Chapter 11
Genetics of Dominant Ataxias

Mario Manto and Daniele Marmolino

Abstract Dominant ataxias represent a clinically and genetically heterogeneous group of hereditary disorders comprising autosomal dominant spinocerebellar ataxias (ADCAs, SCAs) and episodic ataxias (EAs). From the clinical point of view, patients with ADCA exhibit a progressive cerebellar syndrome, either isolated or in combination with extra-cerebellar deficits. EAs are characterized by recurrent episodes of dizziness and ataxia, occurring either in a context of interictal neurological deficits or not. Current genetic classification includes 32 SCA loci (numbered from SCA1 to SCA36, plus dentatorubropallidoluysian atrophy DRPLA) and 7 EA loci (numbered from EA1 to EA7). A group of 12 ADCAs are related to an expansion of CAG repeats (polyglutaminopathies) or to repeats outside the coding region. Disease progression and severity are correlated with the repeat size. Anticipation is due to an instability of the expanded allele during transmission. The other ADCAs are due to conventional gene mutations. Overall, the causative gene is identified in about 60 % of dominant ataxias. There is still no cure for this group of disabling degenerative diseases. Current management is symptomatic.

Keywords Cerebellum • Ataxias • Genes • Dominant • Polyglutamine • Episodic ataxias • Atrophy

The terminology of “ataxia” designates a lack of coordination and balance. Ataxia may be consecutive to a disorder affecting the cerebellum, its afferences and/or its efferences, or the peripheral nerves (the so-called sensory ataxias). Numerous disorders can cause ataxia of cerebellar origin, including sporadic and genetic diseases [1, 2]. This chapter will focus on cerebellar ataxias with a dominant transmission. These rare disorders have an estimated prevalence of 3–4/100,000 individuals [3]. Autosomal recessive ataxias and X-linked ataxias are not discussed in this chapter.

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Classification of Dominant Ataxias

Autosomal dominant spinocerebellar ataxias (ADCAs) were initially classified on the basis of clinical and neuropathological features. Patients were grouped according to the clinical phenotype: presence of a cerebellar syndrome which was pure or associated with brainstem signs, extrapyramidal deficits, signs of peripheral nerve involvement, or retinal deficits. The dominantly inherited pattern was pointed out by Pierre Marie [4]. Neuropathological classification has considered a pattern of olivopontocerebellar atrophy (OPCA) and the cerebellar cortical atrophy (CCA) type, in addition to the cerebello-olivary degeneration of Holmes [5–8]. However, these terms have encompassed both sporadic and genetic ataxias, causing some confusion. The classification of Greenfield [9] has considered predominantly spinal ataxias (such as Friedreich ataxia and hereditary spastic paraplegias), predominantly cerebellar ataxias, and spinocerebellar ataxias involving extra-cerebellar regions. Again, this classification was ambiguous if analyzed from a genetic standpoint, because several modes of transmission were gathered in the same groups of disorders.

The works of Harding clarified greatly the classification of dominant ataxias [10–12]. This author underlined the limits of the neuropathological classification. For instance, she pointed out that patients within the same family fall in distinct neuropathological groups. She suggested a new classification which took into account the clinical presentation, the mode of inheritance, and the presumed biological causes. ADCAs were divided into four types:

1. ADCA type I: cerebellar ataxia “plus” (presence of extra-cerebellar deficits, such as ophthalmoplegia, optic atrophy, cognitive deficits, and extrapyramidal signs)
2. ADCA type II: cerebellar ataxia with visual deficits due to pigmentary retinal degeneration (ophthalmoplegia, dementia, and extrapyramidal deficits may occur)
3. ADCA type III: pure cerebellar syndrome usually starting after the third decade
4. ADCA type IV: cerebellar ataxia with mental retardation, deafness, and myoclonus

The current classification is based on genetics and considers three groups:

1. The spinocerebellar ataxias (SCAs)
2. Dentatorubropallidoluysian atrophy (DRPLA)
3. Episodic ataxias (EAs)

SCAs and DRPLA are progressive disorders characterized by a cerebellar syndrome which may be associated with noticeable extra-cerebellar deficits. The most common SCAs are SCA1, SCA2, SCA3 (Machado–Joseph disease (MJD)), and SCA6 [3]. The incidence and prevalence of the various SCAs varies according to the geographical region of the world. It is important to note that the phenotype of SCAs may vary greatly within the same family and between families. The main clinical feature of EAs is the recurrent aspect of ataxia (crises or attacks of ataxia). Table 11.1 lists the main clinical signs in the various SCAs.

Table 11.1 Clinical phenotype of SCAs

<table>
<tr><td>Pure cerebellar syndrome</td><td colspan="3">SCA5, SCA6, SCA11, SCA26</td></tr>
<tr><td rowspan="17">Cerebellar ataxia combined with extra-cerebellar deficits (“ataxia plus”)</td><td>Cognitive deficits and/or behavioral symptoms</td><td colspan="2">SCA1, SCA2, SCA3, SCA10, SCA12, SCA13, SCA14, SCA17, SCA19, SCA21, SCA27, DRPLA</td></tr>
<tr><td>Seizures</td><td colspan="2">SCA10, SCA17, DRPLA</td></tr>
<tr><td rowspan="5">Oculomotor deficits and/or involvement of eyes</td><td>Downbeat nystagmus</td><td>SCA6</td></tr>
<tr><td>Ocular dyskinesia</td><td>SCA10</td></tr>
<tr><td>Slow saccades</td><td>SCA1, SCA2, SCA3, SCA7, SCA28</td></tr>
<tr><td>Ophthalmoplegia</td><td>SCA1, SCA2, SCA3, SCA28, SCA30</td></tr>
<tr><td>Retinopathy</td><td>SCA7</td></tr>
<tr><td>Pyramidal deficits</td><td colspan="2">SCA1, SCA2, SCA3, SCA4, SCA7, SCA8, SCA10, SCA11, SCA12, SCA13, SCA14, SCA15, SCA28, SCA30</td></tr>
<tr><td rowspan="6">Movement disorders</td><td>Dystonia</td><td>SCA3, SCA14, SCA17</td></tr>
<tr><td>Parkinsonism</td><td>SCA1, SCA2, SCA3, SCA12, SCA17, SCA21</td></tr>
<tr><td>Tremor</td><td>SCA8, SCA12, SCA16, SCA19, SCA20</td></tr>
<tr><td>Dyskinesias</td><td>SCA27</td></tr>
<tr><td>Chorea</td><td>SCA1, SCA17, DRPLA</td></tr>
<tr><td>Myoclonic jerks</td><td>SCA2, SCA14, SCA19, DRPLA</td></tr>
<tr><td>Peripheral neuropathy</td><td colspan="2">SCA1, SCA2, SCA3, SCA4, SCA6, SCA8, SCA27, SCA12, SCA18, SCA22, SCA25</td></tr>
</table>

Adapted from Manto [1]

Establishing the Diagnosis of Dominant Ataxias

Establishing the diagnosis of hereditary ataxia requires:

1. A detailed neurological examination and detection of typical clinical signs including:
   (a) Poorly coordinated gait and finger/hand movements
   (b) Dysarthria (incoordination of speech)
   (c) Eye movement abnormalities such as nystagmus, abnormal ocular saccades, and ophthalmoplegia

2. Brain imaging studies (especially MRI studies)
3. Documentation of the hereditary nature of the disease:
   (a) Positive family history of ataxia
   (b) Identification of an ataxia-causing mutation
   (c) To recognize a clinical phenotype characteristic of a genetic form of ataxia
4. Exclusion of nongenetic causes of ataxia.

Diagnosis

The diagnostic thus relies on the family history, the clinical presentation, the neuroimaging pattern, and the genetic tests. Overall, the genetic tests are currently successful in about 60 % of SCAs (see below). Time should be devoted to construct the family tree in order to determine the mode of inheritance. Families with a history of a predominant cerebellar syndrome during successive generations have a high likelihood to present a SCA when both sexes are affected. Anticipation (discussed below) is an additional argument. However, the family tree may be difficult to set when the other members of the family cannot be examined (following death, for instance) or in case of no apparent symptom in some family members (patients at a presymptomatic stage). The variable penetrance and a possible false paternity or adoption also need to be taken into account. The ethnic and geographical background is also a clue for the diagnosis.

Additional tests may be valuable for the differential diagnosis. Neurophysiological studies such as nerve conduction velocities (NCV) and visual-evoked potentials (VEP) are useful to determine the presence of a peripheral neuropathy and optical nerve disease, respectively. Motor-evoked potentials (MEP) confirm the involvement of the corticospinal tract, especially in SCA1. The presence of periodic leg movements (PLM) during sleep is detected by polysomnography.

Brain Imaging

Brain MRI is noninvasive and is considered as a technique of choice to assess the anatomy of the brain in dominant ataxias (Fig. 11.1). It is important to exclude other causes of ataxia which could mimic a degenerative disorder (brain tumor, stroke, malformation, immune disease, etc.). Although brain MRI may be totally normal at the beginning of the symptoms, it becomes a sensitive tool to quantify atrophy as the disorder evolves with time. The main morphological patterns are the following:

- A pattern of pure cerebellar atrophy (in particular in SCA6).
- A pattern of OPCA with atrophy of the cerebellum and brainstem (typical for SCA1, SCA2, SCA3, and SCA7). The atrophy can extend to the upper segments of the spinal cord.
- A pattern of global brain atrophy (for instance, in DRPLA).

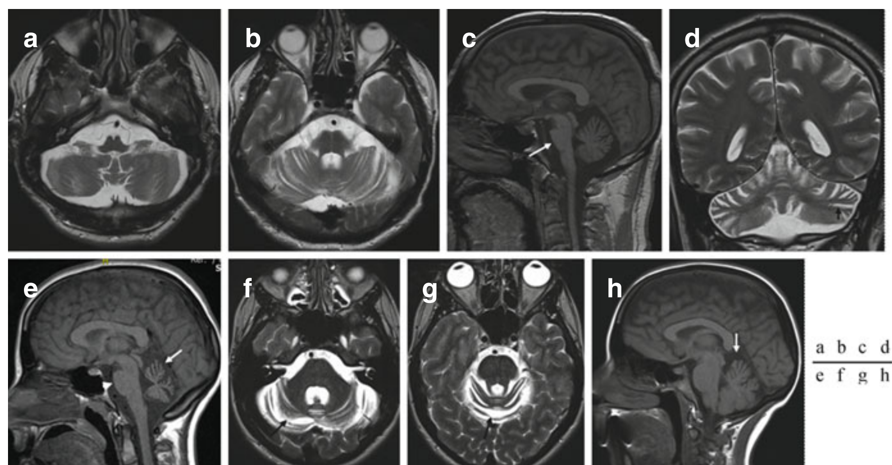

Fig. 11.1 Brain imaging in SCAs. (**a**–**c**) Brain MRI in a 52-year-old man presenting a SCA2. Atrophy of the medulla, pons, and cerebellum on T2-weighted axial images (**a**, **b**). Flattening of the pons on T1-weighted sagittal image (**c**; see *white arrow*). Atrophy of the cerebellar cortex on coronal T2-weighted image (*black arrow*, **d**) in a 44-year-old man with a SCA2. Atrophy of the vermis (*white arrow*) and slight flattening of the pons (*arrowhead*) in a 23-year-old woman presenting a SCA8 (**e**; T1-weighted sagittal image). The atrophy of the cerebellar cortex is well identified on T2-weighted axial images in this patient (**f**–**g**; *black arrows*). Slight atrophy of the upper vermis in a patient presenting EA2 (**h**; sagittal T1-weighted image; *white arrow*)

Some findings may be very suggestive of a given SCA. Dentate nuclei calcifications are observed in SCA20.

Volumetric studies are now available as routine procedures and allow to quantify the degree of regional atrophy and the progression with time.

Differential Diagnosis

Differential diagnosis of hereditary ataxia includes:

Acquired, nongenetic causes of ataxia: alcoholism, vitamin deficiencies, multiple sclerosis, cerebrovascular disease, primary or metastatic tumors, and paraneoplastic diseases associated with occult carcinoma of the ovary, breast, or lung and the idiopathic degenerative disease multiple system atrophy (MSA). An acquired cause of ataxia should be considered in all cases of ataxia.

Molecular Genetic Testing of SCAs

ADCAs are associated to mutations that include nucleotide expansions occurring in either expressed or non-expressed regions of the gene, point mutations, duplications, and deletions. The normal size of CAG repeat allele and of the full-penetrance

disease-causing CAG expansion varies among the disorders (for reviews, see GeneReviews.org). Today, 50–60 % of the dominant hereditary ataxias can be identified with accurate and specific molecular genetic testing. This is the case for SCA1, SCA2, SCA3, SCA6, SCA7, SCA8, SCA10, SCA12, SCA17, and DRPLA. These disorders are characterized by CAG repeats within the coding region of the genes, translating into an elongated polyglutamine tract in the protein. Molecular genetic tests for CAG repeat length are highly specific and sensitive diagnostic tools, and further they are commercially available. However, pursuing tests for multiple genes simultaneously may seem less optimal than serial genetic testing, but their cost is decreasing. Molecular genetic testing results more specific than MRI findings in the hereditary ataxias and guidelines for genetic testing of hereditary ataxia have been published [13]. Testing is also available for some autosomal dominant forms of SCA that are not associated with repeat expansions (SCA5, SCA13, SCA14, SCA15, SCA27, SCA28, and 16q22-linked SCA). Interpretation of results can be an issue in the same case and should be done with caution, and the following aspects should be taken into account:

- The exact range for the abnormal repeat expansion has not been fully established for many of these disorders.
- In some cases, there may be an overlap between the upper range of normal values and the lower range of abnormal CAG repeat size. Such alleles are classified as mutable normal or reduced penetrance. Mutable normal alleles do not cause disease themselves but can expand during the genetic transmission to a reduced or fully penetrant allele. In a few words, children of an individual carrying a mutable normal allele have increased risk of inheriting a disease-causing allele. Therefore, interpretation of results in which the CAG repeat length is at the interface between the allele categories mutable normal/reduced penetrance and reduced penetrance/disease-causing results can be difficult. In such cases, a consultation with the testing laboratory should be considered.
- SCA2, SCA7, SCA8, and SCA10 mutations may present with extremely large CAG expansions in length, only detectable by Southern blot analysis. For these disorders, a test of apparent homozygosity (detection of a single allele by PCR analysis) should be associated to the clinical findings, the family history, and the age of onset of symptoms (to determine whether Southern blot analysis is needed).

The Risk for Family Members

Generally autosomal dominant ataxia patients have an affected parent, although in some cases the family history is negative. For example, family history may not be obvious because of:

- An early death of a parent or a late-onset disorder
- A failure to recognize autosomal dominant ataxia in family members
- A reduced penetrance of the mutant allele in an asymptomatic parent or a de novo mutation

The risk to siblings depends on the genetic status of the proband's parents. If one of the proband's parents has a mutant allele, the risk for the sibs of inheriting the mutant allele is 50 %. Individuals with autosomal dominant ataxia have a 50 % chance of transmitting the mutant allele to each child.

Related Genetic Counseling Issues

At-risk asymptomatic adult can be tested for autosomal dominant cerebellar ataxia after identification of a specific disorder and mutation in their family. Such testing should be performed in the context of formal genetic counseling and will remain a predictive testing and not a diagnostic testing. The test will not predict the age of onset, the severity, the type of symptoms, or the rate of progression. However, molecular genetic testing of asymptomatic individuals younger than 18 years who are at risk for adult-onset disorders for which no effective treatment exists is not considered appropriate. Concern exists regarding the potential unhealthy adverse effects that such information may have on family dynamics, the risk of discrimination and stigmatization in the future, and the anxiety that such information may cause. For more information, see the recommendations of the *National Society of Genetic Counselors resolution on genetic testing of children* and the *American Society of Human Genetics* and *American College of Medical Genetics points*.

New Genetic Technologies

Looking for the exact genetic mutation in patients with a cerebellar ataxia may be difficult, time consuming, and costly. The relatively uniform phenotype of many patients with cerebellar ataxia makes it difficult to decide which gene should be investigated first. Since conventional testing is expensive, many genes that are rarely involved in disease causation may not be tested. Thus, the development of novel technologies such as exome capture and next-generation DNA sequencing (NGS) is very interesting to screen the whole coding part of the genome in one experiment at reduced costs. This has been demonstrated to be a powerful diagnostic approach in the case of ataxia and Charcot–Marie–Tooth disease, which is a similarly heterogeneous disease [14]. The costs for this test decreased dramatically over the last year (it is about 1,000 USD). However, limitations need to be considered, in particular in the diagnosis of ataxia. In fact, currently NGS has a poor ability to sequence stretches of repetitive DNA such as the polyglutamine repeats.

Recently, systems biology approach based on whole-transcriptome gene expression analysis has been used to address the possible relationships among known SCA genes, predict their functions, identify overlapping pathways, and provide a framework for candidate gene discovery. Published results showed that two cerebellar gene coexpression modules were statistically enriched in SCA transcripts and con-

tained established granule and Purkinje cell markers, respectively. One module includes genes involved in the ubiquitin–proteasome system and contains SCA genes usually associated with a complex phenotype, while the other module encloses many genes important for calcium homeostasis and signaling and contains SCA genes associated mostly with pure ataxia [15].

DNA Banking

DNA banking is the storage of DNA (generally from white blood cells) for possible future use. Because it is likely that testing methodology will improve in the future, consideration should be given to banking DNA of affected individuals with dominant ataxias.

Prenatal Testing

Prenatal diagnosis for some of the hereditary ataxias is possible by analyzing fetal DNA (from chorionic villus sampling at about 10–12 weeks' gestation or amniocentesis, usually performed at about 15–18 weeks' gestation) for disease-causing mutations. The disease-causing allele(s) of an affected family member must be identified before prenatal testing. Although most centers would consider decisions about prenatal testing to be the choice of the parents, discussion regarding the purpose of the testing should be considered, like pregnancy termination rather than early diagnosis. Preimplantation genetic diagnosis may also be available when the disease-causing mutation has been identified.

Genetics of SCAs and DRPLA

Historically, SCA1 was linked to chromosome 6 in 1977. SCA1 was identified as the first disorder associated with a trinucleotide repeat expansion [16]. Current numbering of SCAs is based on the chronological order of the gene discovery.

Table 11.2 lists the SCAs and their respective locus, and Table 11.3 provides the normal repeat range, the intermediate repeat range, and the pathological repeat range. A number of 32 genetic loci have been discovered:

- SCA1 to SCA8.
- SCA9 is not attributed.
- SCA10 to SCA15/16 (SCA15 and SCA16 are identical).
- SCA17 to SCA23 (SCA22 is an allelic variant of SCA19).
- SCA24 is not attributed.

Table 11.2 Loci of the SCAs

Disease	Chromosomal locus (mutation)	MIM number (http://www.omim.org)
SCA1	6p23 (CAG expansion)	164400
SCA2	12q24.1 (CAG expansion)	183090
SCA3	14q24.3-q31 (CAG expansion)	607407
SCA4	16q22.1	600223
SCA5	11q13 (point mutations, in-frame deletions)	600224
SCA6	19p13 (CAG expansion)	601011
SCA7	3p14-p21.1 (CAG expansion)	164500
SCA8	13q21 (CTG–CAG expansion)	608768
SCA10	22q13 (ATTCT expansion)	603516
SCA11	15q14-21.3 (point mutations, insertions, deletions)	604432
SCA12	5q31-q33 (CAG expansion)	604326
SCA13	19q13.3-q13.4 (point mutations)	605259
SCA14	19q13.4-qter (point mutations)	605361
SCA15	3p26-p25 (point mutations, deletions)	606658
SCA17	6q27 (CAG expansion)	607136
SCA18	7q22-q32	607458
SCA19	1p21-q21	607346
SCA20	11p13-q11 (duplication)	608687
SCA21	7p21.3-p15.1	607454
SCA22	1p21-q23	607346
SCA23	20p13-12.3 (point mutations)	610245
SCA25	2p15-p21	608703
SCA26	19p13.3	609306
SCA27 (FGF14)	13q34 (point mutations)	609307
SCA28	18p11.22-q11.2 (point mutations)	610246
SCA29	3p26	117360
SCA30	4q34-q35	613371
SCA31	16q22.1 ($TGGAA_n$ repeat)	117210
SCA32	7q32-q33	613909
SCA35	20p13 (point mutations)	613908
SCA36	20p13 (point mutations)	614153
DRPLA	12p13.31 (CAG expansion)	125370

- SCA25 to SCA28.
- SCA29 is an allelic variant of SCA15.
- SCA30 to SCA32.
- SCA35 to SCA36.
- DRPLA.

On the basis of the genetic mutation, three groups of SCAs can be considered (Fig. 11.2).

Table 11.3 Ranges of repeats in SCAs

Disease	Normal range	Intermediate range	Pathological range
SCA1	6–35	35–39	39–83
SCA2	14–31	31–34	34–77
SCA3	12–44	44–52	52–86
SCA6	4–18	18–20	20–33
SCA7	7–19	19–37	37 to >400
SCA8	15–50	50–80	80 to >1,300
SCA10	10–29	280–800	800–4,500
SCA12	4–32	32–51	51–78
SCA17	25–42	42–49	49–66
SCA31	1.2–2.0 kb		2.5–3.8 kb
SCA36	3–8		1,500–2,500
DRPLA	3–35	35–48	48–93

Adapted from Taroni et al. [17].

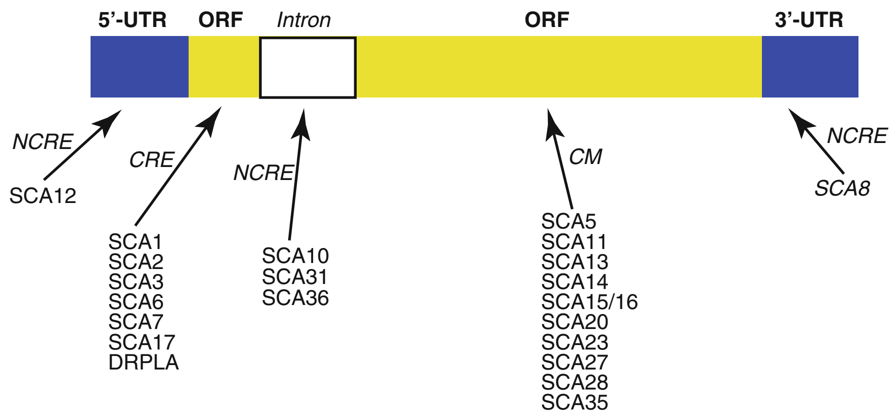

Fig. 11.2 Mutations in SCAs. *NCRE* noncoding repeat expansions, *CRE* coding repeat expansions, *CM* conventional mutations (missense, in-frame deletions, frameshift, nonsense, duplication)

Due to Repeat Expansion

This group is characterized by a CAG repeat expansion within the coding or non-coding parts of the relevant genes [18]. This includes SCA1, SCA2, SCA3, SCA6, SCA7, SCA17, and DRPLA. Because the CAG codon codes for glutamine (Q), the mutation results in the production of mutant protein characterized by a polyQ (poly-glutamine, hence the terminology of polyglutaminopathies). Genotype–phenotype correlations of these disorders are well described [3] with the disease manifesting above a threshold of CAG repeats. The proteins are named ataxin-1 (ATXN1) for SCA1, ATXN2 for SCA2, ATXN3 for SCA3, ATXN7 for SCA7, and atrophin-1 for DRPLA. In SCA6, the mutation involves the calcium channel CACNA1A and in SCA17 the TATA-binding protein (TBP). Three important features are found in this group: (a) there is an inverse relationship between the number of CAG repeats and the age of onset of the clinical deficits, (b) the age of onset is characterized by anticipation, (c) and above a certain threshold in terms of number of CAG repeats, a full penetrance of the disorder occurs. It should be noted that CAG expansions are also found in two disorders usually not classified within ataxias: spinobulbar muscular atrophy (SBMA) and Huntington's disease (HD).

Due to Repeat Expansion Outside the Protein-Coding Region

This group includes SCA8, SCA10, SCA12, SCA31, and SCA36. There is some debate about SCA8 expansion because large repeats have been found in controls or patients with other diseases [19]. The repeat is a CTG triplet. SCA10 is characterized by a repeat expansion of the pentanucleotide ATTCT in intron 9 of the ATXN10 gene. An RNA-mediated toxicity has been proposed for both SCA8 and SCA10. In SCA12, the triplet expansion (CAG) affects the promoter of the PPP2R2B gene. For SCA31, another pentanucleotide (TGGAA) is expanded in an intron shared by the genes BEAN and TK2. SCA36 is due to an expansion of a hexanucleotide GGCCTG in the intron 1 of the NOP56 gene [20]. The pathogenesis is presumed to be due to a gain-of-function toxicity of the expanded RNA, along with a drop in the transcription of miRNA.

Due to Conventional Mutations

A minority of the dominant ataxia syndromes (SCA type 5, 11, 13, 14, 15, 20, 23, 27, 28, and 35) are caused by conventional mutations (deletions, duplications, nonsense, missense, splice). Conventional mutations have been reported to be up to 6 % of all dominant ataxia in France, with repeat expansions accounting for 45 % with

the remaining 48 % being genetically undiagnosed [21]. Genotype–phenotype correlations were difficult to determine due to the limited number of families. A correlation between the degree of functional impairment and the severity of the phenotype has been demonstrated by functional analysis of potassium channels (EA1, SCA13) and calcium channels (SCA6, EA2). These disorders often have a "purer" cerebellar phenotype (ADCAIII), with a slower rate of progression when compared to SCAs due to repeat expansions.

SCA5 is caused by a mutation in the SPTBN2 gene, which encodes the B3 spectrin [22]. A pure cerebellar syndrome with onset between 15 and 50 years has been described in the presence of missense and in-frame deletions. In 1994, 56 affected individuals have been reported for the first time over ten generations. SCA5 has also been reported in French and German pedigrees [23].

SCA11 is caused by stop mutations, frameshift insertions, or deletions in the TTBK2 gene, resulting in a pure cerebellar syndrome with normal life expectancy [24]. The disease was initially reported in British families. Subsequently, pathogenic variants in TTBK2 have been reported in French and German families [25].

SCA13 is caused by missense mutations in KCNC3 encoding for a voltage-gated potassium channel [26]. The disease was initially reported in French and Filipino families. Different missense mutations correlate with a wide phenotypic spectrum. In the case of the childhood-onset form, two variants from European and Filipino families have been associated to the disease: (g.10693G>A p.Arg423His) and (g. 10767 T>C p.Phe448Leu) [27]. In SCA13, motor and mental developmental delay is a common feature. Two missense mutations have been reported. The p.Phe448Leu variant is associated to a more severe phenotype. The p.Arg423His variant has also been described in a Caucasian family in the United States.

SCA14 is caused by mutations in PRKCG [28] and is associated with a variable ataxic phenotype, including myoclonus, dystonia, or peripheral neuropathy. The onset is usually in adulthood, and patients carry in most case mutations (missense) in exons 4, 5, 10, and 18. SCA14 has been described in many families from Europe, Japan, and Australia [29].

SCA15/16 is caused by heterozygous deletions of the 5′ part of the ITPR1 gene [30]. A missense mutation (c.1480G>A p.V494I) has also been reported. The ITPR1 protein is highly expressed in cerebellar Purkinje cells and is an important modulator of intracellular calcium signaling. SCA15/16 is characterized by a mild cerebellar ataxia with slow disease progression. SCA15 was identified in 1.8 % of patients in French families [31]. SCA15/16 also shares a locus with SCA29, raising the hypothesis that they could be allelic disorders.

SCA20 is due to a 260 kb duplication in a region comprising >12 genes at 11q12 [32]. It was originally described in an Australian family. Disease characteristics include dysphonia and spasmodic cough (bulbar symptoms) and dentate nucleus calcifications.

SCA21 has been reported in a French family [33]. The age of onset is variable. Oculomotor deficits are mild. Patients may exhibit akinesia and tendon hyporeflexia. A mild cognitive impairment may be observed.

SCA23 is due to missense mutations of PDYN [34], which encodes prodynorphin protein, an opioid neuropeptide precursor. This causes a relatively pure

cerebellar syndrome with a late onset (43–73 years) and slow progression. The disease has been reported in a single Dutch ataxia family [35].

SCA27 is caused by missense and nonsense mutations in the fibroblast growth factor 14 (FGF14). The gene was identified in Dutch families and is associated with early-onset ataxia [36], plus cognitive deficits, head/limb tremor, and dyskinesia that can be exacerbated by stress or exercise. There is a normal life expectancy. Most affected patients are unable to walk by the seventh to eighth decade. The disease has also been reported in a German ataxia patient.

SCA28 is caused by a mutation in AFG3L2, which encodes a metalloprotease located in the mitochondria [37]. Missense mutations have been reported. They are commonly located in the proteolytic domain of the protein with a mutation hotspot in exons 15–16. SCA28 has a typically early onset between 12 and 36 years and is characterized by a slowly progressive cerebellar ataxia with ophthalmoparesis and lower limb hyperreflexia. The disease is estimated to account for 1.5 % of European ADCA cases [38].

SCA35 is caused by mutations in the cerebral transglutaminase TGM6 and was the first dominant ataxia gene to be identified through exome sequencing [39]. Missense mutations were reported in two Chinese families in which a late-onset cerebellar syndrome with upper motor neuron involvement was reported. There is a moderate rate of progression. Patients use a wheelchair about 20 years after disease onset.

Anticipation

Anticipation is one of the main features of polyglutaminopathies. It designates the tendency of symptoms to start earlier and with a more severe phenotype [40]. Anticipation is related to changes in the size of the repeat expansion during transmission. Expanded alleles are unstable, with a trend towards an increase of CAG repeats (intergenerational elongation of the expansion). The instability is higher for paternal expansions, because the trends towards expansion are greater during spermatogenesis. Anticipation may be particularly marked in SCA7 and DRPLA, so that the disease can manifest in children before the parents develop symptoms. SCA2 is also characterized by anticipation, although to a lesser degree. There is threshold of 35–40 triplets beyond which the polyglutamine adopts an abnormal conformation, with a tendency to form aggregates and to interact with other proteins [40]. Unlike polyglutaminopathies, a phenomenon of contraction of the ATTCT repeat may be observed in SCA10, in particular for paternal transmission.

Prevalence

The prevalence of these disorders is not exactly known. ADCAs in the Netherlands are estimated to be at around 3:100,000 [41], and the prevalence of individual subtypes of ADCA may vary from region to region, because of founder effects. DRPLA

was found to be more common in Japan and rare in North America, while SCA3 is much more common in Portugal, Japan, and Germany than in the United Kingdom [42–44]. SCA2 is relatively common in Korea. Further, SCA3 was originally described in Portuguese families from the Azores and called Machado–Joseph disease. A recent study found evidence of frequency variation between different regions in Japan [45].

Pathogenesis of SCAs

The concept of a toxic effect of polyglutamine expansion is now widely accepted (gain of function), but the intimate mechanisms of the toxicity are still not established. The polyQ tract adopts an impaired conformation (misfolding of the protein) and forms aggregates. These neuronal intranuclear inclusions are a major feature of the following polyglutaminopathies: SCA1, SCA3, SCA7, SCA17, and DRPLA. In SCA2, aggregates occur in the cytoplasm of neurons, whereas they are located in perinuclear regions in SCA6. It is interesting to note that one of the most vulnerable neurons in the cerebellum of SCA patients is the Purkinje cell. However, these neurons do not contain aggregates of proteins. Some consider that this indicates a possible dissociation between neuronal toxicity and the process of aggregation. The mutant proteins may interact with transcription factors such as senseless/Gfi1 by increasing its degradation, for instance, in SCA1 [46]. In case of the Purkinje cell, the mutant protein would impair the functions of ROR-alpha, known to play critical roles for the cerebellar cortex. Transcriptional dysregulation and proteasome inhibition would both contribute to the pathogenesis of polyglutaminopathies. There is a colocalization between the ubiquitin and the nuclear inclusions, suggesting a failure in the attempt to remove the misfolded proteins. There is also a colocalization with heat-shock proteins (HSPs) such as HSP70, HSP40, and CHIp. This is interpreted as an attempt of the cell to transform the misfolded protein in soluble components [47].

Natural Course and Follow-Up of SCAs

SCAs are characterized by a slow worsening of symptoms. The average disease duration in polyglutaminopathies is between 15 and 30 years [40]. A clinical scale called SARA has been designed for SCAs and can be used to monitor the clinical progression of the deficits [48]. Score ranges from 0 (no ataxia) to a maximum of 40. The ICARS (international cooperative ataxia rating scale) scale and the BARS (brief ataxia rating scale) scale can be used also. The extra-cerebellar deficits can be monitored using the INAS inventory (inventory for non-ataxia symptoms; 30 items) [49].

Table 11.4 Symptomatic therapies in SCAs

Seizures	Antiepileptic drugs
Psychiatric manifestations	Psychotropic medications
Tremor	Primidone, gabapentin, propranolol Deep brain stimulation (DBS) in selected cases
Restless legs syndrome	Dopamine agonists
Extrapyramidal deficits	Levodopa, dopamine agonists, amantadine
Spasticity	Baclofen, tizanidine
Muscle cramps	Magnesium, quinine

Therapies of SCAs

There is still no medication which reverts the natural course of SCAs. Table 11.4 shows the symptomatic treatments. Tandospirone and buspirone might improve slightly postural deficits, and acetazolamide may improve ataxia in SCA6 at the beginning of the disease [50]. The positive effects with the amino acid acetyl-DL-leucine acting on vestibular circuits need to be confirmed in a placebo-controlled trial [51]. Therapies under investigation aim to increase the clearance of proteins, to perform gene silencing, to modulate the transcription, or to decrease the expression of a mutated allele [52].

Regular physical therapy, speech/language therapy (which likely decreases the risk of swallowing difficulties), and occupational therapy are recommended. Intensive coordination training (3 × 1 h/week) improves motor activities [53]. Assisting devices (sticks, strollers) may be helpful in selected cases.

Episodic Ataxias

The episodic ataxias are monogenic disorders, also considered as a group of heterogeneous channel disorders. They are characterized by attacks of ataxia, which may be associated with a range of other neurological manifestations including myokymia, migraine, seizures, or chorea. The recurrent episodes of ataxia are often associated with vertigo and dizziness. The absence of impaired consciousness is very suggestive. Usually, the beginning and the end of the attack are clearly identified by the patients.

Eight episodic ataxia syndromes have been described: EA 1–7 and episodic ataxia with paroxysmal choreoathetosis and spasticity (CSE). EA 1 and 2 are the most common and best characterized of these. The genes for EA 1, 2, 5, and 6 (Table 11.5) have been identified with linkage loci mapped in EA 3, 7, and CSE. Episodic ataxia is rare with a combined incidence of <1:100,000.

Table 11.5 Episodic ataxias

EA	Gene (locus)	Mutation	Age of onset (years)
EA1	KCNA1 (12p13)	Point mutations	2–15
EA2	CACNA1A (19p13)[a]	Point mutations Deletions	1–30
EA3	? (1q42)	–	1–42
EA4	? (?)	–	20–60
EA5	CACNB4 (2q22-23)	Point mutations	3–19
EA6	SLC1A3 (5p13)	Point mutations	<20
EA7	? (19q13)	–	13–19

[a]Allelic to SCA6 and FHM (familial hemiplegic migraine)

EA1

Patients exhibit brief attacks of ataxia. They show an ictal dysarthria and typical interictal myokymia (continuous muscle unit activity) especially in the face or the hands. The episodes last from a few seconds to a few minutes, often triggered by stress, exercise (kinesigenic), or startle. Between the episodes, there is usually no ataxia or nystagmus. EA1 is primarily due to missense mutations in KCNA1 [54] although truncated mutations have been reported. The degree of channel impairment correlates with the severity of the phenotype. Mutations associated with severe phenotypes that may be poorly responsive to treatment or are associated with seizures or neuromyotonia show the most significant impairment of potassium channel function.

Patients usually benefit from a therapy with acetazolamide (500 mg/day). The drug reduces the number of attacks. Side effects include numbness, loss of appetite, loss of concentration, and kidney stones. Myokymia may be reduced with clonazepam, carbamazepine, or valproic acid.

EA2

This is the most common EA. The attacks are usually longer as compared to EA1, lasting from hours to days. An interictal nystagmus is commonly observed, and 50 % of the patients complain of headaches and nausea, sometimes with a misdiagnosis of migraine. The triggering factors are usually emotions, exercise, and fatigue. With time, patients develop an interictal mild ataxic syndrome that may mimic a SCA. Vermian atrophy is often detected on MRI (see Fig. 11.1). EA2 is due to a range of mutations in CACNA1A [55], which include missense, nonsense, aberrant splicing, and nucleotide insertions and deletions.

EA2 is allelic with FHM type 1 (migraine, hemiplegia, interictal nystagmus, and progressive ataxia) and SCA6 [56]. Most of the mutations that cause EA2

disrupt the open reading frame, whereas FHM is caused primarily by missense mutations. Acetazolamide (500 mg/day) is very effective. Aminopyridines may be effective also [57].

EA3

This EA has been reported in Canada. Episodes of ataxia, vertigo, and tinnitus last a few minutes [58]. Patients exhibit interictal myokymia. Acetazolamide reduces the number of attacks.

EA4

EA4 was reported in US families. It is also called periodic vestibulocerebellar ataxia (PATX). Patients exhibit attacks of ataxia and vertigo lasting a few hours. They show interictal ataxia and gaze-evoked nystagmus. Ocular pursuit is abnormal. Patients do not respond to acetazolamide.

EA5

EA5 has been described in a single French-Canadian family that was heterozygous for a missense mutation in the beta4-subunit of the calcium channel Cav2.1. Clinical presentation may be similar to EA2 (missense mutation), but mutations may present with a phenotype of generalized epilepsy or juvenile myoclonic epilepsy (heterozygous nonsense mutation) [59]. The precise functional effects of this mutation are not clear as the same mutation was identified in a German family with generalized epilepsy but no ataxia.

EA6

The disorder was initially reported in a child showing episodic ataxia, epilepsy, alternating hemiplegia, and migraine [60]. A de novo mutation was identified in the SLC1A3 gene, which results in complete loss of function of the protein EAAT1, a glutamate transporter localized to astrocytes. A Dutch family has been reported with the p.C186S variant that resulted in a milder phenotype without the manifestations of seizures or alternating hemiplegia [61]. Acetazolamide is effective to reduce symptoms.

Table 11.6 Differential diagnosis of EAs

Disease	Triggering factor
Hartnup disease (SLC6A19 gene – 5p15.33)	Sunlight exposure
	Fasting
	Emotion
	Intake of sulfonamides
Maple syrup urine disease (19q13.2, 7q31)	Intake of branched-chain amino acids
Deficiencies in urea cycle enzymes	Protein loads
	Valproate intake

EA7

In EA7, exertion or excitement provokes ataxia, vertigo, and weakness. Deficits last a few hours to a few days [62].

Differential Diagnosis

Table 11.6 lists the differential diagnosis of EAs.

Conclusion

With an expanding and aging population, the genetic cerebellar ataxias are becoming an increasingly important problem from the healthcare standpoint. The recent genetic progresses have significantly increased our understanding of these clinically heterogeneous disorders, allowing to dissect and better stratify the ataxias. Still, about 40 % of these patients remain with an undetermined etiology. The availability of novel genetic technologies to both research and diagnostic laboratories will facilitate a further rapid progress in this field. In the near future, a greater efficiency in diagnosis and the identification of many new forms of ataxia are therefore expected. The challenges for the future will be the complete understanding of the pathogenetic mechanisms in order to develop new therapies that will ultimately halt or reverse the degeneration and therefore the ataxia.

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