Genetic and molecular aspects of spinocerebellar ataxias

Viktor Honti[1]
László Vécsei[1,2]

[1]Department of Neurology, Albert Szent-Györgyi Medical and Pharmaceutical Center, University of Szeged, Szeged, Hungary; [2]Neurology Research Group of the Hungarian Academy of Sciences and University of Szeged, Szeged, Hungary

Abstract: The group of spinocerebellar ataxias (SCAs) includes more than 20 subgroups based only on genetic research. The "ataxia genes" are autosomal; the "disease-alleles" are dominant, and many of them, but not all, encode a protein with an abnormally long polyglutamine domain. In DNA, this domain can be detected as an elongated CAG repeat region, which is the basis of genetic diagnostics. The polyglutamine tails often tend to aggregate and form inclusions. In some cases, protein–protein interactions are the key to understanding the disease. Protein partners of ataxia proteins include phosphatases and components of chromatin and the transcriptional machinery. To date, investigation of spinocerebellar ataxias involves population genetics, molecular methods, and studying model organisms. However, there is still no efficient therapy for patients. Here, we review the genetic and molecular data gained on spinocerebellar ataxias.

Keywords: ataxia, repeat, polyglutamine, autosomal, dominant

Introduction

Spinocerebellar ataxias are late-onset, progressive neurodegenerative, and movement disorders showing autosomal inheritance. The clinical features of spinocerebellar ataxias include ataxia, dysarthria, dysmetria, and intention tremor. These types of diseases (autosomal dominant cerebellar ataxias, ADCAs) are very heterogeneous. The original classification is based on associated clinical symptoms, such as brain stem signs and retinopathy. The presence of pyramidal and extrapyramidal symptoms and ophthalmoplegia points to the diagnosis of ADCA I; the presence of retinopathy, to ADCA II; and the absence of associated signs, to ADCA III. The new categorization is based on the latest genetic results, which prove that mutations in more than 20 genes are responsible for these complex phenotypes, and even the clinical subgroups are genetically heterogeneous.

Spinocerebellar ataxias are not frequent diseases. Prevalence of the autosomal dominant cerebellar ataxias is estimated to be 3/100 000 in the Netherlands (van de Warrenburg et al 2002). Frequencies of the different types of ataxias may vary among regions and ethnic groups. For example, SCA2 is common in Korea, and SCA3 is much more common in Japan and Germany than in the United Kingdom (Leggo et al 1997; Schols et al 1997; Watanabe et al 1998; Kim et al 2001; Silveira et al 2002).

In the case of ataxias, mutations in completely unrelated genes cause very similar phenotypes. The source of the mutation in many genetic subtypes of ataxias (SCA1, SCA2, SCA3, SCA6, SCA7, SCA12, and SCA17) is the same (CAG repeat expansion), and the resulting protein product contains a long polyglutamine domain.

Some types of ataxias show a partly different molecular background (eg, SCA8, SCA10, SCA12, and some forms of SCA6), since they involve repeats (not necessarily CAG) that are not translated, or they do not involve repeats at all. The mutant allele

Correspondence: László Vécsei
Department of Neurology, University of Szeged, H-6725 Szeged, Semmelweis u. 6, Hungary
Tel +36 62 545 351
Fax +36 62 545 597
Email vecsei@nepsy.szote.u-szeged.hu

responsible for SCA8 codes for a non-coding RNA product, which can associate with RNA-binding proteins like staufen in *Drosophila melanogaster* causing neurodegeneration (Mutsuddi et al 2004). Disease alleles in the case of SCA10 show massive expansion (800–4500 repeats) of a pentanucleotide (ATTCT) and not a trinucleotide repeat in an intron of a gene with unknown function (Matsuura et al 2000). SCA12 is caused by a CAG repeat expansion that is not transcribed to polyglutamine and is speculated to affect the expression of the gene *PPP2R2B*, which encodes a brain-specific regulatory subunit of protein phosphatase PP2A (Holmes et al 1999). Although SCA6 is associated with small expansions of a CAG repeat at the 3′ end of the *CACNA1A* gene, which codes for the pore-forming subunit of calcium channel type P/Q, point mutations in the same gene are responsible for its two allelic disorders (episodic ataxia type 2 and familial hemiplegic migraine) (Mantuano et al 2003). There have been many investigations on the role of molecularly different alleles in causing ataxia. To date, many *SCA* alleles are well characterized, and although many do not involve repeats, one popular field of study in the genetics of ataxias is the description of repeat-expansion alleles and the mechanism of their function.

Table 1 Type and number of repeats belonging to normal, risk, and disease alleles in different types of spinocerebellar ataxias

Disease name	Repeat type/normal number	Intermediate repeat number	Abnormal repeat number
SCA1	CAG/6–44	36–38	39–91
SCA2	CAG/max 31	–	32–500+
SCA3	CAG/max 47	48–51	53–86
SCA4	–	–	–
SCA5	–	–	–
SCA6	CAG/max 18	19	19–33
SCA7	CAG/ 7–35	28–35	36–300+
SCA8	CAG/15–50	50–70	71–800+
SCA9	–	–	–
SCA10	ATTCT/10–22	–	280–4500+
SCA11	–	–	–
SCA12	CAG/7–31 (45)	–	55–78
SCA13	–	–	–
SCA14	–	–	–
SCA15	–	–	–
SCA16	–	–	–
SCA17	CAG/25–42	42–44	46–63
SCA18	–	–	–
SCA19	–	–	–
SCA20	–	–	–
SCA21	–	–	–
SCA22	–	–	–
SCA25	–	–	–

Trinucleotide repeat as a cause of disease

The CAG/CTG repeat in genes is often translated to a polyglutamine domain in proteins. Elongated repeat regions result in elongated polyglutamine tracts. The first protein proven to be involved in neurodegenerative disorders and contain an elongated polyglutamine domain was huntingtin, the factor responsible for Huntington's disease (HD) (Huntington's Disease Collaborative Research Group 1993). To date, besides HD, nine polyglutamine disorders have been characterized, including spinobulbar muscular atrophy (SBMA), dentatorubral-pallidoluysian atrophy (DRPLA), and spinocerebellar ataxias (SCA) 1, 2, 3, 6, 7, and 17. Expansion of the CAG/CTG repeats results in alleles which are genetically dominant because of their toxic gain-of-function characteristics.

Expansion alleles are polymorphic in populations, and under a certain repeat number the CAG repeat length should be considered normal. Alleles carrying intermediate numbers of repeats are risk alleles for late-onset spinocerebellar ataxia (see Table 1 for normal and abnormal repeat numbers in certain types of ataxias). In general, the more repeats, the earlier the onset of the disease.

Furthermore, there is a genetic phenomenon in relation to these repeat expansion alleles, called anticipation. The CAG/CTG repeat sequence is particularly unstable, and de novo mutations can occur during paternal transmissions of intermediate-size alleles. The disease increases in severity in successive generations, and children can have a more severe form, an earlier onset, or a more rapid progression of the disease than their parents. In some ataxias, anticipation may be so extreme that children with an early onset, severe disease may die of disease complications long before the affected parent or grandparent is symptomatic.

In the SCA8 ataxia syndrome, the characteristics of anticipation are unique, since SCA8 is characterized by dramatic repeat instability and a high degree of reduced penetrance. In SCA8, the genetic cause of the disease is a repeat of the CTG trinucleotide instead of CAG. In SCA8, the majority of expansions of CTG repeat occur during maternal (and not the usual paternal) transmission, and extremely large repeats (800 bp) may be associated with an absence of clinical symptoms (Ranum et al 1999).

Anticipation seems to be dependent on the genomic context. Transgenic mice carrying cDNA constructs of *SCA7* show little intergenerational repeat instability, while in mice carrying the *SCA7* genomic fragment, expansion of the CAG

repeat can be observed. Deletion of the 3′ genomic region significantly stabilizes the repeat length in intergenerational transmission of the genomic construct (Libby et al 2003). There are other factors which seem to play a role in repeat stabilization. There are indications that, at least in the case of some ataxia genes, interruptions in the repeat region can stabilize the CAG repeat, while lack of interruptive sequences predisposes alleles towards instability and expansion. In the case of *SCA2*, interruptions by CAA trinucleotides at the 5′ end have such an effect (Choudhry et al 2001). In some cases, contraction of the repeat region can also be observed, indicating that repeat length alterations are dynamic in these types of disorders (Andres et al 2003).

The investigation of CAG repeat length instability in transgenic mice led to the observation that advanced maternal age is an important factor for instability of nucleotide repeats during transmission. If the transgene is maternally transmitted, the instability occurs after meiotic DNA replication and prior to oocyte fertilization (Kaytor et al 1997). However, most of the *SCA* genes show paternal anticipation.

A recent publication implies that anticipation of repeats can be a result of the dysfunction of the DNA repair system (Lahiri et al 2004). The authors observed that expanded CAG repeats activate the DNA damage checkpoint pathway in yeast, and mutation of genes in the pathway can increase repeat fragility.

How the expanded polyglutamine chain exerts its effect is not completely clear. Proteins with long polyglutamine tracts have an increased tendency to aggregate, often as truncated fragments forming ubiquitinated intranuclear inclusion bodies. In some cases, like in the case of ataxin-3 (SCA3), cleavage of the polyglutamine chain promotes aggregation (Paulson et al 1997). The factor responsible for cleaving the polyglutamine proteins might be different in different types of ataxias. This would give a reason for the specific neurotoxic effect of the different ataxia-related genes. It would be practical to find the proteases that do the cleavage in the case of the certain elongated ataxia proteins. The inhibition of the adequate protease might have a therapeutic effect by reducing the tendency of polyglutamine domains to aggregate.

An interesting observation proves that CAG repeat elongation alone is not sufficient to induce the disease. In the case of SCA1, the S776 amino acid is critical in disease development: when changed to A776 the induction of the disease is significantly reduced in transgenic mice, very likely due to lack of phosphorylation at the 776 position in ataxin-1 (Emamian et al 2003). These results suggest that polyglutamine disorders cannot only be explained by aspecific interactions of the elongated domain.

Genes responsible for spinocerebellar ataxias

Molecular information, except for chromosomal position, is not available on most of the *SCA* genes, but the research efforts in this field are increasing exponentially. In the following sections we summarize the information already gained about the most intensively studied ataxia genes (see Table 2 for summarized molecular details). We focus only on the genes for which molecular function was investigated.

SCA1

Using recombination fraction analysis, linkage of *SCA1* to HLA on chromosome 6 (Jackson et al 1977) was shown. Further studies helped to determine the exact position of the gene (Kwiatkowski et al 1993; Lunkes et al 1994). The basic genetic defect in spinocerebellar ataxia-1 consists of expansion of a trinucleotide CAG repeat (Orr et al 1993) in a gene termed ataxin-1 that encodes a 10-kb mRNA transcript (Banfi et al 1994). This was the fifth example of a pathologic state resulting from expansion of an unstable trinucleotide repeat. The expanded *SCA1* alleles are also translated into proteins of apparently normal stability and distribution (Servadio et al 1995).

Human *SCA1* with expanded CAG repeats expressed in Purkinje cells of transgenic mice are sufficient to produce degeneration and ataxia (Burright et al 1995). Although nuclear localization of ataxin-1 is necessary for the development of the disease, nuclear aggregation of ataxin-1 is not required to initiate pathogenesis in transgenic mice (Klement et al 1998).

One key to understanding the mechanism of the disease caused by the mutant ataxin-1 is its interaction with LANP (leucine-rich acidic nuclear protein). LANP is expressed predominantly in Purkinje cells, and its interaction with ataxin-1 is significantly stronger when the number of glutamines is increased (Matilla et al 1997).

Proteases and chaperons in interaction with ataxia-related proteins seem to play important roles in ataxias. Cummings et al (1998) found colocalization of the 20S proteosome and chaperone HSJ2, a member of the Hsp40 family, with large nuclear inclusions of ataxin-1 in brain neurons of patients with SCA1 and in mice transgenic for a mutant *SCA1* allele containing 82 glutamines. In these

Table 2 Chromosomal localization and protein products of genes involved in spinocerebellar ataxias

Disease name	Gene	Locus	Product	Inclusions
SCA1	SCA1	6p23	Ataxin-1	Nuclear inclusions in Purkinje cells containing Hsc 70
SCA2	*SCA2*	12q24	Ataxin-2	Cytoplasmic microaggregates
SCA3	*MJD*	14q24.3-q31	Machado-Joseph disease protein 1	Intranuclear inclusions, colocalization with the proteasome
SCA4	*SCA4*	16q22.1	–	No data
SCA5	*SCA5*	11p11-q11	–	No data
SCA6	*CACNA1A*	19p13	Voltage-dependent P/Q-type calcium channel alpha-1A subunit	Numerous cytoplasmic inclusions, in Purkinje cells, no ubiquitination
SCA7	*SCA7*	3p21.1-p12	Ataxin-7	Ubiquitinated intranuclear inclusions in several brain regions, containing proteasome subunits
SCA8	*SCA8*	13q21	–	No data
SCA9	–	not assigned	–	No data
SCA10	*SCA10*	22q13	Ataxin-10	No data
SCA11	*SCA11*	15q14-q21.3	–	No data
SCA12	*SCA12*	5q31-q33	–	No inclusions
SCA13	*SCA13*	19q13.3-q13.4	–	No data
SCA14	*PRKCG*	19q13.4-qter	Protein kinase C gamma	No inclusions
SCA15	*SCA15*	–	–	No data
SCA16	*SCA16*	8q22.1-q24.1	–	No data
SCA17	*TBP*	6q27	TFIID	Neuronal intranuclear inclusion bodies
SCA18	–	reserved	–	
SCA19	–	1p21-q21	–	No data
SCA20	–	–	–	No data
SCA21	–	reserved 7p21-15	–	No data
SCA22	–	1p21-q23	–	No data
SCA25	–	–	–	No data

nuclear inclusions, there is also faint staining for Hsc70, a member of the Hsp70 chaperone family. Similar colocalization can be seen in HeLa cells transfected with ataxin-1. In the transfected HeLa cells, unlike in the brain, there is apparent induction of Hsc70 chaperone. Overexpression of HSJ2 in these cells reduces aggregation of ataxin-1, suggesting a possible therapeutic strategy.

In SCA1 mice crossbred with mice overexpressing the molecular chaperone inducible *HSP70*, the amount of nuclear inclusions in Purkinje cells persist, but physiologic and histopathologic analysis reveals that high levels of HSP70 protect against neurodegeneration and preserve dendritic arborization in the cerebellum (Cummings et al 2001).

Latest results demonstrate that ataxin-1 interacts with the transcriptional corepressor SMRT (silencing mediator of retinoid and thyroid hormone receptors) and with histone deacetylase 3. Ataxin-1 binds chromosomes and mediates transcriptional repression when tethered to DNA. In Drosophila, genetic interaction between *ataxin-1* and *SMRTER* (the Drosophila cognate of *SMRT*) can be observed (Tsai et al 2004).

SCA2

After determining the exact position of the gene responsible for SCA2, CAG repeats have been proven to have a major role in development of the disorder (Pulst et al 1993).

Mice expressing *ataxin-2* showed functional progressive deficits accompanied with the final loss of Purkinje cells resulting from aggregation in cytoplasm. Despite many similarities to ataxin-3, ataxin-2 does not form inclusions in the nucleus and does not gain detectable ubiquitination (Huynh et al 2000). The expanded form of SCA2 disrupts the structure of the Golgi apparatus, which is the predominant location of the normal protein (Huynh et al 2003).

Datx2, the Drosophila homolog of human SCA2, is a dosage-sensitive regulator of actin filament formation (Satterfield et al 2002).

SCA3

SCA3 was described in descendants of William Machado, a native of an island in the Portuguese Azores. This ataxia is the most frequent one among Portuguese immigrants living in New England (Nakano et al 1972). The disorder

begins as ataxic gait after age 40. The cause of the disorder is a CAG repeat expansion in the respective gene in the 14q24.3-q31 position (Takiyama et al 1993; Sequeiros 1994). Igarashi et al (1996) found association of intergenerational instability of the expanded CAG repeat in Machado-Joseph Disease (MJD) with a CAG/CAA polymorphism in the CAG repeat and a CGG/GGG polymorphism at the 3′ end of the CAG array. Their results strongly suggest that an interallelic interaction is involved in the intergenerational instability of the expanded CAG repeat. The expanded CAG repeats are less stable in paternal transmission than in maternal transmission.

Ataxin-3 adopts a unique conformation when expressed within the nucleus of transfected cells. This novel conformation of intranuclear ataxin-3 is not due to proteolysis, suggesting instead that association with nuclear protein(s) alters the structure of full-length ataxin-3, exposing the polyglutamine domain. This conformationally altered ataxin-3 is bound to the nuclear matrix. The pathologic form of ataxin-3 with an expanded polyglutamine domain also associates with the nuclear matrix (Perez et al 1999). These data suggest that an early event in the pathogenesis of SCA3/MJD may be an altered conformation of ataxin-3 within the nucleus that exposes the polyglutamine domain. The abnormally strong or aspecific interactions of this protein may be the key to the disease.

However, intranuclear aggregations of ataxin-3 can also be observed. Human disease tissue and in vitro models show redistribution of the 26S proteasome complex into polyglutamine aggregates. In neurons from SCA3 brain, the proteasome is localized to intranuclear inclusion bodies containing mutant ataxin-3. Inclusion formation is dependent on the nuclear localization of the mutant protein and occurs in special subnuclear structures recently implicated in the regulation of cell death. Inhibitors of the proteasome cause a repeat-length dependent increase in aggregate formation (Chai et al 1999). These results suggest a central role for protein misfolding in the pathogenesis and that modulating proteasome activity is a potential approach to altering the progression of the polyglutamine diseases.

Frameshift mutations in expanded CAG tracts of *ataxin-3* can generate polyalanine mutant proteins that also form intranuclear inclusions. The frameshifts may more likely occur in longer CAG repeats (Gaspar et al 2000).

The Drosophila model for this disease has led to some new observations. The sensitivity of different cell types is variable to the inclusion of the ataxin-3 protein, and neurons seem to be especially susceptible (Warrick et al 1998). Molecular chaperones Hsp70 and Hdj1 (the Drosophila homolog of human HSP40) show substrate specificity to polyglutamine proteins and alter the solubility of the mutant polyglutamine protein, suppressing neurotoxicity (Chan et al 2000).

Latest results indicate that ataxin-3 is a transcriptional inhibitor. Interactions of ataxin-3 and other regulators of histone acetylation and transcription (p300, CREB-binding protein) have been detected (Li et al 2002).

SCA5

In a family descendant from the grandparents of President Lincoln, Ranum et al (1994) mapped the gene of SCA5 to the centromeric region of chromosome 11 by linkage to DNA markers. The most dramatic examples of anticipation occur with maternal transmission. There are several 3-generation examples of grandmothers having onsets 10–20 years later in life than their daughters, who in turn had onsets 10–20 years later in life than their children. Furthermore, all 4 cases of juvenile onset (10–18 years) are instances of maternal inheritance.

SCA6

SCA6 was mapped by genomewide linkage analysis in 15 Japanese families with autosomal pure cerebellar ataxia (Ishikawa et al 1997). CAG repeat arrays are translated as polyglutamine tracts in the protein product, which is the alpha (1A)-voltage-dependent calcium channel (CACNA1A) (Zhuchenko et al 1997).

The calcium channel mRNA/protein containing the CAG repeat/polyglutamine tract is most intensely expressed in Purkinje cells of normal human brains. In SCA6 brains, numerous oval or rod-shaped aggregates can be seen exclusively in the cytoplasm of Purkinje cells. These cytoplasmic inclusions are not ubiquitinated, which contrasts with the neuronal intranuclear inclusions of other CAG repeat/polyglutamine diseases. In cultured cells, formation of perinuclear aggregates of the channel protein and apoptotic cell death can be seen when transfected with full-length *CACNA1A* coding an expanded polyglutamine tract. It can be stated that the mechanism of neurodegeneration in SCA6 is associated with cytoplasmic aggregations of the alpha-1A calcium channel protein caused by a small CAG repeat/polyglutamine expansion in CACNA1A (Ishikawa et al 1999).

Genetic anticipation in case of these CAG repeat expansions is not so trivial, some alleles seem to be very stable (Ishikawa et al 1997). Point mutant allelic forms of

SCA6 cause different neurologic disorders (as mentioned above).

SCA7

SCA7 has a special clinical symptom: this is the only ataxia associated with retinal degeneration (Froment et al 1937). The pathogenic *SCA7* CAG expansion was cloned by RAPID (repeat analysis, pooled isolation, and detection) from an archived DNA sample from an individual affected with ataxia and retinal degeneration (Koob et al 1998).

Mice expressing mutant human *ataxin-7* show nuclear inclusions of ubiqutinated ataxin-7 protein that recruits subunits of proteases and chaperons. Proteolitic cleavage and transneuronal responses are likely to be involved in pathogenesis (Yvert et al 2000).

In yeast 2-hybrid system, ataxin-7 interacts with CRX, a nuclear transcription factor predominantly expressed in retinal photoreceptor cells. Coimmunoprecipitation experiments colocalized ataxin-7 with CRX in nuclear aggregates. Polyglutamine-expanded ataxin-7 suppresses CRX transactivation in transgenic retinas. *SCA7* transgenic mice faithfully recapitulate the process of retinal degeneration observed in human SCA7 patients. Thus, the specificity of the mutant protein can be explained by interactions with specific partners of the ataxin-7 protein (La Spada et al 2001).

Latest results in the research on interactive partners of the protein show that ataxin-7 is a member of at least three different complexes involved in the regulation of mammalian chromatin structure. Ataxin-7 is an integral component of SAGA-like complexes (SAGA in yeast contains the Gcn5 acetylase), the TATA-binding protein-free TAF-containing complex (TFTC) and the SPT3-TAF9-GCN5 acetyl-transferase complex (STAGA). A Zn-binding domain potentially involved in protein–protein interactions of the ataxin-7 protein was also identified. An interesting finding is that the elongated polyglutamine domain does not affect incorporation of ataxin-7 into the complexes (Helmlinger et al 2004).

SCA8

SCA8 was identified by Koob et al (1999). It was mapped to the 13q21 and was cloned using the RAPID technique.

SCA8 is also a CAG repeat disorder. Repeat length contracts with paternal transmission, but expansion can be observed in maternal transmission. The CAG repeat in the mutant alleles is not translated into a polyglutamine tract, but the CTG repeat in the complement strand is part of a transcribed but not translated RNA. The gene organization in this region is very complex: it is hypothesized that *SCA8* RNA is an endogenous antisense, which is transcribed through the first exon of the gene *KLHL1* (Nemes et al 2000). Thus, the *SCA8* gene codes for an untranslated RNA functioning as a gene regulator (Erdmann et al 2001).

The gene often contains CCG, CTA, CTC, CCA, or CTT interruptions preceding the repeat region that may play a role in reducing the penetrance of disease alleles (Moseley et al 2000).

SCA8 repeat expansion can coexist with *SCA1* and *SCA6* repeats, and the protein product can act through the *SCA6* coded calcium channel (Izumi et al 2003, Sulek et al 2003).

SCA10

SCA10 is determined by a gene which maps to the 22nd chromosome (Zu et al 1999) and includes an ATTCT pentanucleotide repeat region in the 9th intron of the gene (Matsuura et al 2000). Mutant alleles contain expansion of this repeat.

SCA14

The gene responsible for SCA14 ataxia was mapped to the 19q13.4-qter (Yamashita et al 2000). SCA14 type ataxia is not attributable to trinucleotide repeat expansion (Brkanac et al 2002) but to various mutations in the *PRKCG* (protein kinase C gamma) gene which result in altering a highly conserved residue in the cystein rich region of the respective protein (Chen et al 2003).

SCA17

The *SCA17* gene codes for the TATA-binding protein (TBP). Elongated CAG repeats in the coding region cause this type of ataxia (Koide et al 1999). Using anti-TBP and 1C2 (which is used to identify polyglutamine tracts) antibodies, neuronal intranuclear inclusion bodies can be observed in Purkinje cells (Rolfs et al 2003). There is only a weak correlation between the repeat number and the age of onset, but an extremely expanded repeat region can cause very severe phenotypes and early onset (Maltecca et al 2003).

Perspectives and potential therapy

Although molecular aspects of described ataxias are intensively studied, we still need to gain more information to be able to design a treatment of ataxia patients. One possible way could be the inhibition proteases (eg, caspases)

that are involved in the formation of inclusion bodies from the respective polyglutamine proteins. This task requires extensive research of proteases that are specific for the given type of SCA. Another approach to treatment could be modulating proteosome activity. The observation that the elongated form of ataxin-3 in inclusion bodies is colocalized with the 26S proteosome complex (Chai et al 1999) implies that the proteosome could have a major role in the development of the disorder.

It is also proven that polyglutamine proteins need molecular chaperons to gain their conformation, and in some cases elongated polyglutamine tract containing proteins are localized together with chaperons (eg, heatshock proteins) (Cummings et al 1998). Research on the effect of altering the level of specific chaperons could also be very informative in designing a treatment for spinocerebellar ataxias.

The latest results indicate that oxidative stress may have a role in the development of spinocerebellar ataxias. The mutant form of ataxin-1, which contains the expanded polyglutamine tract, recruits Cu/Zn-superoxid dismutase into the nucleus of HeLa cells and also decreases the activity of the enzyme. This process exposes the cells to reactive oxygen species (Kim et al 2003). Increasing superoxid dismutase activity or reducing the level of reactive oxygen species may also delay the development of the disorder.

Inhibition of phosphorylation of certain aminoacids could also hinder the development of the disease by blocking the molecular interactions of the expanded polyglutamine domains (Emamian 2003).

In studying and understanding the pathomechanism and molecular features of ataxias, models (mouse and Drosophila) are going to be indispensable. In some types of ataxias these have already been generated and are in use. This is a great step compared with studies in cell lines, because gaining in vivo data is very important in determining the molecular interactions of ataxia-related proteins. The aim is to gain a wide range of information in the molecular and biochemical alterations in these disorders and to design an effective therapy.

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