The molecular genetics of the spinocerebellar ataxias

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Summary

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The spinocerebellar ataxias (SCA) are a group of autosomal dominantly inherited ataxias that are clinically characterised by progressive ataxia. Until now, 13 genetically distinct SCA subtypes have been identified. In 5 of these disorders (SCA1, SCA2, SCA3, SCA6, SCA7), the mutation is a translated, expanded CAG repeat. SCA8 is caused by a CTG expansion in the 3′ untranslated region, SCA10 by an intronic pentanucleotide repeat expansion, and SCA12 by a CAG repeat expansion in the 5′ untranslated region of the respective genes. In all other SCAs, the mutations remain unknown. In most SCAs, ataxia is not an isolated symptom, but occurs in combination with a variety of non-cerebellar symptoms. In contrast, SCA5, SCA6, SCA8, SCA11 and SCA14 are characterised by an almost purely cerebellar phenotype.

Keywords: autosomal dominant cerebellar ataxia (ADCA); CAG repeat expansion; polyglutamine disorder; spinocerebellar ataxia (SCA)

Zusammenfassung

Die spinozerebellären Ataxien (SCA) sind eine Gruppe autosomal dominant vererbter Ataxien, die klinisch durch progressive Ataxie gekennzeichnet sind. Bis heute sind 13 genetisch unterschiedliche Subtypen der SCA identifiziert worden. Bei 5 dieser Erkrankungen (SCA1, SCA2, SCA3, SCA6, SCA7) ist die Mutation ein translatiertes, expandiertes CAG-Repeat. SCA8 wird durch eine CTG-Expansion in der 3′-nicht-translatierten Region, SCA10 durch eine intronische Pentanukleotid-Repeat-Expansion und SCA12 durch eine CAG-Repeat-Expansion im 5′-nicht-translatierten Bereich des entsprechenden Gens verursacht. Bei den meisten SCA ist Ataxie kein isoliertes Symptom, sondern tritt in Kombination mit einer Vielzahl nicht-zerebellärer Symptome auf. Dagegen sind SCA5, SCA6, SCA11 und SCA14 durch ein weitgehend rein zerebelläres Syndrom gekennzeichnet.

Schlüsselwörter: autosomal dominante zerebelläre Ataxie (ADCA); CAG-Repeat-Expansion; Polyglutamin-Erkrankung; spinozerebelläre Ataxie (SCA)

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Classification of dominant ataxias

The dominantly inherited ataxias are a heterogeneous group of genetically determined disorders that are clinically characterised by progressive ataxia resulting from degeneration of the cerebellar cortex and spinal pathways. In most families, ataxia is not an isolated symptom but occurs in combination with a variety of other neurological symptoms.

Classification of the dominantly inherited ataxias was unsatisfactory as long as the underlying genetic defects were unknown. Traditionally, classifications were based on neuropathological criteria. Thus, Holmes distinguished between spinocerebellar degeneration, degeneration of the cerebellar cortex, and olivopontocerebellar atrophy [1]. More recently, a clinical classification was introduced by Harding. Harding used the term autosomal dominant cerebellar ataxias (ADCA) to denote the dominantly inherited cerebellar ataxias. She separated the ADCAs into three major types, the most common of which, ADCA-I, is characterised by supranuclear ophthalmoplegia, optic atrophy, basal ganglia symptoms, dementia, and amyotrophy. ADCA-II is distinct in having the additional feature of retinal degeneration, where-

Table 1 Genetics of spinocerebellar ataxias (SCA).

disorder	chromosomal localisation	mutation	translated	gene product
SCA1	6p	CAG repeat expansion	yes	ataxin-1
SCA2	12q	CAG repeat expansion	yes	ataxin-2
SCA3	14q	CAG repeat expansion	yes	ataxin-3
SCA4	16q	?	?	?
SCA5	11cen	?	?	?
SCA6	19p	CAG repeat expansion	yes	CACNA1A
SCA7	3p	CAG repeat expansion	yes	ataxin-7
SCA8	13q	CTG repeat expansion	no	?
SCA10	22q	ATTCT repeat expansion	no	?
SCA11	15q	?	?	?
SCA12	?	CAG repeat expansion	no	PP2A-PR55β
SCA13	19q	?	?	?
SCA14	19q	?	?	?

as ADCA-III is characterised by a purely cerebellar syndrome [2].

With the genetic deciphering of the progressive ADCAs the clinical term ADCA has been widely abandoned and replaced by spinocerebellar ataxia (SCA). SCA is used to denote progressive ADCAs to whatever of Harding's subtypes they may belong. The SCAs are distinguished from the dominantly inherited paroxysmal or episodic ataxias (EA). These disorders are characterised by intermittent attacks of ataxia, while ataxia is absent or only mild between attacks. The SCAs are consecutively numbered according to the time of identification of the respective gene locus [3].

Genetic heterogeneity of spinocerebellar ataxias

Genetic heterogeneity of the SCAs has been established, with disease loci assigned to chromosome 6p (spinocerebellar ataxia type 1, SCA1) [4], 12q (SCA2) [5], 14q (SCA3) [6], 16q (SCA4) [7], 11cen (SCA5) [8], 19p (SCA6) [9], 3p (SCA7) [10, 11], 13q (SCA8) [12], 22q (SCA10) [13], 15q (SCA11) [14], 19q (SCA13) [15] and 19q (SCA14) [16]. SCA12 was defined by demonstrating linkage of a large German family to a CAG repeat expansion in the 5′ untranslated region of the gene encoding PP2A-PR55β, a regulatory subunit of the brain phosphatase PP2A (table 1) [17].

In 8 of these disorders, the affected genes have been cloned, and the mutations have been identified. In 5, SCA1, SCA2, SCA3, SCA6 and SCA7, the mutation is an expanded CAG repeat within the coding region of the respective genes [18–23]. In contrast, SCA8 is caused by a CTG expansion in the 3′ untranslated region [12], SCA10 by an intronic pentanucleotide repeat expansion [24], and SCA12 by a CAG repeat expansion in the 5′ untranslated region of the respective genes [17]. In all other SCAs, the mutations remain unknown.

Genotype-phenotype correlations

Although cerebellar ataxia is the prominent symptom in SCA1, SCA2, SCA3 and SCA12, there are several clinical features suggesting extracerebellar involvement [17, 25–27]. These disorders thus correspond to Harding's category ADCA-I. Machado-Joseph disease (MJD) is a dominantly inherited ataxic disorder with large phenotypic variation. This disease was first observed in patients of Azorean descent [28]. Although MJD patients may have clinical features, such as prominent eyes, severe dystonia and amyotrophy, which are less frequent in North American and European ADCA families, there is no clinical evidence to separate Machado-Joseph disease from ADCA-I [2]. Most families with the MJD phenotype carry the SCA3 mutation, although SCA1 or SCA2 mutations have occasionally been found in such families (table 2).

There is an almost perfect correspondence of the SCA7 genotype and the ADCA-II phenotype. In a recent study, the SCA7 mutation was found

Table 2 Genotype-phenotype correlation in spinocerebellar ataxia (SCA).

clinical presentation (Harding)	neuropathological type (Holmes)	traditional classification	mutation
ADCA-I (optic atrophy, ophthalmoplegia, dementia, etc.)	OPCA spinal degeneration spinopontine degeneration	Marie's ataxia OPCA I, IV, V Machado-Joseph disease	SCA1, 2, 12 SCA3
ADCA-II (visual loss)	OPCA	OPCA III	SCA7
ADCA-III (purely cerebellar)	CCA	Marie's ataxia	SCA5, 6, 8, 11, 14
(neuropathy)	spinal degeneration	Biemond's ataxia	SCA4
(epilepsy)	CCA		SCA10
(mental retardation)	OPCA		SCA13

ADCA = autosomal dominant cerebellar ataxia; CCA = cerebellar cortical atrophy; OPCA = olivopontocerebellar atrophy

in 16 out of 17 families with the ADCA-II (table 2) [29].

SCA5, SCA6, SCA8, SCA11 and SCA14 patients have an almost purely cerebellar presentation [8, 9, 12, 14, 16]. These families closely resemble Harding's ADCA-III families. However, detailed examination of SCA6 and SCA8 patients may show signs of sensory impairment and pyramidal involvement (table 2) [30–34].

SCA4 has a distinct phenotype with peripheral sensory neuropathy as a prominent feature [7]. Similar families have been described earlier by Biemond and have been known as Biemond's posterior column ataxia [35]. In SCA10, epilepsy may occur in conjunction with ataxia [13, 36]. Families presenting with clinical phenotypes corresponding to SCA4 and SCA10 were not included in Harding's series that led to the definition of the classical ADCA subtypes (table 2) [2].

In all SCAs intrafamilial phenotypical variation is considerable. In particular, age of onset may range from early childhood to late adulthood. For the SCAs caused by translated CAG repeats (SCA1, SCA2, SCA3, SCA6 and SCA7), clinical variability is partly explained by the variations of the repeat length. In principal, larger expansions are associated with earlier disease onset, a faster disease progression and a more severe clinical presentation [18, 37, 38]. In SCA1, SCA2, SCA3 and SCA7, the expanded repeats are subject to length changes during intergenerational transmission with a tendency to further expansion in the following generation [39]. Instability of the expanded alleles is explained by slippage of the DNA polymerases during meiosis. Due to the inverse correlation between repeat length and age of onset, repeat instability results in anticipation, i.e. earlier disease onset in subsequent generations.

Molecular mechanisms of CAG repeat mutations

The mutations causing SCA1, SCA2, SCA3, SCA6 and SCA7 are unstable, expanded CAG trinucleotide repeats coding for expanded polyglutamine tracts within the respective proteins. These disorders belong to a group of autosomal dominant disorders for which the term polyglutamine disorders has been coined. Apart from the SCAs this group includes Huntington's disease, spinobulbar muscular atrophy and dentatorubro-pallidoluysian atrophy [3, 40]. All available evidence suggests that these disorders are due to a novel deleterious function of the abnormal disease proteins.

The gene products of the SCA genes are designated ataxins and are numbered according to the encoding genes. With the exception of SCA6 which affects the CACNA1A gene that encodes the α_{1A} voltage-dependent calcium channel subunit the function of the ataxins is unknown. In most SCAs, there is no correlation between the distribution of the normal gene products and the sites of pathology. The ataxins are distributed ubiquitiously in nervous and non-nervous tissue, while the pathology is almost exclusively found in the central nervous system with strongest involvement of the cerebellum, brain stem and spinal cord [41–44].

Expanded ataxins have an increased tendency to misfold and aggregate [45]. In some disorders, namely SCA1, SCA3 and SCA7, aggregated ataxins are redistributed to the nucleus where they form neuronal intranuclear inclusions. Although neuronal intranuclear inclusions do not appear to be a prerequisite for neurodegeneration [46], aggregation of ataxins is considered to be a key event in the disease process. This hypothesis is supported by experiments showing that overexpression of molecular chaperones that refold

misfolded proteins and prevent protein aggregation rescue transgenic animals from polyglutamine-induced neurodegeneration [47]. Similarly, genetic screens in a Drosophila model of SCA1 identified genes involved in protein folding as important modifiers of the disease process [48]. In human autopsy material from SCA patients chaperones are redistributed to neuronal intranuclear inclusions suggesting that activation of chaperones is an (ultimately unsuccessful) attempt of the cell to prevent polyglutamine toxicity [49].

At present, the mechanisms by which the expanded and aggregated ataxins exert their deleterious action are poorly defined. One hypothesis says that association of ataxins with the nuclear matrix will lead to disruption of essential nuclear functions resulting in altered gene expression [50, 51]. In addition, expanded ataxins have been shown to recruit and possibly inactivate transcription factors containing glutamine repeats. For example, eyes absent protein (EYA) and TATA-binding protein (TBP) have been localised in neuronal intranuclear inclusions in a transgenic Drosophila model of SCA3 [52]. A further mechanism that may lead to altered gene transcription is sequestration of proteins of the ubiquitin/proteasome proteolytic pathway resulting in altered activation of transcription factors [52].

To test the hypothesis that SCA mutations lead to altered gene expression, Lin et al. performed PCR-based cDNA subtraction using cerebellar mRNA of SCA1 transgenic and wildtype mice [53]. The earliest change in gene expression occurring at postnatal day 11 was downregulation of the gene encoding prenylcystein carboxymethyltransferase (PCCMT). PCCMT is involved in posttranslational lipid modification of several proteins. Later, expression of transcripts encoding the following proteins was downregulated: on postnatal day 14 inositol triphosphate receptor type 1 (IP3R1) and sarcoplasmic endoplasmic reticulum calcium ATPase type 2 (SERCA2), and at an age of 3 to 4 weeks type 1 inositol polyphosphate 5-phosphatase (INPP5A), transient receptor potential type 3 (TRP3) and excitatory amino acid transporter type 4 (EAAT4). All these proteins are involved in calcium store regulation and glutamate metabolism. The relevance of these findings was underlined by demonstration of reduced immunoreactivity of PCCMT, IP3R1, and SERCA2 in cerebellar Purkinje cells of SCA1 patients. In similar experiments performed in a neuronal cell line overexpressing expanded ataxin-3 [54], we recently found upregulation of a number of genes coding for proteins involved in inflammation. The in vitro results were confirmed in human SCA3 brain material [55]. These observations identify transcriptional dysregulation as an important mechanism by which expanded and aggregated ataxins affect cellular homeostasis.

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