedigree of SCA6 patient with uncertain mode of inheritance. Circles indicate females, squares indicate males, a slash through the symbol indicates deceased, filled symbols represent affected individuals and unfilled symbols indicate unaffected individuals. The arrow indicates the index case.
4.2.4 Genetic Test Results in Sporadic Patients

A single sporadic patient had a positive test which was SCA3.

One patient was found to be heterozygous for the Friedreich’s ataxia GAA expansion. Additional genetic testing was performed on this individual to assess the status of the normal sized allele and no abnormality was detected.

4.2.5 Genetic Test Results in Adopted Patients

Neither of the two adopted patients had a positive test.

4.2.6 Diagnostic Utility of Genetic Testing

A positive test result was found in 61.9% of autosomal dominant pedigrees, 50% of autosomal recessive pedigrees, and 11.1% of patients with positive but undefined family histories. Of those patients who lacked a family history of a similar disorder only 1 (3.8%) was found to have a positive genetic test. Neither of the two adopted patients had a positive test (Table 9).
Table 9. Yield of Genetic Testing Among Study Patients

<table>
<thead>
<tr>
<th>Inheritance</th>
<th>Families</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
</tr>
<tr>
<td>Autosomal Dominant</td>
<td>13/21 (61.9%)</td>
</tr>
<tr>
<td>Autosomal Recessive</td>
<td>1/2 (50%)</td>
</tr>
<tr>
<td>Positive but Undefined</td>
<td>1/9 (11.1%)</td>
</tr>
<tr>
<td>All patients with a family history</td>
<td>15/32 (46.9%)</td>
</tr>
<tr>
<td>Sporadic</td>
<td>1/26 (3.8%)</td>
</tr>
<tr>
<td>Adopted</td>
<td>0/2 (0%)</td>
</tr>
<tr>
<td>Sporadic + Adopted</td>
<td>1/28 (3.6%)</td>
</tr>
</tbody>
</table>

Of the people with a positive family history, 46.9% had a positive genetic test (sensitivity). Of the people without a family history, 96.4% tested negative (specificity). Of those who test positive, the proportion who had a positive family history is 93.8% (positive predictive value). Of those who test negative, 61.3% have a negative family history (negative predictive value) (Table 10).

Table 10. Diagnostic Utility of Genetic Testing

<table>
<thead>
<tr>
<th>Positive Genetic Test</th>
<th>Positive Family History</th>
<th>Negative Family History</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genetic Tests Negative</td>
<td>17</td>
<td>27</td>
</tr>
<tr>
<td></td>
<td>15</td>
<td>1</td>
</tr>
</tbody>
</table>
4.3 Clinical Features

The clinical features of all the patients separated by diagnosis is summarized in table 11. All patients had an ataxic gait.

Table 11  Clinical Features of Study Patients Separated by Diagnosis

<table>
<thead>
<tr>
<th></th>
<th>SCA1</th>
<th>SCA2</th>
<th>SCA3</th>
<th>SCA6</th>
<th>SCA8</th>
<th>FA</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>2</td>
<td>3</td>
<td>7</td>
<td>7</td>
<td>1</td>
<td>2</td>
<td>47</td>
</tr>
<tr>
<td>Male</td>
<td>0</td>
<td>1</td>
<td>5</td>
<td>4</td>
<td>0</td>
<td>0</td>
<td>23</td>
</tr>
<tr>
<td>Female</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>3</td>
<td>1</td>
<td>2</td>
<td>24</td>
</tr>
<tr>
<td>Mean Age of Onset (Years)</td>
<td>44.5</td>
<td>33.0</td>
<td>36.3</td>
<td>55.9</td>
<td>29</td>
<td>21.5</td>
<td>49.0</td>
</tr>
<tr>
<td>Range of age of Onset</td>
<td>39-50</td>
<td>18-54</td>
<td>22-55</td>
<td>48-64</td>
<td>29</td>
<td>21-22</td>
<td>18-85</td>
</tr>
<tr>
<td>Mean Duration of Symptoms at Last Visit (Years)</td>
<td>17</td>
<td>23.3</td>
<td>10.7</td>
<td>7</td>
<td>15</td>
<td>13</td>
<td>11.4</td>
</tr>
<tr>
<td>Range of Symptom Duration</td>
<td>9-25</td>
<td>15-31</td>
<td>4-19</td>
<td>1-12</td>
<td>15</td>
<td>10-16</td>
<td>1-44</td>
</tr>
<tr>
<td>Presenting Complaint Gait</td>
<td>2/2</td>
<td>2/3</td>
<td>7/7</td>
<td>6/7</td>
<td>1/1</td>
<td>2/2</td>
<td>35/47</td>
</tr>
<tr>
<td>Dysarthria</td>
<td>2/2</td>
<td>2/3</td>
<td>6/7</td>
<td>4/7</td>
<td>1/1</td>
<td>2/2</td>
<td>35/47</td>
</tr>
<tr>
<td>Nystagmus</td>
<td>2/2</td>
<td>1/3</td>
<td>5/7</td>
<td>6/7</td>
<td>1/1</td>
<td>2/2</td>
<td>23/47</td>
</tr>
<tr>
<td>Saccadic Smooth Pursuit</td>
<td>2/2</td>
<td>2/3</td>
<td>5/7</td>
<td>6/7</td>
<td>1/1</td>
<td>1/2</td>
<td>36/47</td>
</tr>
<tr>
<td>Hyperreflexia</td>
<td>2/2</td>
<td>1/3</td>
<td>4/7**</td>
<td>1/7</td>
<td>0/1</td>
<td>0/2</td>
<td>30/47</td>
</tr>
<tr>
<td>Hyporeflexia</td>
<td>0/2</td>
<td>1/3</td>
<td>4/7**</td>
<td>4/7</td>
<td>1/1</td>
<td>2/2</td>
<td>11/47</td>
</tr>
<tr>
<td>Babinski</td>
<td>1/2</td>
<td>0/3</td>
<td>4/7</td>
<td>0/7</td>
<td>0/1</td>
<td>1/2</td>
<td>9/47</td>
</tr>
<tr>
<td>Spasticity</td>
<td>2/2</td>
<td>0/3</td>
<td>5/7</td>
<td>1/7</td>
<td>0/1</td>
<td>0/2</td>
<td>18/47</td>
</tr>
<tr>
<td>Sensory Findings</td>
<td>2/2</td>
<td>1/3</td>
<td>5/7</td>
<td>1/7</td>
<td>0/1</td>
<td>2/2</td>
<td>21/47</td>
</tr>
<tr>
<td>Limb Ataxia</td>
<td>2/2</td>
<td>3/3</td>
<td>5/7</td>
<td>7/7</td>
<td>1/1</td>
<td>2/2</td>
<td>38/47</td>
</tr>
<tr>
<td>Parkinsonism</td>
<td>0/2</td>
<td>0/3</td>
<td>3/7</td>
<td>0/7</td>
<td>0/1</td>
<td>0/2</td>
<td>7/47</td>
</tr>
<tr>
<td>Dystonia</td>
<td>1/2</td>
<td>1/3</td>
<td>3/7</td>
<td>0/7</td>
<td>1/1</td>
<td>0/2</td>
<td>2/47</td>
</tr>
<tr>
<td>Autonomic Symptoms</td>
<td>0/2</td>
<td>0/3</td>
<td>1/7</td>
<td>0/7</td>
<td>0/1</td>
<td>0/2</td>
<td>7/47</td>
</tr>
</tbody>
</table>

** One patient had a mixture of hyporeflexia and hyperreflexia on the most recent physical examination that was documented in the chart.
4.4 Radiology Results

The results of neuroimaging were available for 55 of the patients. Cerebellar atrophy was reported in 78% of the reports. Twenty percent were found to have brainstem atrophy. Cerebral atrophy was noted in 18.2% of the patients. A normal exam was reported in 18.2% of the patients (Table 12).

Table 12 Neuroimaging Findings for Study Patients (n = 55)

<table>
<thead>
<tr>
<th>Neuroimaging Finding</th>
<th>Number (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cerebellar Atrophy</td>
<td>43 (78.2)</td>
</tr>
<tr>
<td>Brainstem Atrophy</td>
<td>11 (20.0)</td>
</tr>
<tr>
<td>Cerebral Atrophy</td>
<td>10 (18.2)</td>
</tr>
<tr>
<td>Normal exam</td>
<td>10 (18.2)</td>
</tr>
</tbody>
</table>
4.5 **Hereditary vs. Sporadic**

4.5.1 **Clinical Features**

The clinical features of patients with a positive family history versus those patients that had an apparent sporadic disease are summarized in Table 13. Dysarthria \(p = 0.027\) and hyperreflexia \(p = 0.024\) were more common in the sporadic group. Nystagmus was more common in the hereditary group \(p = 0.036\).

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Hereditary (n = 41)</th>
<th>Sporadic (n = 28)</th>
<th>p - value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>16 (39.0)</td>
<td>17 (60.7)</td>
<td>0.077</td>
</tr>
<tr>
<td>Female</td>
<td>25 (61.0)</td>
<td>11 (39.3)</td>
<td>0.077</td>
</tr>
<tr>
<td>Age of onset</td>
<td>44.6</td>
<td>49.3</td>
<td>0.257</td>
</tr>
<tr>
<td>Mean Duration of Symptoms at Last Visit (Years)</td>
<td>12.0</td>
<td>11.11</td>
<td>0.677</td>
</tr>
<tr>
<td>Presenting complaint gait</td>
<td>24 (82.9)</td>
<td>21 (75.0)</td>
<td>0.42</td>
</tr>
<tr>
<td>Dysarthria</td>
<td>27 (65.9)</td>
<td>25 (89.3)</td>
<td>0.027**</td>
</tr>
<tr>
<td>Nystagmus</td>
<td>28 (68.3)</td>
<td>12 (42.9)</td>
<td>0.036**</td>
</tr>
<tr>
<td>Saccadic Smooth Pursuit</td>
<td>31 (75.6)</td>
<td>22 (31.9)</td>
<td>0.774</td>
</tr>
<tr>
<td>Hyperreflexia</td>
<td>18 (43.9)</td>
<td>20 (71.4)</td>
<td>0.024**</td>
</tr>
<tr>
<td>Hyporeflexia</td>
<td>16 (39.0)</td>
<td>7 (25.0)</td>
<td>0.225</td>
</tr>
<tr>
<td>Babinski</td>
<td>8 (19.5)</td>
<td>7 (25.0)</td>
<td>0.587</td>
</tr>
<tr>
<td>Spasticity</td>
<td>13 (31.7)</td>
<td>13 (46.4)</td>
<td>0.215</td>
</tr>
<tr>
<td>Sensory Findings</td>
<td>18 (43.9)</td>
<td>14 (50.0)</td>
<td>0.618</td>
</tr>
<tr>
<td>Limb Ataxia</td>
<td>35 (85.4)</td>
<td>23 (82.1)</td>
<td>0.720</td>
</tr>
<tr>
<td>Parkinsonism</td>
<td>6 (14.6)</td>
<td>4 (14.3)</td>
<td>0.968</td>
</tr>
<tr>
<td>Dystonia</td>
<td>6 (14.6)</td>
<td>2 (7.1)</td>
<td>0.340</td>
</tr>
<tr>
<td>Autonomic symptoms</td>
<td>3 (7.3)</td>
<td>5 (17.9)</td>
<td>0.179</td>
</tr>
</tbody>
</table>

Values represent number (%) unless otherwise indicated
**Statistically significant at p < 0.05**
4.5.2 Neuroimaging

A comparison of the neuroimaging findings of patients with and without a family history of a similar disorder did not reveal any differences in the presence of reported cerebellar, brainstem, or cerebral atrophy (Table 14).

<table>
<thead>
<tr>
<th>Neuroimaging Finding</th>
<th>Hereditary (n = 28) n (%)</th>
<th>Sporadic (n = 27) n (%)</th>
<th>p - value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cerebellar Atrophy</td>
<td>21 (75.0)</td>
<td>22 (81.5)</td>
<td>0.561</td>
</tr>
<tr>
<td>Brainstem Atrophy</td>
<td>6 (21.4)</td>
<td>5 (18.5)</td>
<td>0.787</td>
</tr>
<tr>
<td>Cerebral Atrophy</td>
<td>4 (14.3)</td>
<td>6 (22.2)</td>
<td>0.446</td>
</tr>
<tr>
<td>Normal exam</td>
<td>6 (21.4)</td>
<td>4 (14.8)</td>
<td>0.525</td>
</tr>
</tbody>
</table>
4.6 Male vs. Female

4.6.1 Clinical Features

Of all of the clinical features collected, the only feature that differed significantly was hyperreflexia ($p = 0.019$). This was present in more of the males (69.7%) than the females (41.67%) (Table 15).

Table 15. Clinical Features Male vs. Female

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Male (n = 33)</th>
<th>Female (n = 36)</th>
<th>p – value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age of onset (Years)</td>
<td>47.2</td>
<td>45.9</td>
<td>0.747</td>
</tr>
<tr>
<td>Mean Duration of Symptoms at last visit (Years)</td>
<td>9.8</td>
<td>13.3</td>
<td>0.108</td>
</tr>
<tr>
<td>Presenting Complaint Gait</td>
<td>27 (81.8)</td>
<td>28 (77.8)</td>
<td>0.677</td>
</tr>
<tr>
<td>Dysarthria</td>
<td>26 (78.8)</td>
<td>26 (72.2)</td>
<td>0.527</td>
</tr>
<tr>
<td>Nystagmus</td>
<td>19 (57.6)</td>
<td>21 (58.3)</td>
<td>0.949</td>
</tr>
<tr>
<td>Saccadic Smooth Pursuit</td>
<td>28 (84.9)</td>
<td>25 (69.4)</td>
<td>0.130</td>
</tr>
<tr>
<td>Hyperreflexia</td>
<td>23 (69.7)</td>
<td>15 (41.7)</td>
<td>0.019**</td>
</tr>
<tr>
<td>Hyporeflexia</td>
<td>8 (24.2)</td>
<td>15 (41.7)</td>
<td>0.125</td>
</tr>
<tr>
<td>Babinski</td>
<td>8 (24.2)</td>
<td>7 (19.4)</td>
<td>0.629</td>
</tr>
<tr>
<td>Sensory Findings</td>
<td>16 (48.5)</td>
<td>16 (44.4)</td>
<td>0.737</td>
</tr>
<tr>
<td>Spasticity</td>
<td>15 (45.5)</td>
<td>11 (30.6)</td>
<td>0.202</td>
</tr>
<tr>
<td>Limb Ataxia</td>
<td>29 (87.9)</td>
<td>29 (80.6)</td>
<td>0.407</td>
</tr>
<tr>
<td>Parkinsonism</td>
<td>7 (21.2)</td>
<td>3 (8.3)</td>
<td>0.129</td>
</tr>
<tr>
<td>Dystonia</td>
<td>4 (12.1)</td>
<td>4 (11.1)</td>
<td>0.896</td>
</tr>
<tr>
<td>Autonomic symptoms</td>
<td>5 (15.2)</td>
<td>3 (8.3)</td>
<td>0.377</td>
</tr>
</tbody>
</table>

Values represent number (%) unless otherwise indicated

** Statistically significant at $p < 0.05$
4.6.2 Neuroimaging

A comparison of the neuroimaging findings of all male and female patients did not reveal any differences in the presence of reported cerebellar, brainstem, or cerebral atrophy (Table 16).

Table 16. Neuroimaging Findings Male vs. Female

<table>
<thead>
<tr>
<th>Neuroimaging Finding</th>
<th>Male (n = 28) n (%)</th>
<th>Female (n = 27) n (%)</th>
<th>p - value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cerebellar Atrophy</td>
<td>23 (82.1)</td>
<td>20 (74.07)</td>
<td>0.4689</td>
</tr>
<tr>
<td>Brainstem Atrophy</td>
<td>3 (10.7)</td>
<td>8 (29.63)</td>
<td>0.0796</td>
</tr>
<tr>
<td>Cerebral Atrophy</td>
<td>6 (21.4)</td>
<td>4 (14.81)</td>
<td>0.5249</td>
</tr>
<tr>
<td>Normal exam</td>
<td>5 (17.9)</td>
<td>5 (18.52)</td>
<td>0.9493</td>
</tr>
</tbody>
</table>

4.7 Patients Meeting Diagnostic Criteria for MSA

Using the consensus criteria one patient had possible MSA and 5 patients had probable MSA (Table 17). All of these patients were in the sporadic group (n = 26) as a positive family history excludes the diagnosis of MSA.

Table 17. Patients Meeting Diagnostic Criteria for MSA

<table>
<thead>
<tr>
<th>Criteria Applied</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Consensus – Possible</td>
<td>1 (3.8%)</td>
</tr>
<tr>
<td>Consensus – Probable</td>
<td>5 (20.2%)</td>
</tr>
</tbody>
</table>
4.8 Results of Additional Laboratory Investigations

Vitamin E levels were available for 33 of the patients and no low levels were detected.

The results of anti-endomysial antibody testing were available for 24 of the patients and none were positive.

Anti-GAD antibody testing was performed on 17 of the patients. Two were found to have elevated levels. One patient received intravenous immune-globulin therapy with no alteration of her clinical condition. The other patient did not appear to receive any specific therapy.
CHAPTER V – DISCUSSION

5.1 Distribution of the SCAs

Information about the distribution of the SCAs in a Canadian population has not yet been published. In our clinic population the most common SCA diagnosed by genetic testing is SCA3 followed by SCA2 and SCA6.

As previously discussed the frequency of the different SCAs depends on ethnic and geographic factors. The distribution of the spinocerebellar ataxias found in dominant pedigrees in other countries is summarized in table 18. Our results are most similar to that found in the United States and Germany. The differences between this study and those performed in Asian countries can be explained by the fact that the population of the city of Calgary largely consists of individuals of European descent. In the 2001 Canadian census 17.5% of the population of Calgary consisted of visible minorities (www12.statcan.ca/English/census01/products/analytic/companion/etoimm/subprovs.cfm – Accessed February 6, 2003). Changing patterns of immigration to Canada may result in an alteration of the relative frequencies of the SCAs over time.
Table 18. Distribution of the SCAs in Different Populations

<table>
<thead>
<tr>
<th>Country</th>
<th># of Families</th>
<th>SCA1</th>
<th>SCA2</th>
<th>SCA3</th>
<th>SCA6</th>
<th>SCA7</th>
<th>SCA8</th>
<th>SCA12</th>
<th>DRPLA</th>
<th>Unclassified</th>
</tr>
</thead>
<tbody>
<tr>
<td>Australia</td>
<td>88</td>
<td>16</td>
<td>6</td>
<td>12</td>
<td>17</td>
<td>2</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>47</td>
</tr>
<tr>
<td>USA</td>
<td>47</td>
<td>11</td>
<td>-</td>
<td>11</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>78</td>
</tr>
<tr>
<td>USA</td>
<td>178</td>
<td>5.6</td>
<td>15.2</td>
<td>20.8</td>
<td>15.2</td>
<td>4.5</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>38.7</td>
</tr>
<tr>
<td>USA</td>
<td>53</td>
<td>4</td>
<td>8</td>
<td>14.7</td>
<td>12</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>0</td>
<td>61.3</td>
</tr>
<tr>
<td>Germany</td>
<td>77</td>
<td>9</td>
<td>10</td>
<td>42</td>
<td>22</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>17</td>
</tr>
<tr>
<td>Italy</td>
<td>32</td>
<td>19</td>
<td>31</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>47</td>
</tr>
<tr>
<td>Italy</td>
<td>73</td>
<td>41</td>
<td>29</td>
<td>0</td>
<td>0</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>30</td>
</tr>
<tr>
<td>Spain</td>
<td>87</td>
<td>5.6</td>
<td>15.3</td>
<td>15.3</td>
<td>1.4</td>
<td>2.8</td>
<td>0</td>
<td>1.4</td>
<td>57.3</td>
<td></td>
</tr>
<tr>
<td>Netherlands (Estimated Frequencies)</td>
<td>N/A</td>
<td>6.2</td>
<td>7.1</td>
<td>28.2</td>
<td>15.0</td>
<td>7.5</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>36.0</td>
</tr>
<tr>
<td>Brazil</td>
<td>52</td>
<td>0</td>
<td>0</td>
<td>92</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>-</td>
<td>0</td>
<td>6</td>
</tr>
<tr>
<td>Portugal</td>
<td>46</td>
<td>0</td>
<td>4</td>
<td>74</td>
<td>0</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>22</td>
</tr>
<tr>
<td>Taiwan</td>
<td>74</td>
<td>5.4</td>
<td>10.8</td>
<td>47.3</td>
<td>10.8</td>
<td>2.7</td>
<td>0</td>
<td>-</td>
<td>1.4</td>
<td>21.6</td>
</tr>
<tr>
<td>China</td>
<td>85</td>
<td>4.7</td>
<td>5.9</td>
<td>48.2</td>
<td>0</td>
<td>0</td>
<td>-</td>
<td>-</td>
<td>0</td>
<td>41.2</td>
</tr>
<tr>
<td>Korea</td>
<td>32</td>
<td>6.3</td>
<td>31.3</td>
<td>28.1</td>
<td>6.3</td>
<td>3.1</td>
<td>0</td>
<td>-</td>
<td>-</td>
<td>25.0</td>
</tr>
<tr>
<td>Japan–Hokkaido</td>
<td>155</td>
<td>9.7</td>
<td>7.7</td>
<td>23.9</td>
<td>29.0</td>
<td>0</td>
<td>0</td>
<td>-</td>
<td>2.6</td>
<td>27.1</td>
</tr>
<tr>
<td>Japan–Honshu</td>
<td>117</td>
<td>24.8</td>
<td>0.8</td>
<td>23.9</td>
<td>10.3</td>
<td>1.7</td>
<td>0.8</td>
<td>0</td>
<td>14.5</td>
<td>23.1</td>
</tr>
<tr>
<td>Japan–Kinki</td>
<td>220</td>
<td>3.6</td>
<td>4.9</td>
<td>24.5</td>
<td>31.5</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>12.6</td>
<td>23</td>
</tr>
<tr>
<td>India–East</td>
<td>57</td>
<td>10.5</td>
<td>17.5</td>
<td>7.0</td>
<td>1.8</td>
<td>0</td>
<td>-</td>
<td>0</td>
<td>73.2</td>
<td></td>
</tr>
<tr>
<td>India–East &amp; North</td>
<td>39</td>
<td>7.7</td>
<td>25.6</td>
<td>5.1</td>
<td>0</td>
<td>0</td>
<td>-</td>
<td>0</td>
<td>61.5</td>
<td></td>
</tr>
<tr>
<td>This Study</td>
<td>60</td>
<td>4.8</td>
<td>14.3</td>
<td>23.8</td>
<td>9.5</td>
<td>0</td>
<td>4.8</td>
<td>-</td>
<td>0</td>
<td>38.1</td>
</tr>
</tbody>
</table>
5.2 Diagnostic Utility of Genetic Testing

Given that the majority of individuals with a positive test have a positive family history one should re-evaluate the pedigree carefully if a sporadic patient tests positive. Alternatively this type of patient might represent a new mutation.

5.2.1 Testing of Sporadic Patients

Testing of apparently sporadic cases only yielded the one positive result of a case of SCA3. The details of this patient’s family history were well documented in the chart. The patient was the youngest of eight children. The age of onset of symptoms in this patient was 22 and the expanded allele contained 80 repeats. His mother was 52 years old at the time of the onset of his symptoms but his father died of bowel cancer at age 61. His father had 6 siblings and none were known to be affected. His mother had 4 siblings and none of these individuals were known to have symptoms suggestive of a neurological disorder. The patient’s mother and siblings were all tested for SCA3 and no expansions have been found.

Several possible explanations exist for the appearance of a positive test result in an individual with a negative family history. As anticipation is a feature of most of these disorders, a positive family history may not be evident as an affected parent may have died before manifesting symptoms of the disorder. This may have been the case with our sporadic SCA3 patient. In addition, a large but normal allele or an allele in the indeterminate range might expand sufficiently to cause symptoms. The possibility of
non-paternity can always cloud pedigree analysis. Vague or subtle symptoms may not be noticed or familial contact may not be sufficient to enable the index case to realize whether similar problems exist in family members. In the case of autosomal recessive disorders such as Friedreich’s ataxia, a family history will often not be present.

While a positive result has been found in as many as 22% of sporadic patients tested for the heritable ataxias the single individual testing positive out of 26 tested in this study is similar to half of the other studies but significantly lower than some(Table 19). Our low yield may be the result of more aggressive determination of the presence of other affected family members and fewer patients being labelled as being sporadic. Overall, one can see that the testing of apparent sporadic patients results in a small but potentially important positive result rate. Testing in these individuals is important as the discovery that a patient’s disorder is genetic has significant implications for other family members.

The etiology of sporadic spinocerebellar ataxia has not been established. Possibilities include environmental factors such as toxic or infectious agents. Currently unknown recessive genetic conditions may exist. Autoimmune factors may play a role.
As previously discussed both anti-GAD antibodies and celiac disease have been associated with a cerebellar ataxia. Other autoimmune syndromes may be found in the future to produce spinocerebellar ataxias. It may be that the interplay of environmental and genetic factors will eventually be found to be responsible for this as well as other neurodegenerative disorders.
Table 19. Yield of Genetic Testing in Sporadic Patients

<table>
<thead>
<tr>
<th>Country</th>
<th># of Patients</th>
<th>SCA1</th>
<th>SCA2</th>
<th>SCA3</th>
<th>SCA6</th>
<th>SCA7</th>
<th>SCA8</th>
<th>SCA12</th>
<th>SCA17</th>
<th>FA</th>
<th>DRPLA</th>
<th>Overall Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>USA</td>
<td>134</td>
<td>0</td>
<td>1.5</td>
<td>0.7</td>
<td>1.5</td>
<td>0.7</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>5.2</td>
<td>-</td>
<td>9.6</td>
</tr>
<tr>
<td>USA</td>
<td>35</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>0</td>
</tr>
<tr>
<td>Germany</td>
<td>124</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>7</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>-</td>
<td>8</td>
<td>-</td>
<td>18</td>
</tr>
<tr>
<td>Germany</td>
<td>112</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>6</td>
<td>-</td>
<td>0</td>
<td>-</td>
<td>0</td>
<td>4</td>
<td>-</td>
<td>13</td>
</tr>
<tr>
<td>Italy</td>
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<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1.9</td>
<td>0</td>
<td>-</td>
<td>0</td>
<td>-</td>
<td>1.9</td>
</tr>
<tr>
<td>Spain</td>
<td>60</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>1.7</td>
<td>0</td>
<td>1.7</td>
</tr>
<tr>
<td>Brazil</td>
<td>14</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>7.1</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>0</td>
<td>7.1</td>
</tr>
<tr>
<td>Japan</td>
<td>143</td>
<td>0.5</td>
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<td>1.8</td>
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5.2.2 Patients with Unclear but Positive Family Histories

Often a clinician may find it difficult to accurately classify the patient’s family history. This may occur because the patient knows few details of family members’ medical problems. Some individuals may carry a potentially inaccurate diagnosis such as multiple sclerosis. Vague complaints may have been attributed correctly or incorrectly to another disorder such as back problems or old age.

In this series, 1 of 9 patients with an unclear yet positive family history was found to have an expanded allele at the SCA6 locus. It was not certain that this individual’s family history represented a dominant disorder as parent to child transmission was not clearly apparent. While he did have 2 of 8 older sisters with symptoms, his mother died at age 89 with no apparent medical problems and his father died at age 85 and only had been noted by the patient to have a bit of a limp. Ignoring the father’s symptoms the pedigree may have been interpreted as autosomal recessive but if the limp is considered significant then one would have to assign an autosomal dominant inheritance. As was the case with the sporadic patient who tested positive for SCA3, the tendency for the nucleotide repeat disorders to expand in successive generations was likely a significant factor in this patient’s development of the disorder even though there was not clear parental involvement.

The importance of detailed family histories should be emphasized in cases of progressive neurological disorders. It is also important to personally examine other family members whenever possible.
5.3 **The Fragile X Premutation Tremor/Ataxia Syndrome**

While no FMR1 premutations were found in our SCA patient population there has been one other study which looked for its presence in a group of patients referred with SCA. Macpherson et al. tested 59 SCA patients who had tested negative for SCA types 1, 2, 3, 6, and 7. They found 3 with repeats in the premutation range. One of these patients had onset of ataxia at age 10. Another group reported testing for the FMR1 premutation in 9 males and 4 females with the ataxic form of multiple system atrophy. While they did not find any repeats greater than 50, they felt that there was an excess of repeats greater than 40. The role that this syndrome plays in patients with SCA should be investigated in a larger series of patients.

5.4 **Heterozygosity for the Friedreich's Ataxia Expansion**

One patient in the sample was found to be heterozygous for the Friedreich’s ataxia GAA expansion. Sequencing of the coding region of the normal sized allele was performed in this individual as some patients with Friedreich’s ataxia are compound heterozygotes with an expansion on one allele and a point mutation on the other. No mutations were found in the normal sized allele of this patient and the finding of the single expanded allele in this case was not thought to be significant. Given that the carrier frequency for the FA expansion is approximately 1 in 90, the appearance of 1 heterozygote in a sample of this size is appropriate.
5.5 Parent to Child Transmission in Friedreich's Ataxia

One of the two patients found to have Friedreich's ataxia was felt by the assessing movement disorders clinic physician to have an autosomal dominant disorder. The autosomal dominant inheritance was suggested by the presence of parent to child transmission involving the paternal grandfather to a paternal aunt and uncle. All these individuals had an ataxia but specific clinical and laboratory information was not available. In addition, the patient had a maternal cousin who had a diagnosis of Friedreich’s Ataxia although again there was no documentation available to support this. The patient's parents were described as being normal.

The appearance of Friedreich’s Ataxia in two successive generations has been previously described. This occurs as a result of an affected homozygous individual having children with a heterozygous carrier.182,183

5.6 Friedreich’s Ataxia Presenting in Adulthood

While patients with Friedreich’s ataxia usually present during childhood, onset of symptoms has been described to occur in the adult age group.123-126 The oldest onset of symptoms published is 51 years.127 The paper by Schöls et al looked at the incidence of positive test results for the SCAs as well as Friedrich’s ataxia. Even though the patients who had a typical Friedrich ataxia phenotype were excluded, 10 of 124 patients (8%) were homozygous for the GAA repeat expansion in Friedrich’s ataxia. These patients all had onset of symptoms under age 40.170
Two patients in the Calgary clinic were found to have Friedreich's ataxia. One patient had an apparently autosomal dominant family history while the other had a pedigree consistent with an autosomal recessive pattern of inheritance. The ages of onset in these two individuals was 21 and 22 years old. This was substantially younger than the overall mean age of onset in the clinic's ataxia patients of 46.5 years. Testing for Friedreich's ataxia in adult onset patients appears to be appropriate especially if the age of onset is younger.

5.7 Clinical Features of the Genetically Diagnosed SCAs

The clinical spectrum of the genetically identified SCAs is quite broad. Classification using the scheme proposed by Harding (1993) cannot adequately help in making a clinical diagnosis of one of the genetic disorders with the exception of ADCA II as the only entity currently within that category is SCA7. When taken as a group, the individuals with a specific SCA may appear to have a pattern of findings but, given the amount of overlap that exists and the great variability that occurs even within families, ordering a broad SCA genetic screen may be the most practical means of evaluating these patients. The only circumstance where one can be more focussed is when a family member already has a genetically proven diagnosis.
The number of patients in this study within each of the different genetically confirmed disorders was not significantly large enough to undertake analysis of clinical features which may differentiate one disorder from another.

5.8 Hereditary vs. Sporadic

Sporadic patients accounted for 37.7% of our sample. When comparisons were made between those patients with and without positive family histories a few statistically significant differences were observed. While there was no difference in age of onset, duration of disease symptoms, or gender, the clinical variables dysarthria, nystagmus, and hyperreflexia did differ between sporadic and hereditary patients. These differences are not easily explained. This is likely a spurious finding within the study sample and probably does not represent a clinically significant difference. Studies with larger sample sizes are required to confirm the statistically significant differences observed in the present study. Not only is the phenotype of the numerous genetically defined SCAs very broad but sporadic cases also did not appear to share a consistent clinical pattern.

5.9 Male vs. Female

Analysis looking for differences in the clinical features of male versus female patients failed to reveal any clear sex effects. While there was a statistically significant difference of an increased proportion of males with hyperreflexia the clinical relevance of this finding is not apparent.
5.10 MSA

Of our sporadic patients, 6/26 (23.1%) met criteria for probable (20.2%) or possible (3.8%) MSA. This is similar to the findings of Abele et al (2002) who found that 29% of their sporadic patients met criteria for MSA using the Consensus criteria.\textsuperscript{171}

By definition MSA is a sporadic disorder. None of our patients meeting criteria for MSA were found to carry any of the SCA expansions. Schols et al tested 20 MSA patients for SCA types 1, 2, 3, 6, 7, 8, and 12 and did not find any positive tests.\textsuperscript{170} Bandmann et al did not find the SCA1 or SCA3 mutations in 80 patients with MSA.\textsuperscript{184} Our findings are consistent with these.

5.11 Alternate presentations of SCA2

Not included in the above analysis are 2 individuals from the family described by Furtado et al.\textsuperscript{49} These individuals presented with a levodopa responsive parkinsonian syndrome rather than an ataxia. Other reports of similar SCA2 phenotypes exist.\textsuperscript{47, 48} Given that there may be a small but significant number of patients who carry the SCA2 expansion who manifest their illness with parkinsonism or other non-ataxic problems, the specific prevalence of SCA2 in the population may be higher than this study and other studies have suggested.
5.12 Limitations

This study was subspecialty clinic based rather than population based. Comments about the prevalence of these disorders in a geographically defined population cannot be made. It is likely that not all patients with a spinocerebellar ataxia are referred to the University of Calgary Movement Disorders Clinic. Some may be misdiagnosed with another disorder and not referred to our clinic. One must also consider the possibility that those patients who are not sent may differ in terms of clinical characteristics. They may have milder symptoms which may be mislabelled as being part of the normal aging process. This might occur more commonly in individuals without clear family histories of a similar disorder.

One may be able to get an indirect measure of the relative frequencies of the trinucleotide repeat diseases in a population by looking at the distribution of allele size for the different genes. There is some evidence that the frequency of the CAG expansion diseases in different populations is related to the frequencies of alleles that are large but still in the normal range. Takano et al (1998) found that the relative prevalence of SCA3, SCA6, and DRPLA was higher in Japanese than in Caucasian pedigrees. This correlated with their finding that the frequency of large normal alleles for these disorders were also much higher in the Japanese than in Caucasian populations.185

Retrospective studies have inherent limitations which are unavoidable. During data collection a clinical characteristic was only described as present if it was mentioned in the clinic note. This may underestimate the presence of certain features. As the period
of follow-up of these patients lengthens, the possibility exists that subsequent physical examinations may be less complete than the initial one and a new finding may be missed, especially if the patient denied any new symptoms. Ideally, in a prospective study, there would be a standard means of documenting the physical examination. A rating scale for patients with spinocerebellar ataxias does exist although it has not yet been validated.\textsuperscript{186}

The age of onset of symptoms is a variable which is prone to error. For many of the patients the symptoms had been present for a number of years before their appearance in our clinic and patient recall may not have been accurate. Additionally the true onset of symptoms may not have been clearly noted by the patient or their families. Physical examination may reveal that an individual is more significantly affected than they believe and the diagnosis of a possible hereditary disorder in a family member might result in an individual to seek medical attention earlier than he/she otherwise would have.

Ideally, information regarding ethnic background would have been collected but this information was often not clear from the clinic notes that served as the basis for data collection.

The neuroimaging should have been examined directly rather than relying solely on the official radiologist report. A consistent assessment by a radiologist with expertise in neuroradiology may have revealed additional abnormalities or interpreted more of the examinations as being within normal limits.
Overall, the sample size was very small, making comparisons between groups difficult. In addition, this study included only a single Canadian centre and results might differ significantly in other parts of this country.

5.13 Future Possibilities

Since the prevalence of these disorders is quite low further research is best undertaken through prospective collaboration with other centres.

A number of autosomal dominant pedigrees that lack a specific genetic diagnosis have been identified. One could search for linkage to the other numbered SCAs for which we have not been able to test. This could provide further clinical information and might assist in defining the specific genetic defect. Alternatively yet another SCA locus might be identified.

A population of patients has been identified in our clinic in which clinical trials may be performed to attempt to alter the course of the illness. At present no therapy exists which is known to alter the course of the disorder. Management currently consists of measures directed at specific symptoms such as dysphagia and spasticity as well as the provision of mobility aids such as walkers and wheelchairs.

It is now clear that some potentially important laboratory investigations may have not been performed in all patients. Vitamin E and anti-endomysial test results were only
available for 33 and 24 patients respectively. Only 17 patients had anti-GAD antibodies analyzed. Since both celiac disease and ataxia with vitamin E deficiency are potentially treatable, testing, especially of the sporadic cases, may be warranted. In terms of genetic testing, DRPLA testing could be performed on the remainder of the group to ensure that no cases exist. Now that these missing tests have been conveniently identified it is relatively simple to go back and order these investigations as appropriate. Although the tests are not available at the Molecular Genetics Laboratory at the Alberta Children’s Hospital in Calgary, testing is commercially available for SCA10, SCA12, and SCA17.
CHAPTER VI CONCLUSION

In the Calgary Movement Disorders Clinic the most commonly diagnosed autosomal dominant spinocerebellar ataxia is SCA3. Nearly 70% of autosomal dominant ataxia pedigrees can be given a specific genetic diagnosis using currently available testing methods. A patient with an unclear but positive family history may also obtain a positive test result. The yield of testing sporadic patients is low but may provide useful information for the patient and his or her family. Neither DRPLA nor the fragile X tremor/ataxia syndrome was identified in our SCA patient population.
CHAPTER VII – REFERENCES


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CHAPTER VIII - Appendices

Appendix 1 - MSA Consensus criteria

Table 1 Clinical domains, features, and criteria used in the diagnosis of multiple system atrophy (MSA) (a feature [A] is a characteristic of the disease and a criterion [B] is a defining feature or composite of features required for diagnosis)

I. Autonomic and urinary dysfunction
   A. Autonomic and urinary features
      1. Orthostatic hypotension (by 20 mm Hg systolic and 10 mm Hg diastolic)
      2. Urinary incontinence or incomplete bladder emptying
   B. Criterion for autonomic failure or urinary dysfunction in MSA
      Orthostatic fall in blood pressure (by 30 mm Hg systolic or 15 mm Hg diastolic) or urinary incontinence (persistent, involuntary partial or total bladder emptying, accompanied by erectile dysfunction in men) or both

II. Parkinsonism
   A. Parkinsonian features
      1. Bradykinesia (slowness of voluntary movement with progressive reduction in speed and amplitude during repetitive actions)
      2. Rigidity
      3. Postural instability (not caused by primary visual, vestibular, cerebellar, or proprioceptive dysfunction)
      4. Tremor (postural, resting or both)
   B. Criterion for parkinsonism in MSA
      Bradykinesia plus at least one of items 2 to 4

III. Cerebellar dysfunction
   A. Cerebellar features
      1. Gait ataxia (wide-based stance with steps of irregular length and direction)
      2. Ataxic dysarthria
      3. Limb ataxia
      4. Sustained gaze-evoked nystagmus
   B. Criterion for cerebellar dysfunction in MSA
      Gait ataxia plus at least one of items 2 to 4

IV. Corticospinal tract dysfunction
   A. Corticospinal tract features
      1. Extensor plantar responses with hyperreflexia
   B. Corticospinal tract dysfunction in MSA: no corticospinal tract features are used in defining the diagnosis of MSA
Table 2 Diagnostic category of MSA (the features and criteria for each clinical domain are shown in table 1)

I. Possible MSA: one criterion plus two features from separate other domains. When the criterion is parkinsonism, a poor levodopa response qualifies as one feature (hence only one additional feature is required).

II. Probable MSA: criterion for autonomic failure/urinary dysfunction plus poorly levodopa responsive parkinsonism or cerebellar dysfunction.

III. Definite MSA: pathologically confirmed by the presence of high-density glial cytoplasmic inclusions in association with a combination of degenerative changes in the nigrostriatal and olivopontocerebellar pathways.

Table 3 Exclusion criteria for the diagnosis of MSA

I. History
   Symptomatic onset under 30 years of age
   Family history of a similar disorder
   Systemic disease or other identifiable causes for features listed in table 1
   Hallucinations unrelated to medication

II. Physical examination
   DSM criteria for dementia
   Prominent slowing of vertical saccades or vertical supranuclear gaze palsy
   Evidence of focal cortical dysfunction such as aphasia, alien limb syndrome, and parietal dysfunction

III. Laboratory investigation
   Metabolic, molecular, genetic, and imaging evidence of an alternative cause of features listed in table 1
Appendix 2 – Pedigrees

Autosomal Dominant Families

SCA1 – Pedigree A

SCA2 – Pedigree A
SCA2 – Pedigree B

SCA2 – Pedigree C

Diagnosis = SCA  Diagnosis = Tremor

Diagnosis = SCA
SCA3 – Pedigree A

SCA3 – Pedigree B
SCA3 – Pedigree C

SCA3 – Pedigree D

Diagnosis = SCA

Diagnosis = SCA
SCA3 – Pedigree E

SCA6 – Pedigree A
SCA6 – Pedigree B

SCA8 – Pedigree A
Pseudo-dominant Friedreich’s Ataxia Family

![Genetic Diagram]

Diagnosis = SCA
Autosomal Dominant Tests Negative – Pedigree A

Autosomal Dominant Tests Negative – Pedigree B

Diagnosis = SCA
Autosomal Dominant Tests Negative – Pedigree C

Autosomal Dominant Tests Negative – Pedigree D
Autosomal Dominant Tests Negative – Pedigree E

Autosomal Dominant Tests Negative – Pedigree F

Diagnosis = SCA

Diagnosis = Parkinson's Disease

Diagnosis = SCA

Diagnosis = Multiple Sclerosis
Autosomal Dominant Tests Negative – Pedigree G

[Pedigree diagram showing genetic relationships and diagnosis]

Diagnosis = SCA

Autosomal Dominant Tests Negative – Pedigree H

[Pedigree diagram showing genetic relationships and diagnosis]

Diagnosis = SCA
Autosomal Recessive Pedigrees

Autosomal Recessive Friedreich’s Ataxia – Pedigree A

Diagnosis = FA

Autosomal Recessive Tests Negative – Pedigree A

Diagnosis = SCA
Positive But Undefined Family Histories

Positive But Undefined Family Histories – SCA6 Pedigree A

- Diagnosis = SCA
- Diagnosis = Limp
- Diagnosis = Possible Balance Problems
Positive But Undefined Family Histories – Tests Negative – Pedigree A

Positive But Undefined Family Histories – Tests Negative – Pedigree B
Positive But Undefined Family Histories – Tests Negative – Pedigree C

[Pedigree diagram]

- Diagnosis = SCA
- Diagnosis = Dementia
- Diagnosis = Possible Balance Problems

Positive But Undefined Family Histories – Tests Negative – Pedigree D

[Pedigree diagram]

- Diagnosis = SCA
- Diagnosis = Balance Problems
Positive But Undefined Family Histories – Tests Negative – Pedigree E

Positive But Undefined Family Histories – Tests Negative – Pedigree F
Positive But Undefined Family Histories – Tests Negative – Pedigree G

Diagnosis = SCA

Diagnosis = Dementia

Positive But Undefined Family Histories – Tests Negative – Pedigree H

Diagnosis = SCA

Diagnosis = Multiple Sclerosis

Diagnosis = Tremor