Spinocerebellar ataxia type 6: genotype and phenotype in German kindreds

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Abstract

Objective—Spinocerebellar ataxia type 6 (SCA6) is an autosomal dominant cerebellar ataxia (ADCA) of which the mutation causing the disease has recently been characterised as an expanded CAG trinucleotide repeat in the gene coding for the \( a_{\alpha} \)-subunit of the voltage dependent calcium channel. The aim was to further characterise the SCA6 phenotype.

Methods—The SCA6 mutation was investigated in 69 German families with ADCA and 61 patients with idiopathic sporadic cerebellar ataxia and the CAG repeat length of the expanded allele was correlated with the disease phenotype.

Results—Expanded alleles were found in nine of 69 families as well as in four patients with sporadic disease. Disease onset ranged from 30 to 71 years of age and was significantly later than in other forms of ADCA. Age at onset correlated inversely with repeat length. The SCA6 phenotype comprised predominantly cerebellar signs in concordance with isolated cerebellar atrophy on MRI. Non-cerebellar systems were only mildly affected with external ophthalmoplegia, spasticity, peripheral neuropathy, and parkinsonism. Neither these clinical signs nor progression rate correlated with CAG repeat length.

Conclusions—This study provides the first detailed characterisation of the SCA6 phenotype. Clinical features apart from cerebellar signs were highly variable in patients with SCA6. By comparison with SCA1, SCA2, and SCA3 no clinical or electrophysiological finding was specific for SCA6. Therefore, the molecular defect cannot be predicted from clinical investigations. In Germany, SCA6 accounts for about 13% of families with ADCA. However, up to 30% of SCA6 kindreds may be misdiagnosed clinically as sporadic disease due to late manifestation in apparently healthy parents. Genetic testing is therefore recommended for the SCA6 mutation also in patients with putative sporadic ataxia.

Keywords: spinocerebellar ataxia; phenotype; electrophysiology; genetics

Autosomal dominant cerebellar ataxia (ADCA) is a clinically, pathologically, and genetically heterogeneous group of neurodegenerative disorders characterised by progressive cerebellar dysfunction (causing ataxia of gait, stance, and limbs, dystarthis, and oculomotor disturbances) and variable combinations of cerebral, extrapyramidal, bulbar, spinal, and peripheral nervous system involvement. For decades recurrent efforts have been made to classify ADCA into subgroups using clinical and histopathological criteria (for review see Harding). However, substantial intrafamilial variability and broad overlap of clinical and pathological pictures between families rendered these classifications suboptimal.

Currently, ADCA is characterised increasingly by their underlying genetic defect and are referred to as spinocerebellar ataxias (SCAs). Linkage studies disclosed gene loci for SCA on chromosome 6p (SCA1),\(^1\) chromosome 12q (SCA2),\(^1\) chromosome 14q (SCA3 or Machado-Joseph disease),\(^1\) chromosome 16q (SCA4),\(^1\) chromosome 11 (SCA5),\(^2\) and chromosome 3p (SCA7).\(^3\) The mutations responsible for SCA1, SCA2, and SCA3/Machado-Joseph disease have been characterised as unstable expansions of CAG trinucleotide repeats in the coding region of the responsible gene.\(^4,5\)

The SCA6 gene was recently identified by a large scale genotyping survey using polymorphic CAG repeats and DNA samples from patients with late onset neurodegenerative diseases. A polymorphic CAG repeat was detected in a gene coding for the \( a_{\alpha} \)-subunit of the voltage dependent calcium channel and shown to be expanded in a fraction of patients diagnosed with ADCA.\(^6\) Other mutations in this gene are responsible for episodic ataxia type 2 and for familial hemiplegic migraine.\(^7\) This calcium channel gene is located on chromosome 19p13.\(^8\)

In this study we report the frequency of the SCA6 mutation in a large series of patients of German ancestry with autosomal dominant and sporadic cerebellar ataxia. Furthermore, we define the SCA6 phenotype in comparison with SCA1, SCA2, and SCA3 and correlate phenotype and genotype in patients with SCA6.

Patients and methods

A continuous series of 126 patients from 69 families with ACDAs and 61 further patients with sporadic disease (no other family member in at least two preceding generations had presented with gait or speech disorder) were included in this study. In the sporadic group 46 patients were classified as idiopathic sporadic cerebellar ataxia whereas 15 were diagnosed as multiple system atrophy due to ataxia with additional signs of parkinsonism.
and autonomic failure.\textsuperscript{17} In all sporadic patients the (GAA)\textsubscript{n} repeat expansion responsible for Friedreich’s ataxia was excluded.\textsuperscript{18} All patients were clinically examined by the same neurologist (LS).

Clinical features in all familial cases fulfilled the criteria of ACDA type I (ADCA I) according to Harding\textsuperscript{19} including symptoms such as cerebellar ataxia, dysarthria, cerebellar oculo-motor dysfunction, ophthalmoplegia, dysphagia, pyramidal damage, extrapyramidal dysfunction, dorsal column affection, sphincter disturbance, peripheral neuropathy, and dementia. Families with pigmentary retinal degeneration characterising ADCA type II\textsuperscript{19} were not found. In our series, we did not find families with “pure” cerebellar atrophy (ADCA III) according to Harding\textsuperscript{19} as at least one member of every family had additional signs of ataxia such as peripheral neuropathy or pyramidal affection.

Motor evoked potentials to the first dorsal interosseus and tibialis anterior muscle were measured by a standard technique with a Maglite magnetic stimulator (Dantec, Denmark). Tibial and median nerve somatosensory evoked potentials, concentric needle EMG, and nerve conduction studies were recorded using a Counterpoint MK2 (Dantec, Denmark). Auditory evoked potentials and visual evoked potentials were measured according to standard protocol with an Excel (Cadwell, USA).

Blood samples for molecular genetic analyses were taken in EDTA from all patients after informed consent was obtained. Genomic DNA was extracted from peripheral white blood cells. Genomic DNA (100 ng) was

### Table 1 Clinical features in 17 German patients with SCA6 (in order of increasing repeat length)

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0=normal; (+)=minimal; ++=mild; +++=moderate; ++++=severe; A=akinesia; R=tremor; T=tremor; CA=cerebellar atrophy; *=mild cerebral atrophy additionally to CA.

![Graph](https://example.com/graph.png)

**Figure 1** Progression of disability in patients with SCA6 plotted as a function of CAG repeat number. Various landmarks are indicated by changes in the shading of the bars. Age at onset correlated inversely with repeat length ($r=-0.83$, $p=0.0001$, $n=21$, Pearson’s correlation analysis).
amplified by polymerase chain reaction (PCR) using the primer pair S-5-F1 and S-5-R16 in a total volume of 10 μl. Amplification was carried out for 35 cycles with denaturation at 95°C for one minute, annealing at 60°C for one minute, and extension at 72°C for one minute in a Robocycler (Stratagene). DMSO was added to a final concentration of 10% to avoid non-specific amplification products. The PCR product sizes were determined by comparison with an M13 sequencing ladder.

For statistical analyses, means were compared using unpaired t tests. Frequency of symptoms were compared with a χ² test using Yates’ correction when appropriate. Correlation coefficients were calculated with Pearson’s correlation analysis.

Results

FREQUENCY OF EXPANDED ALLELES IN PATIENTS WITH FAMILIAL AND SPORADIC ATAXIA

CAG repeat lengths in the SCA6 gene ranged from 4–16 CAG units in healthy controls. Allele frequencies and population genetic aspects will be described by Riess (in preparation). Expanded alleles were found in 17 of 126 patients from nine of 69 families with ADCA proving that 13% of our families with ADCA were genetically classified as SCA6. Additionally, four of 61 sporadic patients had expanded alleles in the SCA6 gene. Before genetic tests for SCA6 were available all four “sporadic” cases had been classified as having idiopathic sporadic cerebellar ataxia and none as having multiple system atrophy. Repeat expansions ranged from 22 to 28 CAG units in familial cases whereas all four sporadic patients carried a (CAG)₉ allele. Retrospective revision of the family history in “sporadic” cases disclosed that the mother of one patient (onset at 53 years) had gait difficulties beyond the age of 88. The fathers of two further patients (onset at 54 and 47 years) were killed in the second world war. Other family members were not known to have ataxia. The fourth patient presented first clinical signs at the age of 80. Her mother died at the age of 59 from myocardial infarction without a history of gait or speech disturbance in the family.

THE PHENOTYPE OF SCA6

Age at onset in 21 patients with SCA6 varied between 30 and 71 years of age (mean: 52.0 (SD 11.7)). Duration of the disease was 11.0 (SD 9.7) (range 1 to 40 years). Seventeen patients with SCA6 were available for detailed clinical examination. Cerebellar signs were the prominent feature in all of them. Disease started uniformly with gait ataxia as the initial symptom. Additionally, many patients complained of stiffness at the beginning of the disease, often without clinical signs of spasticity. Cerebellar oculomotor deficits were present at the first consultation in all patients including impaired smooth pursuit (15), gaze evoked nystagmus (15), impaired visual suppression of the vestibulo-ocular reflex (10), dysmetric saccades (nine) and decreased gain of the optokinetic nystagmus (seven). Fifty per cent of patients complained of intermittent diplopia but no patient decided to use prisms to compensate for this problem. Upper limb ataxia and cerebellar dysarthria was minimal at the beginning and progressed with duration of disease (table 1). Dysphagia was a frequent problem in patients with longstanding disease (duration>five years). Incomplete external ophthalmoplegia was present as limitation in upper gaze (three), horizontal gaze palsy, (three) and ptosis (one). Parkinsonian signs were seen in mild form in two patients (tremor at rest in one patient and mild bradykinesia with rigidity in another (table 1). Other signs of extrapyramidal involvement were missing. Mild spasticity of the legs or increased knee and ankle jerks were present in eight of 17 patients. Interestingly, plantar response was normal in all patients and no patient complained of spinal automatism. Signs of mild peripheral neuropathy were present in seven of 17 patients including mild reduction in vibration sense, reduced ankle jerks, wasting of the extensor digitorum brevis muscle, and muscle cramps. However, no patient had dysaesthesiae, wasting of foreleg muscles, or paresis in foot dorsiflexion despite old age in some patients. One patient complained of urgent frequency with incontinence, but this may be related to prostatic hyperplasia or diabetes.
both present in this patient. On clinical grounds there were no signs of intellectual impairment in any of our patients. Clinical features associated with other disorders caused by mutations in the \(\alpha_{1C}\) calcium channel such as migraine, episodes of hemiplegia, or periodic changes in intensity of ataxia were not found in our SCA6 cohort with the exception that one patient experienced a stroke with left sided hemiparesis at the age of 71 with near complete recovery within one year.

**GENOTYPE-PHENOTYPE CORRELATION**

Age at onset was significantly influenced by the size of the CAG expansion with earlier onset in patients with larger repeats (fig 1). Size of the CAG expansion accounted for about 70% of variance in age at onset \((r = -0.83, p<0.0001, n=21, \text{Pearson's correlation analysis})\).

There were five parent/offspring pairs in our group to study meiotic stability of expanded CAG repeats. The parental chromosomes carried a \((\text{CAG})_{22}\) allele in four transmissions and a \((\text{CAG})_{26}\) allele in the other. Repeat size was stable in all five transmissions (four maternal, one paternal). However, age at onset in offspring differed from parental onset by −21 years (father 71, son 50 years) in our only paternal transmitted case and by −1, −3, +7, and +13 years in maternal transmissions. In other forms of SCA patients with early onset often inherited the mutation from their affected fathers. In our patients with SCA6 with comparatively early onset (before the age of 40) the disease was transmitted by the mother in three cases and by the father in one.

The influence of the repeat length on the course of the disease was estimated for two progression stages: (1) the time point when independent walking became impossible and (2) the time point when patients became confined to wheelchairs. Multiple Cox regression models did not show a significant influence of repeat length on progression but this may be hampered by the small group of patients. Progression to dependence on a walking aid varied from four to 18 years after gait difficulties started. A wheelchair was needed nine to 37 years after onset of symptoms. Influence of the repeat size on frequency of clinical features in patients with SCA6 was estimated comparing patients with shorter repeats, \((\text{CAG})_{22-23}\) to the group with larger repeats, \((\text{CAG})_{26-28}\). Extrapyramidal signs and peripheral neuropathy were not found in the group with larger repeats (table 1). However, groups were small and differences were not significant.

**ELECTROPHYSIOLOGICAL CHARACTERISTICS AND MRI FINDINGS**

Table 2 shows the results of nerve conduction studies. These were normal in four of 10 patients with SCA6 and disclosed mild sensorimotor peripheral neuropathy with axonal and demyelinating elements in six patients. Sensory nerve action potentials were the most sensitive index for SCA6 associated peripheral neuropathy with reduced potentials in five of 10 patients. Motor nerve conduction studies were abnormal in four of 10 patients; distal latency was prolonged and compound muscle action potential was reduced in amplitude in three patients, respectively. Motor nerve conduction velocity was slowed in two and minimal F wave latency was increased in four patients. Needle EMG showed chronic neurogenic changes in all but one cases with abnormal nerve conduction studies.

Motor evoked potentials were obtained in five patients and disclosed prolonged peripheral motor conduction time to the first dorsal interosseus and the tibialis anterior muscle in one patient with reduced motor nerve
conduction velocity and increased F wave latency. Central motor nerve conduction velocity to the first dorsal interosseus was normal in all five patients and prolonged for the tibialis anterior muscle in one patient (table 2).

In one patient somatosensory evoked potentials disclosed prolonged peripheral and central conduction time after median and tibial nerve stimulation. In two other patients somatosensory evoked potentials were normal despite mild sensory deficits in clinical examination. Visual evoked potentials had normal latencies and amplitudes in all nine patients studied. Auditory evoked potentials were normal in five recordings whereas wave I was missing in three patients.

Skull CT and MRI were available in 13 patients and showed cerebellar atrophy of the vermis and cerebellar hemispheres in all patients (fig 2). Brainstem structures appeared normal even in patients with swallowing problems and gaze limitation. Mild diffuse cerebellar atrophy was found in three patients.

**Comparison of the SCA6 phenotype with SCA1, SCA2, and SCA3**

Onset was substantially later in SCA6 compared to all other forms of SCA (table 3). There were no early onset patients (before 25 years) in our SCA6 group but nine of 21 patients had onset beyond 55 years of age. By comparison, all patients with SCA1 and SCA2 and all but one patient with SCA3 manifested before the age of 55. Duration did not differ significantly between groups. However, patients with SCA6 often reached old age with nine of 21 patients older than 65 years and three patients older than 80 (up to 90 years). By comparison, none of our patients with SCA1 (p<0.05), two with SCA2 (p<0.05), and two with SCA3 (p<0.001) were older than 65 but none reached 80 years.

Diplopia and cerebellar oculomotor disturbances, especially saccadic smooth pursuit and gaze evoked nystagmus, were significantly more frequent in SCA6 than in SCA1 and SCA2 (table 3). Peripheral neuropathy was less frequent compared with all other groups of SCA and was less severe not causing foot drop or relevant amyotrophy in any patient with SCA6. Similarly, pyramidal and extrapyramidal disorders were less severe when present in SCA6. Interestingly, Babinski’s sign was negative in all patients with SCA6.

**Discussion**

Our data confirm that an expanded CAG trinucleotide repeat in the human α1A-calcium channel gene is the mutation causing disease in a group of families with the SCA6 variant of ADCA.° We found the SCA6 mutation in about 13% of German families with ADCA and additionally in four patients considered as having sporadic ataxia before molecular diagnosis was available. The prevalence of SCA6 seems to be similar or slightly higher than SCA1 (six of 69 families) and SCA2 (eight of 69 families) but much less frequent than SCA3 (31 of 69 families). However, 15 of 69 families of our series remain to be characterised genetically and are
presented as sporadic ataxia indicating that about one third (four of 13) of our SCA6 kindreds had been misdiagnosed as having sporadic disease before. Retrospectively, family history was not strictly informative in all four patients as in three cases one parent died at a younger age than ataxia manifested in their offspring. In the fourth case the mother had gait difficulties ascribed to old age (88 years) whereas the son developed ataxia at the age of 53. However, in all four kindreds no further family member was affected by the disease. Although in these cases retrospectively a hereditary disease cannot be excluded, SCA6 seems to be more frequent in patients with putative sporadic ataxia than other forms of SCA. In our series all patients with SCA1 and SCA3 had a family history of definite dominantly inherited disease. In SCA2, one patient presented as sporadic ataxia but in this patient a de novo mutation from an unstable intermediate allele was established. Increased frequency of putative sporadic patients with SCA6 may be due to the late manifestation of the disease (in nine of 21 patients beyond the age of 55) and to less prominent anticipation (earlier onset, more rapid progression, and more severe disease in successive generations) in SCA6 compared with SCA1, SCA2, and SCA3. This leads to higher frequencies of uninformative family histories and misinterpretation of gait disturbances as disability related to old age or other disorders such as stroke. Therefore, we recommend that patients with apparently sporadic ataxia are tested for the SCA6 mutation. Incomplete penetrance would be another explanation for the presence of the SCA6 mutation in patients with apparently sporadic ataxia, but we did not find asymptomatic gene carriers in healthy controls. Meiotic instability and anticipation is a prominent feature in SCA1, SCA2, and SCA3. However, we did not find transmission instability in our small SCA6 cohort. Despite stable repeat lengths anticipation occurred up to 21 years in personally examined cases. In a "sporadic" patient (onset at 53 years) who’s mother had gait disturbance beyond the age of 88 anticipation could be 35 years, but neither personal examination nor molecular testing was available in the mother.

The phenotypes of SCA1, SCA2, SCA3, and SCA6 show enormous variability within the diseases and a substantial overlap between them (table 3; for details of our patients with SCA1, SCA2, and SCA3 see Schöls et al22–24). Despite the great variety of symptoms accompanying ataxia no clinical sign was restricted to one genetically defined subgroup of ADCA. This non-specificity prevents the prediction of the underlying molecular defect from clinical investigations, at least for individual cases. However, onset beyond 55 years of age and a predominantly cerebellar syndrome with less prominent involvement of non-cerebellar systems is frequent in SCA6. Nevertheless, SCA6 is not a "pure" cerebellar ataxia described as ADCA type III by Harding25 as it was accompanied by mild forms of external ophthalmoplegia, spasticity, or peripheral neuropathy in all patients of our series with a duration of more than five years. Dysphagia was a frequent symptom in SCA6 and is regarded as a sign of bulbar involvement in spinocerebellar ataxias. As gag reflexes and upward motion of the soft palate were normal in our patients with SCA6 swallowing problems may be caused by "ataxia" of the palatopharyngeal muscles and cannot be regarded as a proof of multisystem involvement.

Diplopia was a frequent symptom in patients with SCA6 or SCA3 but was essentially missing in patients with SCA1 or SCA2. However, diplopia seems to be less disturbing among patients with SCA6 as this group was not interested in testing prism glasses to compensate for the problem. By contrast, for patients with SCA3 diplopia was a frequent and major problem obstructing reading as well as other activities. Prism glasses were at least of some help in SCA3. Visual evoked potentials were normal in SCA6 but showed reduced amplitudes in a substantial number of patients with SCA1, SCA2, or SCA3.22–24

MRI disclosed predominantly cerebellar atrophy without significant brainstem involvement despite swallowing problems and ophthalmoplegia in many patients. These findings are consistent with the original report15 and with neuropathological findings in a family supposed to have SCA6 showing severe loss of Purkinje cells and moderate loss of granule cells, dentate nucleus neurons, and neurons in the inferior olive but only very mild atrophy of the brainstem.

The $\alpha_{1A}$-isoform involved in SCA6 has been shown to constitute P, or Q, or both types of calcium channels, which are the predominant calcium channels in Purkinje and cerebellar granule cells.26 27 The finding that mutations in the $\alpha_{1A}$-calcium channel cause ataxia and cerebellar degeneration (of Purkinje and granule cells) in toowering (tg) and leaner (tg*$^*$) mice that show cerebellar ataxia and seizures$^{16}$ supports the hypothesis that this channel is essential for normal function of Purkinje and cerebellar granule cells. By contrast with the dominant nature of the SCA6 mutation, the tg and tg*$^*$ mutations are regarded as recessive. However, careful quantitative studies of Purkinje cells in mice heterozygous for the tg and tg*$^*$ mutation are missing.

Recently, Ophoff et al$^{16}$ have shown that four missense mutations in the $\alpha_{1A}$-calcium channel gene cause familial hemiplegic migraine and two mutations disrupting the open reading frame of the same gene cause episodic ataxia type 2. Therefore, familial hemiplegic migraine, episodic ataxia type 2, and SCA6 have to be considered as allelic disorders. This may explain why familial hemiplegic migraine as well as episodic ataxia type 2 are associated with cerebellar atrophy.27 30 Interestingly, in
familial hemiplegic migraine only families linked to chromosome 19p13, the locus of the \( \alpha_{1A} \)-calcium channel, had cerebellar atrophy.28 Clinically, nystagmus is the only permanent sign in episodic ataxia type 2, whereas some patients with familial hemiplegic migraine develop ataxia beside cerebellar ocular motor disturbances.29 30 Although the same ion channel is involved in episodic ataxia type 2, familial hemiplegic migraine, and SCA6, patients with SCA6 did not have features of episodic ataxia type 2 or familial hemiplegic migraine. Ataxia may be experienced as an intermittent problem in the beginning of SCA6 but this is similar in other forms of SCA. The impression of intermittent changes is often related to periods of emotional stress multiplying motor system problems. Otherwise no episodic character of symptoms was reported by our patients with SCA6. Furthermore, none of our patients with SCA6 complained of episodic headache by contrast with patients with episodic ataxia type 2.27

The pathogenic mechanism induced by expanded CAG repeats is supposed to be a gain of function probably mediated by associated proteins.31 However, pathophysiology may be different in SCA6 as the SCA6 gene codes for a protein that is essential for Purkinje and granule cell survival. Voltage dependent calcium channels mediate the entry of calcium into neurons and play an important part in membrane excitability, transmitter release, and gene expression.32 Calcium channels consist of multiple subunits with the \( \alpha_{1} \)-subunit as the main pore forming unit mediating channel activity. As the CAG repeat expansion in the SCA6 gene is translated into an expanded glutamine stretch, it may directly interfere with the normal function of the \( \alpha_{1} \)-calcium channel.

Identification of SCA6 as an ion channel disorder, which is caused by the same voltage dependent calcium channel as in episodic ataxia type 2 and familial hemiplegic migraine may have important implications for new therapeutic strategies. Acetazolamide is supposed to modulate function in voltage dependent ion channels via producing metabolic acidosis. Interestingly, it is effective in reducing frequency and intensity of attacks in episodic ataxia type 2. Furthermore, calcium channel blockers such as flunarizine are potent drugs in preventing migraine. Finally, the description of the gene and mutation responsible for SCA6 offers the opportunity to characterise this ion channel pharmacologically in normal and mutant variants. This potential raises hopes for rational concepts of a causative therapy at least in one form of SCA.

Spinocerebellar ataxia type 6: genotype and phenotype in German kindreds

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