

Adult Onset Spinocerebellar Ataxia in a Canadian Movement Disorders Clinic

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ABSTRACT: Background: The spinocerebellar ataxias (SCAs) are a genetically and clinically heterogeneous group of neurodegenerative disorders. Relative frequencies vary within different ethnic groups and geographical locations. **Objectives:** 1) To determine the frequencies of hereditary and sporadic adult onset SCAs in the Movement Disorders population; 2) to assess if the fragile X mental retardation gene 1 (FMR1) premutation is found in this population. **Methods:** A retrospective chart review of individuals with a diagnosis of adult onset SCA was carried out. Testing for SCA types 1, 2, 3, 6, 7, and 8, Dentatorubral-pallidolusian atrophy (DRPLA), Friedreich ataxia and the FMR1 expansion was performed. **Results:** A total of 69 patients in 60 families were identified. Twenty-one (35%) of the families displayed autosomal dominant and two (3.3%) showed autosomal recessive (AR) pattern of inheritance. A positive but undefined family history was noted in nine (15%). The disorder appeared sporadic in 26 patients (43.3%). In the AD families, the most common mutation was SCA3 (23.8%) followed by SCA2 (14.3%) and SCA6 (14.3%). The SCA1 and SCA8 were each identified in 4.8%. FA was found in a pseudodominant pedigree, and one autosomal recessive pedigree. One sporadic patient had a positive test (SCA3). Dentatorubral-pallidolusian atrophy and FMR1 testing was negative. **Conclusion:** A positive family history was present in 53.3% of our adult onset SCA patients. A specific genetic diagnosis could be given in 61.9% of dominant pedigrees with SCA3 being the most common mutation, followed by SCA2 and SCA6. The yield in sporadic cases was low. The fragile X premutation was not found to be responsible for SCA.

RÉSUMÉ: Ataxie spinocérébelleuse débutant chez l'adulte dans une clinique de désordres du mouvement au Canada. Contexte: Les ataxies spinocérébelleuses (ASCs) constituent un groupe hétérogène de maladies neurodégénératives tant au point de vue génétique qu'au point de vue clinique. Leur fréquence relative est très variable selon le groupe ethnique et le lieu géographique. **Objectifs:** 1) déterminer la fréquence d'ASCs héréditaires et sporadiques débutant chez l'adulte chez des patients fréquentant une clinique de désordres du mouvement ; 2) évaluer si on retrouve chez ces patients des prémutations du gène FMR1 causant le syndrome de retard mental du X fragile. **Méthodes:** Nous avons procédé à une revue rétrospective de dossiers de patients chez qui un diagnostic d'ASC de l'adulte a été posé. Des tests de biologie moléculaire ont été faits pour détecter des anomalies des gènes responsables de l'ASC de type 1, 2, 3, 6, 7 et 8, de l'atrophie dentato-rubro-pallido-lusienne (ADRPL), de l'ataxie de Friedrich (AF) ainsi que l'expansion de FMR1. **Résultats:** 69 patients appartenant à 60 familles différentes ont été identifiés. Chez 21 familles (35%), l'hérédité était autosomique dominante (AD) et chez 2 (3,3%) l'hérédité était autosomique récessive (AR). Une histoire familiale positive mal définie était présente chez 9 familles (15%). La maladie semblait sporadique chez 26 patients (43,3%). Chez les familles où l'hérédité était AD, la mutation la plus fréquente était une mutation du gène ASC3 (23,8%) suivie d'ASC2 (14,3%) et d'ASC6 (14,3%). Une mutation du gène ASC1 et ASC8 a été identifiée chez 4,8% des patients. Une mutation du gène de l'AF a été identifiée dans un pedigree où la maladie était pseudo dominante et dans un où la maladie était AR. Chez un cas sporadique on a trouvé une mutation du gène ASC3. Les tests pour l'ADRPL et le FMR1 étaient négatif. **Conclusion:** Une histoire familiale positive était présente chez 53,3% des patients atteints d'ASC adulte. Un diagnostic génétique spécifique a pu être établi chez 61,9% des pedigrees où l'hérédité était dominante et une mutation du gène ASC3 était l'anomalie la plus fréquente, suivie d'ASC2 et d'ASC6. Le rendement était faible chez les cas sporadiques. La prémutation du gène responsable du syndrome du X fragile n'était pas responsable de l'ASC chez nos cas.

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The spinocerebellar ataxias (SCAs) 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 degenerations 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

The dominantly inherited SCAs were classified in the past according to a scheme suggested by Harding.¹ In this system, the autosomal dominant cerebellar ataxias (ADCA) were separated clinically into three types. In addition to cerebellar ataxia, ADCA I patients had variable degrees of dementia, supranuclear

ophthalmoplegia, optic atrophy, and extrapyramidal features. Patients classified as having ADCA Type II developed pigmentary retinal degeneration which could precede the development of the ataxia. Autosomal dominant cerebellar

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Table 1: Summary of the Dominantly Inherited SCAs

Name	Locus	Clinical Features in Addition to Gait and Limb Ataxia
SCA1 ^{2, 89, 90}	6p23	Oculomotor defects, muscle weakness, decreased vibration sense, pyramidal signs
SCA2 ^{3-5, 52, 68-70, 91, 92}	12q23-q24.1	Slow saccades, hypotonia, Parkinsonism
SCA3 ^{6, 93-97}	14q24.3-q32	Type I – pyramidal and extrapyramidal findings, progressive external ophthalmoplegia and minor cerebellar deficits Type II – cerebellar and pyramidal deficits, without extrapyramidal signs with or without progressive external ophthalmoplegia Type III – distal symmetrical muscle atrophy with cerebellar findings with or without progressive external ophthalmoplegia and pyramidal signs Type IV – Parkinsonism and peripheral neuropathy
SCA4 ^{20, 21}	16q22.1	Two families – one with sensory neuropathy and the other with dysarthria and no sensory neuropathy
SCA5 ²²	11p11-q11	Predominantly cerebellar. Very slow progression
SCA6 ⁷	19p13	Predominantly cerebellar
SCA7 ^{8, 9, 98}	3p21.1-p12	Pigmentary retinopathy
SCA8 ¹⁵	13q21	Spasticity and decreased vibration sense. Controversial
SCA9 ³⁷	Reserved	
SCA10 ^{99, 100}	22q13	Seizures in 20 to 100%
SCA11 ²³	15q14-q21.3	Predominantly cerebellar
SCA12 ¹³	5q31-q33	Early upper extremity tremor and late dementia
SCA13 ²⁴	19q13.3-q13.4	Childhood onset. Mental retardation
SCA14 ^{25, 26}	19q13.4-qter	Predominantly cerebellar but axial myoclonus if younger age of onset
SCA15 ^{34, 101}	3p26.1-p25.3	Predominantly cerebellar. Postural/action tremor. Very slow progression
SCA16 ²⁷	8q22.1-q24.1	Predominantly cerebellar with head tremor
SCA17 ^{10, 11}	6q27	Intellectual deterioration
SCA18 ²⁸	7q22-q32	Sensory loss, pyramidal tract signs, muscle weakness
SCA19 ^{29, 102}	1p21-q21	Mild ataxia with cognitive impairment, myoclonus, and a low frequency postural tremor
SCA20 ³³	11p13-q11	Palatal tremor, dysphonia, and dentate nucleus calcification
SCA21 ^{30, 103}	7p21.3-p15.1	Hyporeflexia, postural tremor, parkinsonism, cognitive impairment. Extraocular movements generally normal
SCA22 ³¹	1p21-q23	Predominantly cerebellar with hyporeflexia. Slow progression
SCA23 ³⁵	20p13-p12.2	No published information available
SCA24 ³⁶	None	Likely recessive. Saccadic intrusions, increased saccadic speed, sensory neuropathy, and myoclonus
SCA25 ³²	2p21-p13	Sensory neuropathy

ataxias Type III was described as a relatively pure cerebellar syndrome.

At present, classification of the SCAs is largely based on genetic mutations rather than clinically defined syndromes. A summary of the chromosomal loci and clinical characteristics of the currently described SCAs is presented in Table 1. In the SCAs where a genetic defect has been identified, the abnormality has thus far involved expansion of unstable repeat sequences of deoxyribonucleic acid (DNA). The most common 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 17.²⁻¹¹ Dentatorubral-pallidolusian atrophy (DRPLA) is another autosomal dominant ataxic disorder that has been found to result from expansion of a polyglutamine sequence.¹²

Expansion of trinucleotide repeats in non-coding regions of a gene may also lead to disease. Although the genetic abnormality

in SCA12 is a CAG repeat, it appears to occur outside of the translated portion of the gene so a polyglutamine tract is not created.¹³ Friedreich ataxia (FA) is caused by an intronic GAA triplet repeat expansion.¹⁴ SCA8 is thought to be the result of a non-coding cytosine/thymine/guanine (CTG) expansion, although the significance of the expansion has been questioned.¹⁵⁻¹⁸ In the case of SCA10 the expansion is of an ATTCT (adenine/thymine/thymine/cytosine/thymine) pentanucleotide repeat.¹⁹ The pathologic repeat numbers in these disorders are generally much larger when it affects the non-coding, rather than the coding regions.

For many dominantly inherited SCA families a chromosomal locus for the disorder has been described but a specific genetic defect has not yet been discovered. This is the case for SCA types 4, 5, 11, 13 to 16, 18 to 22 and 25.²⁰⁻³⁴ The human genome organisation (HUGO) Gene Nomenclature Committee website lists a locus for SCA23 but without clinical data.³⁵ The disorder

currently labelled SCA24 appears to be recessive.³⁶ The label SCA9 is currently reserved.³⁷

As is common with most genetic disorders, the relative frequencies of the SCAs vary within different populations. To date, there is no published data regarding the distribution of the SCAs or diagnostic yield of SCA testing in a Canadian population; this paper aims to provide such information.

Recently, a syndrome consisting of tremor, cerebellar dysfunction, parkinsonism, and cognitive decline associated with the fragile X premutation has been described. Fragile X syndrome is caused by an expansion of CGG repeats greater than 200 in the fragile X mental retardation 1 gene (FMR1).³⁸ Repeats falling within the range of 50 to 200 repeats are considered to be premutations and individuals in subsequent generations are at risk of further expansion. The prevalence of the premutation is approximately one in 700 males and one in 250 females.³⁹ The initial report of the fragile X tremor/ataxia premutation syndrome consisted of case reports of five men over the age of 57 who were all grandfathers of children with fragile X syndrome.⁴⁰ Several other reports have been published describing clinical, radiological, and pathological findings of other individuals with this disorder. Common neuroradiological findings 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.⁴¹⁻⁴⁵ The diagnostic utility of testing for this disorder in patients presenting with SCA has not yet been established.

The main objective of the present study was to determine the distribution of the hereditary spinocerebellar ataxias in patients who are followed at the University of Calgary Movement Disorders Clinic. The proportion of patients who had a family history suggestive of other affected individuals with a similar disorder was examined and the yield of genetic testing in patients with and without a positive family history was determined. In addition the SCA group was assessed for the frequency of the FMR1 premutation.

METHODS

Patients were identified by a search of the University of Calgary Movement Disorders Clinic patient registry for the diagnoses of spinocerebellar ataxia, Friedreich ataxia (FA), and multiple system atrophy–olivopontocerebellar atrophy. 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.

Patients who had been seen between January 1, 1996 and 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.

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.

Genetic testing for SCA1, SCA2, SCA3, SCA6, SCA7, SCA8, FA, DRPLA and the FMR1 expansion was performed in the Molecular Diagnostics Laboratory of the Alberta Children's Hospital in Calgary, Alberta using standard testing methods as previously published.^{2,3,6-9,12-15,38} A test was labelled positive if a repeat expansion in the pathological range was discovered. The number of tests performed in each of the families varied because not all of these tests became available at the same time. Testing using newly offered tests was only carried out if prior testing did not provide a specific genetic diagnosis.

Testing for DRPLA was part of the SCA assessment in our clinic initially but, as all patients were negative and the yield in non-Asian populations has been shown to be negligible, we have stopped doing this on a regular basis.^{46,47}

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 parent to child transmission. 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. Relatives of the index cases were examined if available and attempts were made to obtain their medical records.

RESULTS

A total of 69 patients in 60 families were identified as having an adult onset spinocerebellar ataxia. 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 one to 44 years.

Thirty-two (53.3%) of individuals studied had a positive family history with the majority (35%) being autosomal dominant (see Table 2 for full description). Age of onset in the autosomal dominant and sporadic groups was twice that of the autosomal recessive group.

The results of genetic testing by family history classification are summarized in Table 3. The most common mutation in the autosomal dominant families was SCA3 (five families – 23.8%). This was followed by SCA2 (three families – 14.3%) and SCA6 (two families – 9.5%). The SCA1 and SCA8 expansions were only identified in one family (4.8%) each.

The DRPLA testing was done on 21 of the families and all results were negative.

Of the 44 families without a genetic diagnosis, two did not

Table 2: Family History Category Among Study Families

Family History	n (%)	Mean Age of Symptom Onset (Years)
Autosomal Dominant	21 (35.0)	43.2(range = 18-72)
Autosomal Recessive	2 (3.3)	28.3(range = 22-35)
Positive but Undefined	9 (15.0)	54.6(range = 42-64)
Sporadic	26 (43.3)	49.4(range = 20-85)
Adopted	2 (3.3)	47.5(range = 30-65)
Total	60 (100)	46.5 (range = 18-85)

have DNA available for FMR1 testing. The index cases of the remaining 42 (22 males and 20 females) were tested for the FMR1 premutation. No premutation or pathological range expansions of the FMR1 gene were found. The highest number of repeats found was 38.

Although the family history was suggestive of a dominant disorder, one patient was found to have FA. A patient in one of the two autosomal recessive appearing families tested positive for FA.

One of nine individuals (11.1%) with a positive but undefined family history tested positive for SCA6. Two of his eight sisters also had an ataxic syndrome. 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 injury. As it was unclear whether he was affected the undefined category was chosen. It can be postulated that he was indeed affected.

Only one of the 26 (3.8%) sporadic patients had a positive test. This individual tested positive for SCA3. The age of onset of symptoms was 22 years and the expanded allele contained 80 repeats. His father died of cancer at age 61. His mother and seven siblings were all asymptomatic, and all tested negative for SCA3. None of his father's six siblings were known to be similarly affected. His mother had four siblings and none of them

had any symptoms suggestive of a neurological disorder. It is suspected that this represented a new mutation, although paternity testing was not done.

One patient was found to be heterozygous for the Friedreich ataxia GAA expansion. Symptoms of gait dysfunction began at age 66 and other clinical features included dysarthria, nystagmus, saccadic smooth pursuit, hyporeflexia, as well symptoms of autonomic dysfunction. Sensory abnormalities were not noted. Sequencing of the coding region of the normal sized allele was performed in this individual as some patients with Friedreich ataxia are compound heterozygotes with an expansion on one allele and a point mutation on the other.⁴⁸ No mutations were found in the normal sized allele of this patient. The normal sized allele was sequenced and no mutations were identified in the coding regions. The expansion was felt to be an incidental finding.

A positive test result was found in 61.9% (13/21) of autosomal dominant pedigrees, one out of two autosomal recessive pedigrees, and one of nine patients with positive but undefined family histories. Of those patients who lacked a family history of a similar disorder, only 1/26 (3.8%) was found to have a positive genetic test. Neither of the two adopted patients had a positive test (Table 3).

The clinical features of all the patients separated by diagnosis

Table 3: Results of Genetic Testing – Families (%)

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

AD = Autosomal Dominant AR = Autosomal Recessive

Table 4: Clinical Features of Study Patients Separated by Diagnosis

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

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

Table 5: Distribution of the SCAs in Dominant Pedigrees of Different Populations

Country	# of Families	Frequency %								
		SCA1	SCA2	SCA3	SCA6	SCA7	SCA8	SCA12	DRPLA	Unclassified
Australia ⁴⁹	88	16	6	12	17	2	-	-	-	47
USA ⁵⁰	178	5.6	15.2	20.8	15.2	4.5	-	-	-	38.7
USA ^{51, 52}	53	4	8	14.7	12	-	-	-	0	61.3
Germany ⁵³	77	9	10	42	22	-	-	-	-	17
Italy ⁵⁴	32	19	31	3	0	0	0	0	-	47
Italy ⁵⁵	73	41	29	0	0	-	-	-	-	30
Spain ⁵⁶	87	5.6	15.3	15.3	1.4	2.8	-	-	1.4	57.3
Brazil ⁵⁷	52	0	0	92	0	2	0	-	0	6
Portugal ⁵⁸	46	0	4	74	0	-	-	-	-	22
Taiwan ⁵⁹	74	5.4	10.8	47.3	10.8	2.7	0	-	1.4	21.6
China ⁶⁰	85	4.7	5.9	48.2	0	0	-	-	0	41.2
Korea ⁶¹	32	6.3	31.3	28.1	6.3	3.1	-	-	-	25.0
Japan-Hokkaido ⁶²	155	9.7	7.7	23.9	29.0	0	0	-	2.6	27.1
Japan-Honshu ⁶³	117	24.8	0.8	23.9	10.3	1.7	0.8	-	14.5	23.1
Japan-Kinki ⁶⁴	220	3.5	4.9	24.5	31.5	0	0	0	12.6	23
India-East ⁶⁵	57	10.5	17.5	7.0	1.8	0	-	-	0	73.2
India-East & North ⁶⁶	39	7.7	25.6	5.1	0	0	0	-	0	61.5
This Study	21	4.8	14.3	23.8	9.5	0	4.8	-	0	38.1

are summarized in Table 4. All patients had an ataxic gait. Considerable variability existed between, as well as within, each of the diagnostic categories. Dysarthria, extraocular movement abnormalities, and reflex changes were commonly found in all groups. Parkinsonism, dystonia, Babinski, and autonomic symptoms were uncommon. A much younger age of onset of symptoms was noted in the two patients diagnosed with Friedreich ataxia.

DISCUSSION

The distribution of the spinocerebellar ataxias found in dominant pedigrees in other countries is summarized in Table 5. In the University of Calgary Movement Disorders Clinic population the most common SCA diagnosed by genetic testing is SCA3 followed by SCA2 and SCA6. The frequency of the different SCAs depends on ethnic and geographic factors. The finding that this genetic profile is most similar to that found in the United States and Germany is not surprising given that the population of southern Alberta is largely of European descent.⁴⁹⁻⁶⁶ In the 2001 Canadian census 17.5% of the population of Calgary consisted of visible minorities.⁶⁷ Changing patterns of immigration to Canada may result in an alteration of the relative frequencies of the SCAs over time.

Not included in the above analysis are two brothers followed in this clinic from the family described by Furtado et al (2002).⁶⁸ These individuals presented with a levodopa responsive parkinsonian syndrome rather than an ataxia and were subsequently found to have the SCA2 mutation. Other reports of similar parkinsonian SCA2 phenotypes exist.^{69,70} 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 and other studies have suggested.

Just over half of our SCA patients have positive family histories and most of these pedigrees are autosomal dominant. The dominant spinocerebellar ataxias have rapidly expanded from disorders classified into a handful of clinical groups to 20 or more separate genetic entities. Even though testing is only available for a few of these disorders, current testing was able to provide a genetic diagnosis in 61.9% of the dominant pedigrees in our clinic.

While some dominant pedigrees may be easily apparent, a clinician may find that it is difficult to accurately classify the patient's family history in other cases. This may occur because the patient knows few details of family members' medical problems. Vague complaints may have been attributed correctly or incorrectly to another disorder such as back problems or old age. The tendency for the nucleotide repeat disorders to expand in successive generations with earlier age of onset and more severe symptoms may also result in a lack of evidence of clear parental involvement. The importance of examining all available family members, deemed clinically affected or unaffected, in order to determine who else is truly affected cannot be overemphasised.

Recessive spinocerebellar ataxias with onset in adulthood are much less common than dominant forms. The few patients with recessive pedigrees found in this clinic were significantly younger than the dominant and sporadic patients, with one of the

patients testing positive for FA. While patients with FA usually present during childhood, onset of symptoms has been described to occur in the adult age group.⁷¹⁻⁷⁵ There is a report of symptom onset as high as 67 years.⁷⁶ Testing for FA in adult onset patients appears to be appropriate.

The expanded FA gene was also found in a couple of less characteristic situations. One of the two patients found to have FA appeared to have an autosomal dominant disorder. The appearance of FA in two successive generations has been previously described. This occurs as a result of an affected homozygous individual having children with a heterozygous carrier.^{77,78}

One patient in the sample was found to be heterozygous for the FA GAA expansion. Given that the carrier frequency for the FA expansion is approximately one in 90, the appearance of one heterozygote in a sample of this size is appropriate.^{79,80}

Just under half of our SCA patients lacked a positive family history. These individuals had ages of onset that were similar to those of the autosomal dominant patients. The etiology of SCA in these sporadic cases was not clear, and may represent a non-genetic disorder.

Testing of apparently sporadic cases only yielded one positive result. 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. Symptoms may not be sufficient to enable the index case to realize that similar problems exist in family members. 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.

While a positive result has been reported in as many as 22% of sporadic patients tested for the inheritable ataxias, the single individual testing positive out of 26 tested in this study is somewhat lower than most other studies.^{50-52,54,56,57,59-61,64,81-83} Our lower yield in this group may be the result of a more aggressive assessment of the family history resulting in fewer patients being classified as sporadic. Overall, one can see that the testing of apparent sporadic patients results in a small but potentially significant 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. Given the lack of positive results in our patients and the reported rarity in patents of European descent, DRPLA testing appears to be of little value for non-Japanese patients presenting with spinocerebellar ataxia.^{46,47} Testing might be more appropriate in individuals who have the additional features of chorea, dementia, or epilepsy.

There has been increasing interest in the role that premutation range expansions of the FMR1 gene has in degenerative disorders characterized by tremor, ataxia, Parkinsonism, and dementia. 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 al⁸⁴ tested 59 SCA patients who had tested negative for SCA types 1, 2, 3, 6, and 7. They found three with repeats in the premutation range. One of the patients had onset of

ataxia at age ten. Another group reported testing for the FMR1 premutation in nine males and four 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 40.⁸⁵ There has been one report of two females with the association of tremor and ataxia with the FMR1 premutation.⁸⁶ While females carrying the full mutation have been thought to have no clinical manifestations, 16% of women with the premutation develop premature menopause.⁸⁷

At present, it appears that the fragile X premutation is only occasionally identified in patients presenting with SCA. Given that the prevalence of the premutation is relatively common (approximately one in 700 males and one in 250 females) and that as many as 20% of male premutation carriers over the age of 50 have symptoms suggestive of this disorder, one might wonder why the yield of testing SCA patients is not higher.⁸⁸ Perhaps this disorder is much less common than has been suggested or additional genetic and/or environmental factors play a role in its development. It is possible that features other than the ataxia may be more prominent leading to diagnoses such as essential tremor, Parkinson's disease, or dementia. In addition, the white matter abnormalities might be interpreted as being indicative of a demyelinating disorder. The role that this syndrome plays in degenerative neurological disease should be investigated in a larger series of patients with these types of disorders.

In the University of Calgary Movement Disorders Clinic the most commonly diagnosed autosomal dominant spinocerebellar ataxia is SCA3 followed by SCA2 and SCA6. Over 60% 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. The fragile X tremor/ataxia syndrome was not identified in our SCA patient population.

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