Autosomal dominant spinocerebellar ataxias

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Abstract
Autosomal dominant spinocerebellar ataxias (ADCA) are a clinically and genetically heterogeneous group of disorders characterized by a slowly progressive ataxia of gait, stance and limbs, dysartrhia and/or oculomotor disorder due to cerebellar degeneration in the absence of coexisting diseases. The degenerative process can be limited to the cerebellum (ADCA type III) or may additionally involve the retina (ADCA type II), optic nerve, ponto-medullary systems, basal ganglia, cerebral cortex, spinal tracts or peripheral nerves (ADCA type I). Prevalence of ADCAs has been estimated between 0.8 and 3.5:100,000. Onset is usually between ages 30 and 50 years, although early onset in childhood and later onset after age of 60 years have been reported. In the genetic classification based on ataxia loci and genes, ADCAs are referred to as spinocerebellar ataxias (SCAs) and numbered in the order of gene descriptions (SCA1-SCA22). Many identified mutations consist of an expansion of repeated trinucleotides, the variability of which is responsible for variability in age of onset with larger repeats in early onset cases. Additionally, instability of expanded alleles leads to the phenomenon of anticipation (earlier onset and more severe disease in successive generations). Current treatment is only symptomatic and management of ataxia relies on physiotherapy. Genetic testing enables identification of the causative gene in 50-80% of ADCA cases.

Key-words
Cerebellar degeneration, SCA, ADCA, CAG repeat expansions

Disease name and synonyms

Autosomal dominant spinocerebellar ataxias, Autosomal dominant cerebellar ataxias (ADCA), Spinocerebellar ataxias (SCA), Hereditary ataxias

Diagnostic criteria / Definition

Autosomal dominant spinocerebellar ataxias (ADCA) are a clinically and genetically heterogeneous group of disorders characterized by a slowly progressive cerebellar syndrome presenting as ataxia of gait, stance and limbs, dysartrhia and/or oculomotor disorder due to

cerebellar degeneration in the absence of coexisting diseases. The degenerative process can be limited to the cerebellum or can spread further to retina, optic nerve, ponto-medullary systems, basal ganglia, cerebral cortex, spinal tracts or peripheral nerves.

Classification

ADCAs have been first classified according to detailed clinical and pathological descriptions (Menzel 1891; Nonne 1891). The pathoanatomical classification (Greenfield 1954) differentiated ataxias with primarily spinal degeneration, from spinocerebellar, cerebellar, olivo-ponto-cerebellar and dentato-rubral atrophies. Harding (1982) classified ataxias according to their mode of inheritance and clinical features (ADCA type I – III, see tables).

The genetic classification, which derived from ataxia loci and genes reported in a steadily increasing number since 1993, was the first classification that reached general acceptance. In this molecular classification, ADCAs are referred to as spinocerebellar ataxias (SCAs) and numbered in the order of gene descriptions. The term SCA is used irrespective of the pathoanatomic findings and subsumes cerebellar, spinocerebellar and olivo-ponto-cerebellar atrophies. The genetic loci ascribed for SCA are listed in **Tables 1,2,3**:

Table 1: Loci described for 'pure' cerebellar ataxia not shortening life-span (ADCA type III)

SCA subtype	Locus	Mutation	MIM	References
SCA5	11	Unknown	600224	Ranum 1994
SCA6	19q13	CAG>19	183086	Zhuchenko 1997
SCA11	15q14-21.3	Unknown	604432	Worth 1999
SCA14	19q13.4-qter	PM in PKCg	05361	Yamashita 2000, Chen 2003
SCA15	3p24.2-pter	Unknown	606658	Knight 2003
SCA16	8q22.1-q24.1	Unknown	606364	Miyoshi 2001

Table 2: Loci described for cerebellar ataxia with pigmentary macular degeneration (ADCA type II)

SCA subtype	Locus	Mutation	MIM	References
SCA7	3p12-13	CAG>37	164500	David 1997

The association of SCA and pigmentary macular degeneration has also been described in rare cases of SCA2 and SCA3 and in a family in which defined SCA genes (especially SCA7) had been excluded.

Table 3: Loci described for cerebellar ataxia with variable additional signs like optic atrophy, ophthalmoplegia, bulbar signs, spasticity, extrapyramidal features, peripheral neuropathy, sphincter disturbance and dementia (ADCA type I)

SCA subtype	Locus	Mutation	MIM	References
SCA1	6p23	CAG>39	164400	Orr 1993
SCA2	12q24.1	CAG>32	183090	Pulst 1996, Imbert 1996, Sanpei 1996
SCA3	14q32.1	CAG>54	109150	Kawaguchi 1994
SCA4	16q22.1	Unknown	600223	Flanigan 1996
SCA8	13q21	CTG 110-250?	603680	Koob 1999
SCA10	22q13	ATTCT>550	603516	Matsuura 2000
SCA12	5q31-33	CAG>66	604326	Holmes 1999
SCA13	19q13.3-q13.4	Unknown	605259	Herman-Bert 2000
SCA17	6q27	CAG>44	607136	Koide 1999
SCA18	7q22-q32	Unknown	-	Brkanac 2002
SCA19	1p21-q21	Unknown	607346	Verbeek 2002
SCA20	11?	Unknown	-	Unassigned
SCA21	7p21.3-p15.1	Unknown	607454	Vuillaume 2002
SCA22	1p21-q23	Unknown	-	Chung 2003
FGF14	13q34	PM in FGF14	601515	Van Swieten 2003

PM: Point mutations; PKC: Protein kinase C; FGF: Fibroblast growth factor

Prevalence

Epidemiological data on SCAs are limited. Most of them had been performed in isolated populations in remote regions. In these studies the prevalence of SCAs had been estimated between 0.8 and 3.5: 100,000 (Leone *et al*. 1995, Silva *et al*. 1997, van de Warrenburg *et al*. 2001). However, in specific populations frequencies can be much higher due to founder effects, *e.g.* 1:750 for SCA2 in Holuguin on Cuba (Orozco Diaz *et al*. 1990) or 1:140 for SCA3 in Flores on the Azores (Sequeirios 1993).

The frequency of genetic subtypes of SCA vary substantially in different ethnic groups. In general SCA1, SCA2, SCA3, SCA6 and SCA7 are the most frequent forms and account for 50 - 80% of ADCA families in most studies. SCA10 has been described only in families of Mexican

descent. At least 20% of ADCA families do not carry one of the yet identified SCA genes.

Clinical description

SCAs caused by CAG expansions (SCA1, 2, 3, 6, 7, 17) show inverse correlation between age at onset and CAG repeat length, with the largest repeats found in the early onset cases. Anticipation (earlier onset and more severe disease in successive generations) has been described in many SCA subtypes. In disorders associated with CAG repeats, anticipation is caused by instability of expanded CAG tracts and prolongation during transmission. Additionally CAG repeat length partially drives phenotypic variability within single SCA subtypes. For example, SCA3 patients with less than 73 CAG repeats frequently develop marked peripheral neuropathy in addition to ataxia, whereas spasticity is much more frequent in patients with more than 73 CAG repeats (Schols *et al*. 1996).

As a rule, phenotypes are highly variable even within genetically defined SCA subtypes and within single families. Variability concerns age at onset as well as severity of symptoms and the spectrum of neuronal systems involved in the disease. Due to this variability, the genotype cannot reliably be predicted by clinical analyses. However, some signs are more characteristic for one subtype than for others (Schols *et al*. 1997). Such signs are marked bold in **Table 4** which summarizes the typical phenotype of genetic SCA subtypes.

Table 4: Phenotypes of SCA subtypes

SCA subtype	Age at onset [ys] Mean (range)	Characteristic signs	CT/MRI findings	References
SCA1	37 (5-65)	A, D, N Variable: Slow saccades, ophthalmoplegia, spasticity, PNP, executive dysfunction MEP: PMCT + CMCT increase	OPCA	Sasaki 1996
SCA2	32 (1-65)	A, D Slow saccades, hyporeflexia, tremor Rare: Parkinsonism	OPCA (early)	Geschwind 1997, Orozco Diaz 1990
SCA3	36 (5-70)	A, D, N Lid retraction, diplopia, facio-lingual fasciculation, dystonia, parkinsonism, restless legs, temperature discrimination reduced Onset <35ys: Ataxia + spasticity Onset >45ys: Ataxia + PNP	OPCA (mild) 4th ventricle enlargment	Schols 1996 Sequeiros 1993
SCA4	? (19–72)	A, D ± Sensory axonal neuropathy, pyramidal signs	CA	Flanigan 1996
SCA4	? (19–72)	A, D ± Sensory axonal neuropathy, pyramidal signs	CA	Flanigan 1996
SCA5	30 (10–68)	'Pure' A, D (Normal life expectancy)	CA	Ranum 1994
SCA6	52 (30-71)	'Pure' A, D, N (Normal life expectancy) Frequent: diplopia Rare or mild: PNP, pyramidal signsFamily history may be negative due to late onset	CA	Matsumura 1997
SCA7	35 (0.1-60)	A, D Visual loss due to pigmentary retinopathy Slow saccades, pyramidal signs	OPCA	Enevoldson 1994
SCA8	40 (1-73)	A, D, N Tremor	CA	Day 2000
SCA9	-	-	CA	unassigned
SCA10	36 (26-45)	A, D, N Epilepsy	CA	Grewal 2002
SCA11	25 (15-43)	'Pure' A, D, N (Normal life expectancy) Rare: Hyperreflexia	CA	Worth 1999
SCA12	35 (8–55)	A, N Tremor, bradykinesia, hyperreflexia	Cerebral atrophy	O'Hearn 2001
SCA13	Childhood (<1 - 45)	A, D, N Hyperreflexia, mental + motor retardation. Slow progression	CA (vermis), pontine atrophy	Herman-Bert 2000
SCA14	27 (12-42)	A (slow progression) ±(early onset) head tremor / myoclonus	CA (vermis)	Yamashita 2000
SCA15	26 (10-50)	'Pure' A, D, N (Normal life expectancy) Some: Hyperreflexia	CA (vermis)	Storey 2001
SCA16	40 (20-66)	'Pure' A, D, N (Normal life expectancy) Some: Head tremor	CA	Miyoshi 2001
SCA17	33 (6-48)	A, D, N + dementia saccadic slowing or epilepsy, hyperreflexia, akinesia, dystonia, chorea, psychosis, mutism	CA, some:general atrophy	Nakamura 2001
SCA 18	15 (12-25)	A, D, N Sensory-motor axonal neuropathy, Babinski sign	CA	Brkanac 2002
SCA19	34 (11-45)	Mild A, D, N Cognitive impairment, myoclonus, tremor, hyporeflexia, hyperreflexia	CA, some: cerebral atrophy	Schelhaas 2001
SCA20	-	-	-	unassigned
SCA21	18 (7-30)	A, D akinesia , rigidity, postural + rest tremor, hyporeflexia, cognitive impairment	CA	Devos 2001
SCA22	? (10-46)	A, D, N (slow progression) Hyporeflexia	CA	Chung 2003
FGF14	34 (27-40)	A, D, N Tremor, psychiatric episodes	CA	Van Swieten 2003

A: Ataxia, CA: cerebellar atrophy, D: Dysarthria, N: Gaze evoked nystagmus, MEP: Motor evoked potentials, OPCA: olivopontocerebellar atrophy, PMCT: Peripheral motor conduction time; CMCT: Central motor conduction time.

Differential diagnosis

Direct genetic tests are currently available for SCA1, SCA2, SCA3, SCA6, SCA7, SCA10, SCA12, SCA14, SCA17 and SCA with mutations in the protein kinase C gamma. Tests for SCA8 imply several uncertainties as explained in the section about genetic counseling. A positive result in genetic testing spares all the tests required in the differential diagnosis of ataxias described below. Thus, genetic testing is a highly economic tool in the work-up of SCAs and enables a definite diagnosis in an outpatient setting. If direct genetic tests fail to detect a causative mutation in a patient with a family history of ataxia, this family may suffer from a SCA subtype for which the responsible gene has not been discovered. Since mapping of SCA loci is only available on a research basis and is restricted to larger families with several affected and healthy individuals, other disorders expressing ataxia as a secondary sign have to be considered.

Dominantly inherited diseases with phenotypic overlap with SCAs

The *Gerstmann-Sträußler* variant of prion disease may mimic SCAs to some extend and requires electroencephalography, expression of protein 14-3-3 in cerebrospinal fluid and, in some cases, brain biopsy for diagnosis. Genetic diagnosis reveals mutations in the *PRNP* gene.

Dentato-rubral pallido-luysian atrophy (DRPLA) is an autosomal dominant neurodegenerative disorder that has predominantly been reported in Japanese families and is rare in Europe. Patients with onset before age 20 frequently present with progressive myoclonus epilepsy. Patients with onset after 40 years of age frequently exhibit choreoathetosis and psychiatric symptoms, whereas ataxia and dementia appear regardless of the age at onset or repeat length (Ikeuchi et al. 1995).

Hereditary spastic paraplegias (HSP) are a clinically and genetically heterogeneous group of neurodegenerative disorders primarily affecting the pyramidal tracts of the spinal cord. Ataxia occurs with involvement of the spinocerebellar tracts. In some 'complicated' forms, dysarthria and oculomotor disturbances can occur.

SCAs and *Huntington's disease (HD)* show broad phenotypic overlap including ataxia, spasticity, Parkinsonian features, dystonia, chorea, dementia and mood disorders. The later three symptoms in a hereditary context should favor a genetic test for HD. However, similar phenotypes have been observed in SCA17.

Parkinsonian features can be part of SCAs. Furthermore, the association of Parkinsonism and ataxia is frequently observed in *multiple system atrophy (MSA)* with autonomous dysregulation and characteristic neuropathology with glial cytoplasmic inclusions. However, hereditary forms of MSA have not been described. Additionally, ataxia has not been described as an additive symptom in hereditary forms of Parkinson's disease (PARK1 – PARK10).

Hereditary motor-sensory neuropathies (HMSN) frequently cause prominent afferent ataxia and have to be differentiated from SCAs by electrophysiological studies demonstrating the predominantly peripheral cause of ataxia.

Essential tremor (ET) shows autosomal dominant inheritance in about 60% of cases. Ataxia can be observed in some individuals but remains mostly mild. Improvement of symptoms with moderate alcohol intake strongly argues in favor of ET and against SCA.

Some subtypes of *familiar hemiplegic migraine* (*e.g.* due to mutations in the *CACNA1A* gene) are accompanied with slowly progressive ataxia and cerebellar atrophy on MRT. Recently a large Portuguese family has been described in which familial hemiplegic migraine and SCA6 are caused by the same missense mutation in the *CACNA1A* gene (Alonso *et al*. 2003).

Autosomal recessive, X-linked or mitochondrial diseases with phenotypic overlap with SCAs

Leukodystrophies are a heterogeneous group of autosomal recessive or X-linked disorders which frequently manifest in early childhood. However, juvenile and adult forms with ataxia have been described for many leukodystrophies. Especially X-linked adrenoleukodystrophy/adrenomyeloneuropathy can be mistaken for SCA if female gene carriers develop ataxia due to mild adrenomyeloneuropathy and more pronounced symptoms develop in male offspring, suggesting anticipation. It should be stressed that MRT does not necessary detect leukodystrophic white matter lesions.

Ataxia is a frequent sign in mitochondrial dysfunction. *Hereditary forms of mitochondrial cytopathies* comprises disorders like Kearns-Sayre syndrome, myoclonus epilepsy with ragged red fibers (MERRF), mitochondrial encephalopathy with lactic acidosis and stroke-like episodes (MELAS), neuropathy with ataxia and retinitis pigmentosa (NARP) or Leigh syndrome with mutations in the mitochondrial DNA (mtDNA). Since mtDNA is transmitted exclusively by the mother, mitochondrial cytopathies show maternal inheritance and can be excluded when paternal transmission of the disease occurs in the family.

Autosomal recessive and X-linked ataxias frequently show early onset but adult forms and even onset beyond 50 years of age have been described *e.g.* for *Friedreich's ataxia (FRDA)*.

Since FRDA is the most frequent form of hereditary ataxia (frequency of gene carriers 1:90 in Caucasians), pseudo-dominant forms rarely occur. Since genetic tests for other forms of autosomal recessive ataxias are costly or not available for routine diagnosis, differential diagnosis orientates predominantly towards clinical syndromes and biochemical tests such as alphafetoprotein for ataxia teleangiectasia, phytanic acid for Refsum's disease or ceruloplasmin and urinary copper excretion for Morbus Wilson.
Myoclonus epilepsies are frequently associated with ataxias. This clinically and genetically heterogeneous group of disorders mostly show autosomal recessive inheritance and onset within the first or second decade.

Non-hereditary ataxias
In individuals with ataxia in which the hereditary character of the disease remains questionable, the whole spectrum of nutritive, metabolic, toxic, inflammatory, auto-immune, neoplastic, vascular, physical and traumatic disorders causing ataxia as well as malformations and idiopathic ataxias have to be taken into consideration. This list cannot be covered in this review.

Management
In SCA6, the causative mutation occurs in the a1A-subunit of the voltage-gated neuronal calcium channel. Increasing evidence supports the hypotheses that SCA6 is caused by impaired calcium flux into neurons. Episodic ataxia type 2 (EA2) and familial hemiplegic migraine (FHM) are caused by mutations of the same calcium channel subunit. Since acetazolamide is beneficial in EA2 and calcium channel blockers are effective in migraine prophylaxis, these substrates are candidates for trials in SCA6. A first open trial claims improvement of ataxia in SCA6 with administration of acetalazolamide (250-500 mg/d) over 88 weeks (Yabe *et al*. 2001).
In other subtypes of SCA, current treatment is purely symptomatic. Parkinsonian features can be effectively treated with levodopa and/or dopamine agonists for 10 and more years in SCA2 and SCA3 (Lu *et al*. 2002; Tuite *et al*. 1995). Amantadine is beneficial for clumsy movements and bradykinesia in SCA3 (Woods *et al*. 1972). Treatment of tremor in SCAs is most problematic and frequently requires probatory administration of multiple substances like budipine, clonazepam and clozapine. Recently, successful treatment of tremor in a SCA2 patient has been reported with chronic thalamic stimulation (Pirker *et al*. 2003). Dystonia can be treated effectively with botulinum toxin. However, caution is recommended in diseases affecting anterior horn cells like SCA3, since severe and persistent atrophy may develop in muscle injected with botulinum toxin. Muscle cramps are frequent and disabling in SCAs, especially SCA3. Magnesium, chinine or mexiletine treatment substantially ameliorates this symptom (Kanai *et al*. 2003). Spasticity is treated with baclofen, tizanidine or memantine with variable success. Urinary urgency and frequency are substantially ameliorated with spasmolytics or alpha receptor blockers. Sleep disturbances are frequently overlooked but cause substantial disability in several SCA subtypes. Restless legs and periodic leg movements in sleep are especially frequent in SCA3 patients and improve with dopaminergic treatment in most cases (Schols *et al*. 1998; Abele *et al*. 2001). Ataxia is a most difficult symptom for drug treatment. 5-Hydroxytryptophan and buspirone are of almost limited effect. Trimethoprim sulfamethoxazole has been suggested for SCA3 but had no effect in a large placebo-controlled trial (Schulte 2001). Ataxia of gait, stance and limbs is best treated by physiotherapy on a regularly basis. Dysarthria as well as dysphagia warrant logopedic treatment. Diplopia should not be treated surgically since squint angles frequently vary during the course of the disease. Most patients find substantial relief with prism glasses which compensate the main angle of strabismus. Splints and ortheses may prevent trauma from supination or pain from overextension of the knee. Walking aids like sticks, stroller and wheelchair should be prescribed before fractures from falls cause long lasting immobilization.

Diagnostic methods
The diagnosis is first suspected on the basis of clinical examination, family history, CT/MRI findings and confirmed by genetic testing for SCAs whose causative gene has been identified. Tests required in the differential diagnosis of SCAs are multiple and discussed in the section above.

Genetic counselling
SCAs are defined as autosomal dominantly inherited diseases. Penetrance is age-dependent but reach 100% if gene carriers get old enough. Reduced penetrance has only been reported for SCA17 (Zühlke *et al*. 2003). In other subtypes, children of affected individuals are at 50% risk of developing the disease.
Family history in SCAs may be negative in cases of false paternity or in subtypes with late onset of symptoms like SCA6 (Matsumura *et al* 1997), massive anticipation like SCA7 (Van de Warrenburg *et al*. 2001), reduced penetrance like SCA17 (Zühlke *et al*. 2003), substantial

phenotypic variability like SCA3 when different clinical features mislead to the assumption of different underlying diseases in one family (Schols 1996).
Genetic counseling is especially difficult in SCA8. SCA8 has been mapped to chromosome 13q21 in a large ADCA family. In this family, repeats of 110 to 250 CTG in the 3' UTR of a novel gene are associated with the disease, whereas smaller repeats (71-110 CTG) as well as larger alleles (250-800 CTG) are postulated to show reduced penetrance (Koob *et al*. 1999). The finding of 'SCA8 expansions' in healthy controls and in patients with variable diseases, such as schizophrenia, bipolar affective psychosis and Lafora disease, as well as in SCA6 families have raised questions regarding the disease-causing character of the CTG expansion at the SCA8 locus (Schols *et al*. 2003). With the current knowledge, genetic tests for SCA8 should be interpreted with great caution and presymptomatic testing appears not to be appropriate.

Outlook

Increasing knowledge of molecular mechanisms underlying SCAs substantiates hope for future therapies. From the pathogenic point of view SCAs can be divided in channelopathies (SCA6, EA2, EA1), polyglutamine disorders (SCA1, SCA2, SCA3, SCA7, SCA17) and ataxias with impaired gene/protein expression (SCA8?, SCA10, SCA12, SCA14 and PKCg; for review see Margolis 2002).
Transgenic SCA animal models of polyglutamine disorders revealed an increasing number of strategies that prevent disease manifestation or delay its progression. For example, up-regulation of chaperones (Warrick *et al*. 1999), prevention of nuclear transport of ataxin-1 (Klement *et al*. 1998) or inhibition of caspases (Chen *et al*. 2000) potentially diminish polyglutamine toxicity in animal models.
However, in humans trials of NMDA antagonists (ketamine, remacemide) and glutamate-release inhibitors (baclofen, lamotrigine) as well as mitochondrial support agents (coenzyme Q10, creatine) addressing the theses of excitatory dysfunction and mitochondrial deficits in the pathogenesis of polyQ disorders failed to proof an effect.
In HD, which is another polyglutamine disorder, a first trial has been started using minocycline, an inhibitor of caspase-1 and caspase-3 expression. Furthermore, transplantation of neuronal stem cell may become a promising approach at least in HD (Bachoud-Levi *et al*. 2000; Hauser *et al*. 2002).
Apart from such pilot trials, present research focuses on improving our understanding of the molecular mechanisms underlying SCAs and will hopefully help to develop strategies improving therapeutic options in the future.

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