Spinocerebellar ataxia type 8 in Scotland: genetic and clinical features in seven unrelated cases and a review of published reports

A Zeman, J Stone, M Porteous, E Burns, L Barron, J Warner

PAPER

A taxia and cerebellar atrophy are the principal features of the enlarging family of dominantly inherited spinocerebellar ataxias.1 Some of these disorders also affect the retina, the peripheral nerves, the pyramidal and extrapyramidal systems, and cognitive function. SCA 1, 2, 3, 6, 7, 12, and DRPLA result from expansion of CAG trinucleotide repeats, coding for polyglutamine tracts. The pathogenic ranges of the repeat expansions giving rise to these disorders are moderately well defined. Anticipation occurs throughout this group of ataxias and is particularly marked in the autosomal dominant ataxia and cerebellar atrophy of type 2 (SCA 2) and Spinocerebellar ataxia type 6 (SCA 6). In families with SCA 2, affected females tend to have a more severe phenotype and to display symptoms at an earlier age than affected males, and transmit the disorder to their sons but not their daughters.2

The SCA 8 transcript, containing the CTA expansion, has been identified in brain tissue and weakly in lung, kidney, and testis.5 Its most 5’ exon is transcribed anti-sense to the first exon of a gene coding for a novel actin binding protein, Kelch-like 1 (KLHL1).6 KLHL1 is primarily expressed in the cerebellum, frontal lobe, and subthalamic nucleus7 8—the SCA 8 transcript may modify its expression by several mechanisms.10 11 Comparative study in the mouse indicates that the RNA transcript containing the SCA 8 expansion has been conserved over the course of mammalian evolution.9

In the large family reported by Koob et al, MN-A, CTA/CTG repeat lengths in affected individuals ranged from 110 to 130 (107 to 127 CTG repeats).12 The phenotype was typical of the SCA group, consisting of cerebellar ataxia with variable limb spasticity and impaired vibration sense. It was linked to the SCA 8 expansion on 13q21 with a highly significant lod score of 6.8. The penetrance of the expansion was low, however, with ataxia in only 13 of 35 carriers of the expansion. CTG repeat lengths were significantly greater among affected than unaffected carriers (116 ± 90).

We have previously described a mother and son with the SCA 8 expansion,13 mild cerebellar ataxia, cognitive and psychiatric symptoms, and signs of a dysexecutive (“frontal lobe”) disorder, raising the possibility that the phenotype of the disorder is wider than first envisaged. In addition, since Koob’s original paper, several reports have cast doubt on the validity of the SCA 8 syndrome given that the SCA 8 expansion occurs surprisingly often among apparently healthy individuals in some control populations.14 15

Abbreviations: ACE, Addenbrooke’s cognitive examination; DSM-IV, Diagnostic and Statistical Manual of Mental Diseases, 4th edition; HADS, hospital anxiety and depression scale; MMSE, mini-mental state examination.
In an effort to reduce the uncertainties surrounding the diagnosis of SCA 8 we have addressed the following questions. First, is the SCA 8 expansion associated with ataxia in our own ataxic and control populations? Second, what is the range of clinical phenotypes associated with the expansion? Specifically, is the expansion associated with neuropsychological or neuropsychiatric features? And third, do our findings agree with the results of a systematic review of published reports?

METHODS

Subjects
Leucocyte DNA from the following groups was screened for the SCA 8 expansion:

- 1190 anonymised healthy controls;
- 137 patients undergoing investigation for possible Huntington's disease with a negative result;
- 176 patients with schizophrenia;
- 173 patients with undiagnosed ataxic syndromes, in whom the expansions associated with spinocerebellar ataxias 1, 2, 3, 6, 7, or DRPLA had been excluded.

We assessed the five subjects with the SCA 8 expansion (combined CTA/CTG repeats >100) identified among the ataxic group above (one of these, patient 5, was the case we had reported previously). Two further ataxic patients with CTA/CTG repeats >100 were identified in the course of routine clinical testing; one has been fully assessed and limited clinical details are available for the second.

DNA analysis
All DNAs were amplified with the original primers SCA 8–1 and SCA 8–2 using the published method. One of the primers (SCA 8–2) was 5′ FAM labelled and all products were resolved on a high resolution polyacrylamide/urea gel on an automatic sequencer. Sequences that appeared homozygous on the sequencer were reamplified with primers SCA 8–2 and SCA 8–3 (TGC TGC TGC TGC TGC ATT TTT TAA) which produce a characteristic ladder of fragments with a 3 bp periodicity in the presence of a large repeat.

Clinical assessment
A consultant neurologist and consultant clinical geneticist took a structured clinical history from each of the six subjects who underwent full assessment, and carried out a standard neurological examination. The seventh subject was assessed by another consultant neurologist in a routine clinical setting.

Cognitive assessment
This comprised the mini-mental state examination (MMSE) and the Addenbrooke’s cognitive examination (ACE).

Psychiatric assessment
Subjects were assessed with the structured clinical interview for DSM-IV axis I disorders, such as depression, anxiety, and psychosis. The hospital anxiety and depression scale (HADS) was used to obtain dimensional ratings of current mood disorder.

Radiology
Magnetic resonance imaging (MRI) findings were reviewed in all patients.

Review of published reports
We reviewed all available published reports on SCA 8 ascertained by a Medline search (1996 to March 2003), using the search terms “SCA8”, “SCA 8”, and “spinocerebellar ataxia type 8”, by inspection of the OMIM SCA 8 site, and by obtaining all relevant papers referred to in those produced by the original search. The papers were reviewed and data abstracted by two of us independently. Points of disagreement were discussed and resolved by referring back to the papers.

Statistics
We analysed differences between the proportions of patients heterozygous for a SCA8 expansion of greater than 91 CTA/CTG repeats among ataxic patients, in the control groups represented in the current study, and in summary data obtained from the literature review. Analysis was carried out using Fisher’s exact test. Odds ratios and their 95% confidence intervals were calculated using StatsDirect.

RESULTS

Current series
Prevalence of the SCA 8 expansion
These results are shown in table 1 and fig 1. Over 98% of SCA 8 patients have a CTA/CTG repeat length in all four groups fell between 14 and 40. Repeats of greater than 91 were seen in 3.5% of the ataxic group (six unrelated subjects), 0.3% of the anonymised control group (three subjects, p<0.0005), 1.5% of the Huntington's control group (two subjects, NS), and none of the schizophrenia control group (p<0.05). Repeats over 100 were seen in five ataxic patients, but in only one patient from the three control groups—an anonymised healthy control (p<0.0001). Comparison of all controls with ataxic subjects yielded an odds ratio of 10.8 (95% confidence interval 2.7 to 45.0) for an SCA 8 CTA/CTG combined repeat length greater than 91 among ataxic subjects.

Clinical features
The clinical features are summarised in table 2.

Demographics
Our subjects developed symptoms at ages ranging from 13 to 47 years. Five were female, two male. Three subjects gave a family history of a similar disorder. Patient 5, described in our previous report, had a similarly affected mother whom we have examined. Patient 6 had an apparently similarly affected, now deceased, father; three of her father’s siblings have neurological diagnoses, although we are uncertain of the grounds for these (one “Parkinson’s disease”, one “motor neurone disease”, one “Parkinson’s disease or motor neurone disease”). Patient 7 has a similarly affected brother. All patients had been screened carefully for other causes of ataxia.

Presenting symptoms—neurological
Gait disturbance was a prominent symptom in all our patients. Four complained of dysarthria, two of dysphagia; four reported motor symptoms in the limbs other than gait disorder, two urinary urgency, and one sensory disturbance. One patient had developed torticollis. Three complained of Raynaud’s phenomenon.

Presenting symptoms—cognitive and psychiatric
These were assessed systematically in patients 1–6. Five patients had cognitive complaints at presentation. The academic performance of patient 4 declined markedly at the time of his personality change, in his early teens, described below. Personality change was a prominent feature in two of our patients (4 and 5), preceding the onset of cerebellar features in patient 4 by about four years. In patient 4 the change involved loss of interest in other people, loss of empathy, decline of interpersonal skills, and loss of enthusiasm for hobbies. Patient 5 became irritable, inflexible, and...
Mood disturbance or lability was prominent in patients 2, 3, and 6. This was particularly marked in patient 6 who reported several episodes of uncontrolled laughter and crying.

Neurological signs
All subjects had clinical signs of cerebellar involvement, except possibly for patient 6, in whom prominent upper and lower motor neurone signs complicated the interpretation of her limb ataxia and gait disturbance. Four patients had clear evidence of pyramidal tract dysfunction, with equivocal evidence in a fifth (patient 5). There were minor sensory features in three patients. Patient 6 was unusual in displaying some lower motor neurone signs: wasting and weakness in the hands, weakness of ankle plantar flexion, and absence of the ankle jerks in the face of pathologically brisk reflexes in the arms.

Cognitive examination
Screening with the MMSE and ACE did not reveal evidence of dementia in any of the patients. These tests are insensitive to subtle neuropsychological deficits and executive dysfunction, which we had previously demonstrated in patient 5. However, the tests exclude gross cognitive impairment.

Psychiatric examination
Two patients gave histories of past major depression and panic disorder (patients 1 and 2). In both patients these disorders occurred soon after the onset of ataxia. Patient 3 had current obsessive-compulsive disorder, with onset four years after her first neurological symptoms: she reported a time consuming obsession with even numbers, for example counting her footsteps to make sure that they summed to an even number, buying even numbers of cans, and chopping even numbers of vegetables. The results on the HADS indicated that none of the patients was significantly anxious or depressed at the time of testing. No subjects had a personality disorder.

Radiology
Brain MRI revealed cerebellar atrophy in five of the seven patients. In patient 2 an initial scan in 1996 had been reported as normal, but by 2000 a second scan showed clear cut cerebellar atrophy (fig 2). In retrospect the 1996 scan showed borderline changes, with enlargement of the fourth ventricle. No other significant changes were noted in the scans.

Review of published reports
The prevalence and range of the SCA 8 expansion
Table 3 compares the frequency of SCA 8 expansions >91 combined CTA/CTG repeats in unrelated patients with undiagnosed ataxia with the frequency among healthy and pathological controls in all published series. We have not included cases in which there was a plausible alternative explanation for the ataxia or ataxic cases with SCA 8

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**Figure 1** Combined CTA/CTG repeat frequencies in healthy controls, ataxic subjects, subjects who tested negative for Huntington’s disease, and subjects with schizophrenia. The five patients and single control subject with repeat lengths of >100 are indicated (patients 6 and 7 were identified subsequently in the course of clinical testing).
expansions of <91 CTA/CTG repeats. (Our choice of 91 repeats as a cut off value is discussed further below.) Table 3 shows that combined CTA/CTG repeats over 91 occur significantly more often among patients with undiagnosed ataxia (3.4%) than among all controls (0.7%), healthy controls (0.54%), psychiatric controls (1.2%), and controls with other neurological disorders (0.8%) (p<0.0001 for all comparisons, Fisher’s exact test). Cases with a family history were more likely than sporadic cases to have an expansion greater than 91 (p<0.01). Comparing all controls with ataxic subjects yielded an odds ratio of 5.0 (95% confidence interval, 3.5 to 7.2) for an SCA 8 CTA/CTG combined repeat length of greater than 91 among ataxic subjects. The data suggest that within their large family repeat lengths were greater in affected than unaffected carriers of the expansion.1 There is a tendency for the CTA/CTG repeat to expand on maternal and contract on paternal transmission.2 5 6 However, most series document cases with paternal transmission.

### Clinical features of the SCA 8 expansion

The clinical features of SCA 8 expansion are summarised in Table 4. The most common and obvious manifestation of the SCA 8 phenotype is a cerebellar syndrome, with gait ataxia in almost all patients, and limb incoordination and dysarthria in the majority. About half the patients develop upper motor neurone signs. Lower motor neurone signs, bladder disturbance, and sensory symptoms occur in a few. Published reports indicate that cognitive features can occur. These are more prominent in patients with onset in childhood or adolescence,5 6 sometimes amounting to dementia,6 although to date there are no group studies of patients with SCA 8 detailing the results of neuropsychological assessment. The possibility has been raised that rates of the SCA 8 expansion may be increased in patients with psychiatric diagnoses.30 Our review indicates that the likelihood of an SCA8 expansion is higher in psychiatric samples than in healthy controls (p=0.02). However, there have been no systematic reports of neuropsychiatric features to date. Myoclonic epilepsy occurred in one patient with onset in the first year of life.3 One series has reported consistent abnormalities on neurophysiological testing,4 but other studies have not detected these (table 4). The reported ages of onset range from the first year of life to 65. The majority of cases have onset in early to mid adulthood. Progression of the

### Table 2 SCA 8 patients: demographic details, repeat lengths, MRI findings, and clinical features

<table>
<thead>
<tr>
<th>Patient No</th>
<th>Sex</th>
<th>Age at onset (years)</th>
<th>Age at assessment (years)</th>
<th>CTA/CTG combined repeat length</th>
<th>Family history?</th>
<th>Cerebellar atrophy on MRI?</th>
<th>Symptoms</th>
<th>Psychiatric symptoms</th>
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*Personality change reported by a family member.

ACE, Addenbrooke’s cognitive examination; DSM-IV, Diagnostic and Statistical Manual of Mental Diseases, 4th edition; DTR, deep tendon reflexes; F, female; JPS, joint position sense; M, male; MMSE, mini-mental state examination; N/A, not assessed; OCD, obsessive compulsive disorder; pt, palmar reflex; vib, vibration sense.

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**Penetrance of the expansion and transmission within SCA 8 families**

The limited data available suggest that the penetrance of the SCA expansion among carriers within affected families is around 50% (35 of 64 subjects).2 5 15 16 27-30 Koob et al reported that within their large family repeat lengths were greater in affected than unaffected carriers of the expansion. There is a tendency for the CTA/CTG repeat to expand on maternal and contract on paternal transmission. However, most series document cases with paternal transmission.

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disorder is slow and severity highly variable. Some cases have come to light only on neurological assessment. In Koob’s original family, “severely affected family members were non-ambulatory by the fourth to sixth decade.”

It is unclear whether the size of the repeat expansion influences the age of onset or severity of the disorder.

DISCUSSION

Is the “SCA8 expansion” associated with ataxia?

While Koob’s original observations appeared to prove that the SCA 8 expansion could cause an ataxic syndrome, subsequent reports indicated an unexpectedly high rate of repeat expansions in unaffected controls. The data summarised in table 3 clarify the relation between the SCA 8 expansion and ataxia. The expansion is common among unaffected controls, occurring in around 0.5%. However, it is significantly more common among unrelated patients with unexplained ataxia, particularly among those with a family history of ataxia, showing that there is an association between the SCA 8 expansion and ataxia. The high background rate among controls suggests that the expansion may best be regarded as a risk factor for ataxia which only gives rise to disease in the presence of some other factor or factors, discussed below.

What is the pathogenic range of the SCA 8 expansion?

The great majority of patients with SCA 8 have combined CTA/CTG repeat expansions in the range 91 to 200. We chose the cut off of 91 combined CTA/CTG repeats in table 3 somewhat arbitrarily—this was the upper end of the control range identified by Koob et al in their original paper, and it was possible to extract the frequencies of repeats above and below this value from the other published series. The published data suggest that a small number of subjects with repeats in the 80s are symptomatic, as are a small number with repeats over 200. It has been suggested that very large expansions may be transcriptionally silent and therefore unlikely to cause disease.

What is the SCA 8 phenotype?

SCA 8 causes cerebellar ataxia almost invariably, upper motor neurone signs commonly, and lower motor neurone signs, sensory features, and bladder disturbance occasionally. Our data suggest that cognitive and psychiatric symptoms occur quite commonly. We have not demonstrated objective cognitive impairment in our patients, but the screening tests reported here are insensitive to subtle changes in cognitive function of the kind we have described previously in a single family. The variation in the reported rates of cognitive and psychiatric features in published series may well reflect varying approaches to assessment. Marked cognitive decline occurs in some patients, and is particularly common in cases with onset in childhood or adolescence. This could reflect the observation that the KLHL1 protein plays a more active role in the developing brain than in the adult brain, the role of the cerebellum in cognitive development, or both. Cognitive impairment is more often observed in early than in late onset.

Figure 2. Magnetic resonance imaging of the brain in patient 2 in 1996 (left) and 2000 (right), showing progression from borderline cerebellar atrophy in 1996 to marked atrophy in 2000.
myotonic dystrophy, another genetic disorder caused by a transcribed but untranslated CTG repeat expansion.

Why is the penetrance of the SCA 8 expansion low?
The SCA 8 expansion is of low penetrance in two distinct senses: first, the data from healthy controls indicate that the majority of carriers of the expansion in the general population do not have ataxia. Indeed, assuming a rough prevalence of 1:100 000 for ataxia resulting from SCA 8, and given that the expansion is present in around one in 200 of the population, only about one in 500 individuals with the SCA 8 expansion is likely to manifest the disease. Second, although the risk that a carrier will show ataxia is much increased within symptomatic families (to around 50%), many carriers in affected families never manifest the disease.

Several factors may help to explain these findings, but their relative importance is unclear: effects of the CTA/CTG ratio or interruptions within the repeat sequence; somatic mosaicism; the presence of modifying alleles elsewhere in the genome, including co-occurrence of other SCA mutations; other epigenetic factors; late emergence of symptoms in subjects within affected families; and the presence of subtle but

Table 3
The prevalence of the SCA 8 expansion (>91 CTA/CTG repeats) in unrelated patients with undiagnosed ataxia and controls

<table>
<thead>
<tr>
<th>Series</th>
<th>-91 repeats</th>
<th>Sample size</th>
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<td>(209f)</td>
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<td>(73f)</td>
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<td>disorder</td>
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<td>653</td>
<td>Mixed*</td>
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<td>-</td>
<td>0</td>
<td>64</td>
<td>Other neurological</td>
<td>disorder</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Izumi³⁰</td>
<td>3</td>
<td>327</td>
<td>Healthy</td>
<td></td>
<td>13 (5f)</td>
<td>362 (119f)</td>
<td>(119f)</td>
</tr>
<tr>
<td>-</td>
<td>0</td>
<td>70</td>
<td>Schizophrenia</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Juvonen (this study)</td>
<td>3</td>
<td>1190</td>
<td>Healthy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-</td>
<td>0</td>
<td>158</td>
<td>Alzheimer’s</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-</td>
<td>1</td>
<td>224</td>
<td>Parkinson’s</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subtotals</td>
<td>28</td>
<td>5192 (0.54%)</td>
<td>Healthy</td>
<td></td>
<td>6</td>
<td>173</td>
<td>(173)</td>
</tr>
<tr>
<td>-</td>
<td>19</td>
<td>1730 (1.16%)</td>
<td>Psychiatric</td>
<td></td>
<td>p&lt;0.0001</td>
<td>48 (4.46%)</td>
<td>(4.46%)</td>
</tr>
<tr>
<td>-</td>
<td>6</td>
<td>741 (0.81%)</td>
<td>Other neurological</td>
<td>disorder</td>
<td>p&lt;0.0001</td>
<td>23 (2.28%)</td>
<td>(2.28%)</td>
</tr>
<tr>
<td>-</td>
<td>5</td>
<td>653 (0.92%)</td>
<td>Mixed*</td>
<td></td>
<td>p&lt;0.0001</td>
<td>77 (3.41%)</td>
<td>(3.41%)</td>
</tr>
<tr>
<td>Totals</td>
<td>58</td>
<td>8316 (0.70%)</td>
<td>All controls</td>
<td></td>
<td>p&lt;0.0001</td>
<td>2259</td>
<td>(2259)</td>
</tr>
</tbody>
</table>

†Fisher’s exact test compared with all ataxic subjects.
*Mixed healthy and pathological (non-ataxic) controls.
**Excluding data from this study.

SCA 8 expansion is likely to manifest the disease. Second, although the risk that a carrier will show ataxia is much increased within symptomatic families (to around 50%), many carriers in affected families never manifest the disease. Several factors may help to explain these findings, but their relative importance is unclear: effects of the CTA/CTG ratio or interruptions within the repeat sequence; somatic mosaicism; the presence of modifying alleles elsewhere in the genome, including co-occurrence of other SCA mutations; other epigenetic factors; late emergence of symptoms in subjects within affected families; and the presence of subtle but
unnoticed symptoms and signs—neurological, cognitive or psychiatric—among “healthy” controls.

Is SCA 8 an example of the cognitive-affective cerebellar syndrome?
Schmahmann has drawn attention to the occurrence of cognitive and affective change in patients with focal cerebellar lesions.\(^{39}\) Anatomical findings and functional imaging also suggest that the cerebellum contributes to cognition. It is possible that the cognitive and psychiatric features of SCA 8, and other spinocerebellar ataxias, reflect this contribution. However, it is likely that the molecular pathology of SCA 8 and other spinocerebellar ataxias extends beyond the cerebellum—for example, into the frontal lobes and basal ganglia.\(^{11}\) This more extensive cerebral involvement, rather than cerebellar pathology of its own, may well be the explanation for the cognitive and affective features of SCA 8.

Should the SCA 8 probe be used in routine diagnostic practice?
We agree with the conclusion of Juvonen et al.,\(^ {24}\) that DNA analysis for the SCA 8 expansion is a helpful test in patients with otherwise unexplained ataxia. Their data suggested that the predictive value of an expansion length of between 80 and 800 repeats for the diagnosis of SCA 8 was 68% overall among patients with ataxia, rising to 86% in patients with a family history of dominantly inherited ataxia, and falling to 47% among those with sporadic ataxia. It is noteworthy, however, that these predictive values are significantly lower than those usually provided by diagnostic tests in clinical genetics. A positive result should not discourage a thorough search for other causes of ataxia. Moreover, testing for SCA 8 is of no value in asymptomatic subjects in the general population, and should not be used as a predictive test in patients with ataxia from families unaffected by SCA 8. However, our laboratory’s growing experience of the probe indicates that SCA 8 is the second most commonly identified genetic association of ataxia in our population, after SCA 6.

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