Hereditary ataxias represent a heterogeneous group of neurodegenerative disorders, clinically characterized by a cerebellar syndrome with imbalance, unsteady gait and limb incoordination, dysarthria, and disturbed eye movements. Often there are additional neurological or systemic signs, which are highly variable depending on the genetic subtype and on the individual phenotype. The genetic background of heredoataxias has been largely identified during recent years. Heredoataxias have to be delineated from non-hereditary ataxias, which may be either acquired or sporadic (Table 1). This review aims to give an overview on recent advances and current knowledge about the frequency, clinical presentation, genetic background, management, and prognosis of heredoataxias.

From the Krankenanstalt Rudolfstiftung, Vienna, Austria, Europe.

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Correspondence to: Josef Finsterer, Postfach 20, 1180 Vienna, Austria, Europe.
The heredoataxias first described in history was Friedreich ataxia (FA). Under the title “Degenerative atrophy of the posterior columns of the spinal cord” FA was first mentioned in the literature by Nicholaus Friedreich, a professor of Medicine in Heidelberg, Germany in the second half of the 19th century. SCA3 was first described in 1972 in descendants of William Machado, a native of an Azore island. The CAG-expansion responsible for SCA1 was detected in 1993. The genetic cause of FA was first described in 1996.

For all heredoataxias a prevalence of 6/100000 is reported but estimations of the prevalence of heredoataxias are quite variable between countries and continents. The prevalence of autosomal dominant (AD) spinocerebellar ataxias (SCAs) is estimated to be 1-4/100000 or 0.9-3/100000. The prevalence of SCAs in the Netherlands is reported to be 3/100000. A much higher prevalence of SCAs of 18.5/100000 is reported from Japan. The prevalence of SCA1 and 2 was 2.4/100000 in the province of Padua. The prevalence of AR ataxias is estimated to be around 7/100000. The prevalence of FA, the most common of the heredoataxias, is estimated to be 1/50,000 in Southern Europe and 0.6/100000 in Japan. Other studies found a prevalence of 2.2/100000 for autosomal recessive (AR) heredoataxias and of 3/100000 for AD heredoataxias. Ataxia telangiectasia has an estimated prevalence between 1/40000 to 1/100000. X-linked ataxias are rare. In rare cases cerebellar ataxia may represent the main clinical finding of inherited mitochondrial disorders (MIDs). Among all SCAs SCA3 is the most frequent genotype accounting for 20-50% of the SCAs worldwide. SCA2 is the second most frequent genotype (15-20%) being common in the USA, India and Italy. SCA1 is frequent in South Africa (41%), Italy, India, and Germany. In Japan SCA6, SCA3, and DRPLA are the most frequent SCAs. In China the most frequent SCAs were SCA3, SCA2, SCA1, SCA6, SCA7, SCA8, SCA10, SCA12, SCA14, SCA17, and DRPLA. SCA2 is common in Korea. SCA3 is more common in Japan and Germany than in the UK. FA is frequent in Germany but only a few cases with AOA or IOSCA (twinkle) have been diagnosed there. Polyglutamine (poly-Q) SCAs are the most common of the AD heredoataxias and account together for 50% of these disorders.

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### Classification

Heredoataxias may be classified according to various criteria. First they can be classified according to the trait of inheritance into AD, AR, X-chromosomal, or maternal forms (Table 1). Second they can be classified according to the cause into hereditary forms and non-hereditary forms (Table 1). Third, according to the phenotype, whether they manifest only with the classical phenotype as pure cerebellar syndrome or if they exhibit additional neurological or non-neurologic features. Fourth, according to the onset of the clinical manifestations into early and late onset forms. Heredoataxias may be also classified according to whether ataxia is progressive or stable. Today, there is a wide consensus to classify heredoataxias according to the mode of inheritance, as in the following presentation.

### Table 1: Classification of heredoataxias and non-hereditary ataxias

<table>
<thead>
<tr>
<th>Category</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heredoataxias</td>
<td></td>
</tr>
<tr>
<td>Autosomal dominant</td>
<td>Friedreich ataxia-like phenotype</td>
</tr>
<tr>
<td></td>
<td>Friedreich ataxia</td>
</tr>
<tr>
<td></td>
<td>Ataxia due to vitamin E deficiency</td>
</tr>
<tr>
<td></td>
<td>Ataxia due to Abeta-lipoproteinemia</td>
</tr>
<tr>
<td></td>
<td>Friedreich ataxia-like phenotype with cerebellar atrophy</td>
</tr>
<tr>
<td></td>
<td>Late-onset Tay Sachs disease</td>
</tr>
<tr>
<td></td>
<td>Cerebrotendineous xanthomatosis</td>
</tr>
<tr>
<td></td>
<td>Spinocerebellar ataxia with axonal neuropathy</td>
</tr>
<tr>
<td></td>
<td>AR mitochondrial disorders with ataxia (AR-CPEO, SANDO, SCAE, AHS, IOSCA,</td>
</tr>
<tr>
<td></td>
<td>MEMSA, LBSL CoQ-deficiency, PDC-deficiency)</td>
</tr>
<tr>
<td>Early-onset ataxia with cerebellar atrophy</td>
<td>Friedreich ataxia telangiectasia</td>
</tr>
<tr>
<td></td>
<td>Friedreich ataxia telangiectasia-like disorder</td>
</tr>
<tr>
<td></td>
<td>Ataxia with oculomotor apraxia 1 (AOA1)</td>
</tr>
<tr>
<td></td>
<td>Ataxia with oculomotor apraxia 2 (AOA2)</td>
</tr>
<tr>
<td></td>
<td>Spastic ataxia of Charlevoix-Saguenay</td>
</tr>
<tr>
<td></td>
<td>Cayman ataxia</td>
</tr>
<tr>
<td></td>
<td>Marinosco-Sjögren syndrome</td>
</tr>
<tr>
<td>X-chromosomal</td>
<td>Fragile X tremor/ataxia syndrome</td>
</tr>
<tr>
<td></td>
<td>X-linked mitochondrial disorders with ataxia (XLSA/A)</td>
</tr>
<tr>
<td>Maternally inherited heredoataxias</td>
<td>Point mutations (homoplasmic and heteroplasmic)</td>
</tr>
<tr>
<td></td>
<td>tRNAs or rRNA genes (MELAS, MERRF)</td>
</tr>
<tr>
<td></td>
<td>RC subunit genes (LHON, NARP, LS, MILS)</td>
</tr>
<tr>
<td></td>
<td>Single, large-scale deletions/duplications (sporadic, heteroplasmic)</td>
</tr>
<tr>
<td></td>
<td>CPEO, PS, KSS</td>
</tr>
<tr>
<td>Non-hereditary ataxias</td>
<td></td>
</tr>
<tr>
<td>Acquired</td>
<td>Alcohol cerebellar degeneration</td>
</tr>
<tr>
<td></td>
<td>Lithium intoxication</td>
</tr>
<tr>
<td></td>
<td>Phenytoin intoxication</td>
</tr>
<tr>
<td></td>
<td>Intoxication with solvents</td>
</tr>
<tr>
<td></td>
<td>Paraneoplasic cerebellar degeneration</td>
</tr>
<tr>
<td></td>
<td>Gluten sensitivity</td>
</tr>
<tr>
<td></td>
<td>Superficial siderosis</td>
</tr>
<tr>
<td>Sporadic</td>
<td>Pure adult onset cerebellar ataxia</td>
</tr>
<tr>
<td></td>
<td>Olivopontocerebellar atrophy (OPCA)</td>
</tr>
<tr>
<td></td>
<td>Cerebellar type of multi-system atrophy</td>
</tr>
</tbody>
</table>

See abbreviations list on page 424.
AUTOSOMAL DOMINANT HEREDOATAXIAS

According to the current genetic classification, the AD cerebellar ataxias are designated as SCAs (spinocerebellar ataxias), EAs (episodic ataxias), and AD inherited MIDs.

A. SPINOCEREBELLAR ATAXIAS

1. Phenotypic classification

At present 28 genetic loci for SCAs have been identified: SCA1-8, SCA10-15, SCA17-23, SCA25-30 (Table 2)\(^\text{17,19}\) and the one for dentato-rubro-pallido-luysian atrophy (DRPLA), which is commonly included in this group (Table 2). According to the phenotypic presentation, three different types are distinguished\(^\text{19}\). Type I includes those SCAs, which, in addition to the cerebellar manifestations, also exhibit manifestations outside the cerebrum. Type II includes SCAs, which exhibit cerebral manifestations in addition to the cerebellar abnormalities. Type III SCAs comprise the so called “pure” SCAs those that appear to elude neurological features outside the cerebellum (SCA5, SCA6, SCA14)\(^\text{19}\).

2. Genetic classification

On the basis of the type of mutation, three major classes of SCAs have been recognized. The first category includes DRPLA and SCA1, 2, 3, 6, 7, and 17, which are caused by a CAG-repeat expansion within exons of the corresponding gene resulting in the production of a mutant protein with an expanded poly-Q stretch. This type of mutation constitutes the most common cause of dominantly inherited heredoataxias world-wide. The CAG-repeat expansion results in depletion of mtDNA and there are indications that the amount of depletion correlates with the length of the CAG repeat\(^\text{20}\). Longer expansions are associated with earlier onset and more severe disease\(^\text{17}\). Altogether nine poly-Q disorders have been detected so far (Huntington’s disease (HD), bulbospinal muscular atrophy Kennedy, DRPLA, and the six SCAs). Except for SCA6, which forms cytoplasmic aggregates negative for ubiquitin, all other poly-Q disorders accumulate the mutated protein I large intranuclear inclusions\(^\text{21}\). Mutations causing AD SCAs segregate in a dominant manner because of their toxic gain-of-function characteristics\(^\text{4}\).

A second category of repeat expansions is localized in introns (outside the protein-coding region) of the responsible genes. Thus, the pathogenic expansion does not encode glutamine or any other amino acid\(^\text{17}\). Most likely, expanded RNA repeats sequester RNA-binding proteins, leading to aberrant RNA splicing\(^\text{17}\). This group includes SCA8, SCA10 and SCA12\(^\text{5}\).

A third category is represented by the AD ataxias SCA4, 5, 11, 13, 14, 15/16, 27, 28, 29, and 30, which are caused by conventional deletions, missense, nonsense, or splice site mutations in their respective genes (Table 2). Altogether the mutated gene has been identified in 18 SCAs. The other ten SCAs are caused by mutations in genes so far unknown (Table 2).

3. Anticipation

Anticipation is a main feature of SCAs (Table 3), and is particularly prominent in SCA7\(^\text{17}\). Anticipation may be so extreme in some cases that affected children die long before the affected parent or grandparent becomes symptomatic\(^\text{4}\). Anticipation may be explained by the fact that expansions frequently enlarge upon transmission and by the fact that large expansions cause earlier onset of the disease\(^\text{17}\). Disease progression increases with increasing repeat size\(^\text{22}\).

4. Pathogenesis

The pathogenesis of SCAs is largely unknown but for exonic poly-Q SCAs it is known that long poly-Q tracts have an increased tendency to aggregate, often as truncated fragments forming ubiquitinated intranuclear inclusion bodies\(^\text{4,21}\). Expansion of the poly-Q stretch causes misfolding and conformational alterations of the gene-product leading to pathological protein-protein interactions, and the aggregation and subsequent deposition as intranuclear inclusion bodies in affected neurons\(^\text{23}\). In some cases, cleavage of the poly-Q chain promotes aggregation. In other cases aggregation may result from misfolding of the protein into a beta-sheet dominant structure (conformational transition)\(^\text{17,21,22}\). Misfolding may then lead to assembly of the host proteins into insoluble beta-sheet-rich amyloid fibrillar aggregates (“exposed beta-sheet hypothesis”)\(^\text{23}\). Inhibition of proteases that cleave elongated SCAs might have a therapeutic effect, by inhibiting poly-Q domains to aggregate\(^\text{4}\).

A second pathogenetic theory assumes that poly-Q proteins, which mostly reside within the nucleus (except for SCA6) and accumulate there during the disease, perturb gene expression\(^\text{17}\). Interactions of poly-Q proteins may functionally deplete certain transcription factors and other nuclear proteins, resulting in altered activity at specific promoters or perturbed chromatin modification by histone acetyltransferases\(^\text{17,21}\). There are also indications that unstable CAG-repeats may secondarily cause mtDNA mutations\(^\text{24}\).

5. Clinical presentation

SCAs are clinically characterized by a slowly progressive cerebellar syndrome with various oculomotor abnormalities, dysarthria, dysmetria, tremor, or ataxia\(^\text{6}\). Several types of SCAs may express abnormalities in addition to the cerebellar syndrome, which have some value in predicting the genotype (Table 4). A feature of SCAs is also their relentless progression leading to death over a period of 15-30y\(^\text{17}\). On cerebral MRI three patterns of atrophy can be identified: 1. a pure cerebellar atrophy, 2. a pattern of olivo-ponto-cerebellar atrophy, and 3. global diffuse brain atrophy\(^\text{6}\). In SCA20 the nucleus dentatus is typically calcified\(^\text{6}\). Quantification of the degree of atrophy is now possible by application of three-dimensional true volumetric methods\(^\text{25}\). Histopathologically, there is atrophy of the molecular, Purkinje cell and granular cell layers as well as the deep cerebellar nuclei\(^\text{17}\). Except for SCA6 all poly-Q SCAs exhibit brainstem involvement. There may be also involvement of the basal ganglia and the cerebral cortex, most notably in SCA17, the spinal cord, or even the peripheral nerves\(^\text{17}\). The frequent occurrence of cognitive impairment in SCAs might be explained by data suggesting that the cerebellum contributes to aspects of memory and executive functions\(^\text{26}\).
<table>
<thead>
<tr>
<th>Disease</th>
<th>Gene</th>
<th>Locus</th>
<th>Mutation</th>
<th>Gene product</th>
<th>Additional manifestations</th>
<th>Age at onset</th>
</tr>
</thead>
<tbody>
<tr>
<td>SCA1</td>
<td>ATXN1</td>
<td>6p23</td>
<td>CAG-expansion</td>
<td>Ataxin-1</td>
<td>Pyramidal signs, nystagmus, slow saccades, neuropathy, dementia, ophthalmoparesis</td>
<td>4-74</td>
</tr>
<tr>
<td>SCA2</td>
<td>ATXN2</td>
<td>12q24.1</td>
<td>CAG-expansion</td>
<td>Ataxin-2</td>
<td>Slow saccades, neuropathy, hyporeflexia, asymmetric wasting, myoclonus, dementia, ophthalmoparesis</td>
<td>6-67</td>
</tr>
<tr>
<td>SCA3</td>
<td>ATXN3</td>
<td>4q24.3-4q31</td>
<td>CAG-expansion</td>
<td>Ataxin-3</td>
<td>Extrapyramidal signs, nystagmus, neuropathy, spasticity, diplopia, eye-lid retraction, ophthalmoparesis</td>
<td>5-65</td>
</tr>
<tr>
<td>SCA4</td>
<td>Paratrophin-1 (PLEKHG4) -III Spectrin (SPTBN2)</td>
<td>16q22.1</td>
<td>Pm</td>
<td>Paratrophin-1 (PLEKHG4) -III Spectrin (SPTBN2)</td>
<td>Pure cerebellar syndrome or additionally axonal sensory nystagmus</td>
<td>19-72</td>
</tr>
<tr>
<td>SCA5</td>
<td>ATXN7</td>
<td>11q13</td>
<td>Pm, Del</td>
<td>ATXN7</td>
<td>Pure cerebellar syndrome, slow progression, down-beat nystagmus</td>
<td>15-50</td>
</tr>
<tr>
<td>SCA6</td>
<td>CACNA1A</td>
<td>19p13</td>
<td>CAG-expansion</td>
<td>CACNA1A</td>
<td>Pure cerebellar syndrome, slow progression, ataxia</td>
<td>19-77</td>
</tr>
<tr>
<td>SCA7</td>
<td>ATXN8</td>
<td>1p14-p21.1</td>
<td>CAG-expansion</td>
<td>Ataxin-8</td>
<td>Pigmentary retinopathy, ophthalmoplegia, pyramidal signs</td>
<td>0.1-76</td>
</tr>
<tr>
<td>SCA8</td>
<td>PRKCG</td>
<td>13q21</td>
<td>CTG-expansion</td>
<td>PRKCG</td>
<td>Sensory neuropathy, slow progression</td>
<td>0.73</td>
</tr>
<tr>
<td>SCA9</td>
<td>TTBK2</td>
<td>5q14-21.1</td>
<td>CAG-expansion</td>
<td>TTBK2</td>
<td>Seizures, pyramidal signs, extrapyramidal signs</td>
<td>10-40</td>
</tr>
<tr>
<td>SCA10</td>
<td>ATXN10</td>
<td>22q13</td>
<td>ATTCT-expansion</td>
<td>ATXN10</td>
<td>Pure cerebellar syndrome</td>
<td>17-33</td>
</tr>
<tr>
<td>SCA11</td>
<td>PPP2R2B</td>
<td>5q31-q33</td>
<td>CAG-expansion</td>
<td>PPP2R2B</td>
<td>Upper extremity and head tremor, parkinsonism, hyperreflexia, dementia, neuropathy</td>
<td>8-55</td>
</tr>
<tr>
<td>SCA12</td>
<td>ATXN10</td>
<td>19q13.3-13.4</td>
<td>Pm</td>
<td>KCNC3</td>
<td>Delayed motor development, mental retardation</td>
<td>4-60</td>
</tr>
<tr>
<td>SCA13</td>
<td>ATXN10</td>
<td>19q13.4-qt</td>
<td>Pm</td>
<td>PRKCG</td>
<td>Facial myokymia, rare myoclonus and focal dystonia, slow progression, incomplete penetrance</td>
<td>10-59</td>
</tr>
<tr>
<td>SCA14</td>
<td>ATXN10</td>
<td>1q32-qter</td>
<td>Pm</td>
<td>ATXN10</td>
<td>Pure cerebellar syndrome or additionally head tremor, slow progression</td>
<td>10-66</td>
</tr>
<tr>
<td>SCA15</td>
<td>ATXN10</td>
<td>1p21-q21</td>
<td>Uk</td>
<td>ATXN10</td>
<td>Pure cerebellar syndrome</td>
<td>10-59</td>
</tr>
<tr>
<td>SCA16</td>
<td>ATXN10</td>
<td>1p11-q11</td>
<td>Uk</td>
<td>ATXN10</td>
<td>Pure cerebellar syndrome or associated with sensory loss, pyramidal signs</td>
<td>4-56</td>
</tr>
<tr>
<td>SCA17</td>
<td>ATXN10</td>
<td>7p21.3-p15.1</td>
<td>Uk</td>
<td>ATXN10</td>
<td>Severe sensory neuropathy, FA-like</td>
<td>1.5-39</td>
</tr>
<tr>
<td>SCA18</td>
<td>ATXN10</td>
<td>1p21-21.2</td>
<td>Uk</td>
<td>ATXN10</td>
<td>Severe sensory neuropathy, FA-like</td>
<td>1.5-39</td>
</tr>
<tr>
<td>SCA19</td>
<td>ATXN10</td>
<td>1p21-q21</td>
<td>Uk</td>
<td>ATXN10</td>
<td>Slowly progressive, posterior tremor, dyskinesia, cognitive impairment, behavioral abnormalities</td>
<td>12-40</td>
</tr>
<tr>
<td>SCA20</td>
<td>ATXN10</td>
<td>1q32-qter</td>
<td>Uk</td>
<td>ATXN10</td>
<td>Ophthalmoparesis, nystagmus, hyperreflexia, ptosis slow progression</td>
<td>12-36</td>
</tr>
<tr>
<td>SCA21</td>
<td>ATXN10</td>
<td>3p26</td>
<td>Uk</td>
<td>ATXN10</td>
<td>Non progressive, highly variable phenotype</td>
<td>Congenital</td>
</tr>
<tr>
<td>SCA22</td>
<td>ATXN10</td>
<td>4q34.3-4q35.1</td>
<td>Uk</td>
<td>ATXN10</td>
<td>Slowly progressive ataxia, mild pyramidal signs, hypermetric saccades, nystagmus</td>
<td>Mid-late life</td>
</tr>
<tr>
<td>SCA23</td>
<td>ATXN10</td>
<td>12p13.31</td>
<td>CAG-expansion</td>
<td>Atrophin-1</td>
<td>Seizure, chorea, dementia, myoclonus</td>
<td>10-59</td>
</tr>
</tbody>
</table>

Uk: unknown, Pm: point mutation, Del: deletion, Ins: insertion. See abbreviations list on page 424.

**SCA1**

SCA1 is a late onset condition characterized by a cerebellar syndrome, variable degrees of ophthalmoplegia, pyramidal or extrapyramidal signs, and peripheral neuropathy. Symptoms at onset include gait disturbance, double vision, dysarthria, impaired handwriting, or episodic vertigo. Single patients may develop vocal cord adductor paralysis or even psychosis. SCA1 is due to a CAG-repeat expansion in the ataxin-1 gene (Table 2). Only 64% of the onset variability is determined by the CAG-repeat length, suggesting non-repeat factors to substantially influence disease onset.

**SCA2**

SCA2 manifests as cerebellar syndrome with gait disturbance, double vision, dysarthria, impaired handwriting, episodic vertigo or Parkinsonism. There may be also saccade slowing, hyporeflexia, postural or action tremor, myoclonus, muscle cramps, or retinopathy. In the later stages the thalamus, brainstem or spinal cord is involved. There may be also involvement of the central somato-sensory system. The disease course is slowly progressive but ultimately fatal. Single patients may exclusively presented with Parkinsonism or MSA.
with Parkinsonism. Neuropathological investigations may also show subclinical involvement of the auditory brainstem system. Histopathological investigations may reveal olivoponto-cerebellar atrophy, neuronal loss in the substantia nigra, intranuclear ubiquitin-ataxin-2-positive neuronal intranuclear inclusions and severe demyelination or axonal loss in the cerebral white matter. Neuronal intranuclear inclusions are less frequent than in other poly-Q diseases. The condition is caused by a CAG-repeat expansion in the ataxin-2 gene. Only 67% of the onset variability is determined by CAG-repeat length, suggesting non-repeat factors to substantially influence disease onset. Anticipation regarding onset and rapidity of disease progression is frequently present (Table 3).

SCA3

SCA3 is the most prevalent SCA in nearly all countries world-wide. Symptoms at onset are variable and include gait disturbance, double vision, dysarthria, impaired hand writing, and episodic vertigo. Most frequently SCA3 starts with ataxic gait after age 40. Later on, patients develop anarthria, saccadic dysfunction, vestibular dysfunction, executive dysfunction, frequent falls, dysdiadochokinesia, Parkinsonism, somato-sensory deficits, and axonal neuropathy. Other extra-cerebellar manifestations include dystonia and chorea. Almost half of the patients complain about muscle cramps and a quarter develops fasciculations. The disease course is slowly progressive and ultimately fatal. Neuropathological investigations may show subclinical involvement of the auditory brainstem system. SCA3 is due to mutations in the puratrophin-1 (PLEC) gene on chromosome 16q22.1. Anticipation may be extreme and is more pronounced with maternal than paternal transmission.

SCA4

SCA4 also known as hereditary ataxia with sensory neuropathy, is a rare progressive SCA presenting with ataxia, dysarthria, diplopia, gaze-evoked nystagmus, auditory impairment, saccadic smooth pursuits, dysphagia, or somato-sensory deficits. Neuropathologically, there is widespread cerebellar and brain degeneration with obvious demyelination and axonal fiber loss. SCA4 is due to point mutations in the PLEC gene on chromosome 16q22.1.

SCA5

SCA5 is one of the rare “pure” cerebellar SCAs sometimes presenting with nystagmus (Table 2). Magnetic resonance imaging shows global cerebellar atrophy. SCA5 is due to mutations in the SPTBN2 gene encoding for beta-III spectrin. Involvement of a cytoskeletal component suggests that organelle stability, altered membrane protein dynamics, may play an important pathogenetic role together with altered Ca++ homeostasis, transcriptional dysregulation, or impaired protein degradation. Anticipation may be extreme and is more pronounced with maternal than paternal transmission.

SCA6

SCA6 is clinically characterized by a severe form of late onset slowly progressive pure cerebellar ataxia, with nystagmus,
reduced smooth pursuit, or cognitive dysfunction\textsuperscript{43,44}. Early functional deficits may include impaired saccade velocity, saccade metrics, or pursuit gain\textsuperscript{45}. Neuropsychological tests may reveal impaired visual memory, verbal fluency, or executive functions\textsuperscript{46}. In accordance with these deficits SPECT may show prefrontal hypoperfusion\textsuperscript{46}. SCA6 is due to a CAG-repeat expansion in the alpha-1A voltage dependent calcium channel subunit (CACNA1A) gene (Table 2). The alpha-1A subunit is the main pore-forming subunit of the P/Q-type voltage-gated calcium channel\textsuperscript{47}. There may be significant anticipation in the absence of genetic instability on transmission (Table 3). SCA6 is the disorder, in which most frequently intermediate expansion sizes cause sporadic, late-onset SCA\textsuperscript{17}.

SCA7

SCA7 presents clinically as severe cerebellar ataxia, achronolopiasia with cone-rod retinal dystrophy degeneration, and macular degeneration\textsuperscript{48,49}. It is the only SCA with pigmentary retinopathy\textsuperscript{4}. Occasionally, spastic paraparesis may be the onset presentation of the disease\textsuperscript{50}. Rarely, patients additionally develop cranio-cervical dystonia\textsuperscript{49}, dysarthria, dysphagia, pyramidal signs, parkinsonism, impaired writing, smooth pursuits, pupillary impairment, sensory deficits, hypoacusis, or cognitive impairment\textsuperscript{51}. Neuropathological investigations may show subclinical involvement of the auditory brainstem system\textsuperscript{52}. SCA7 is due to a CAG-expansion in the ataxin-7 gene encoding for a transcription factor (Table 2). SCA7 is unique among poly-Q disorders for the strong inter-generational variability of the repeat length (Table 3)\textsuperscript{48}. The correlation between the repeat-length and the clinical severity is positive\textsuperscript{48}. The expansion is made responsible for abnormal processing and stability of ataxin-7, and abnormal transcriptional regulation via interaction of poly-Q-expanded ataxin-7 with other transcriptional regulators\textsuperscript{48}. In a patient with 13 and 70 CAG repeats in the ataxin-7 gene the phenotype resembled that of KSS\textsuperscript{52}.

SCA8

SCA8 is clinically characterized by adult-onset, slowly progressive cerebellar ataxia, ataxic dystasia, and nystagmus with additional features, such as cognitive impairment, dysexecutive syndrome, deficits in attention, information processing, concept formation, reasoning, executive functions, verbal production, memory, learning, visuoperceptual, or visuconstructive functions\textsuperscript{53}, mood disturbance, parkinsonism, impaired writing, smooth pursuits, pupillary impairment, sensory deficits, hypoacusis, or cognitive impairment\textsuperscript{54}. The expansion is made responsible for abnormal processing and stability of ataxin-7, and abnormal transcriptional regulation via interaction of poly-Q-expanded ataxin-7 with other transcriptional regulators\textsuperscript{48}. In a patient with 13 and 70 CAG repeats in the ataxin-7 gene the phenotype resembled that of KSS\textsuperscript{52}.

SCA10

SCA10 first was reported in a large Portuguese ancestry family with pure cerebellar ataxia. Later on, SCA10 has been also described in Brazilian and Mexican families, which additionally presented with epilepsy\textsuperscript{66,67}, myoclonus, pyramidal signs, and cognitive and neuropsychiatric impairment [68]. MRI shows cerebellar atrophy\textsuperscript{69}. SCA10 is due to an expansion of an ATCT repeat of up to 4500 copies (normal: 10–22 copies) in tandem\textsuperscript{71}. The expansion is made responsible for abnormal processing and stability of ataxin-7, and abnormal transcriptional regulation via interaction of poly-Q-expanded ataxin-7 with other transcriptional regulators\textsuperscript{48}. In a patient with 13 and 70 CAG repeats in the ataxin-7 gene the phenotype resembled that of KSS\textsuperscript{52}.
SCA13

SCA13 is a slowly progressive, relatively pure SCA with childhood onset, delayed motor development and mental disturbances. SCA13 is due to point mutations in the KCNC3 gene, encoding for the voltage-gated potassium channel Kv3.3, highly enriched in the cerebellum. Mutations are expected to change the output characteristics of fast-spiking cerebellar neurons, in which KCNC3 confers the capacity for high-frequency firing.

SCA14

Patients with SCA14 present with gait ataxia, cervical dystonia, positional vertigo, retinal degeneration, and facial muscle weakness. Rare manifestations are executive dysfunction, axial myoclonus, myorhythmia, tremor, or decreased vibration sense. SCA14 is due to missense mutations in the protein kinase C gamma gene (PRKCG) encoding protein kinase Cy, highly expressed in Purkinje cell dendrites and reduce synapse formation. These mutations lead to sustained Ca++ influx and disturb the development of Purkinje cell dendrites and reduce synapse formation. There is also aggregation of mutant PRKCG, which impairs the ubiquitin-proteasome system and induces endoplasmatic reticular stress, leading to apoptosis.

SCA15/16

SCA16 was first described in 2001 in an Anglo-Celtic family from Australia. Affected individuals present with cerebellar ataxia, gaze-evoked horizontal nystagmus and tremor. Later on Japanese patients with the same phenotype were described and designated as SCA15 and SCA16. MRI shows cerebellar, particularly vermian atrophy exclusively. However, meanwhile it turned out that both types are due to partial deletion of exons 1-48 (313318bp) of the ITPR1 gene with the telomeric breakpoint located in the middle of the intergenic region between ITPR1 and SUMF1.

SCA17

SCA17 is a typical poly-Q disease and the third most frequent SCA genotype. The phenotype of SCA17 is often severe with involvement of the cerebral cortex, the striatum and the cerebellum. Patients present with cerebellar signs, cognitive impairment in 80% of the cases, choreatic movements in 66%, pyramidal signs, bradykinesia, and dystonia in about 50% of the cases. Onset is extremely variable but the responsible mutation has been mapped to chromosome 7p in a single family from France but the responsible gene remains to be identified.

Sofar only a single pedigree with SCA20 has been reported. Patients presented with palatal tremor, dysarthria, dysphonia, and hypermetric saccades. An MRI shows pancebellar atrophy, dentate calcification, and in some cases olivary pseudohypertrophy. The mutated gene responsible for SCA20 has not been identified yet, but the locus has been mapped to 11q12. Recently, a 260kb duplication has been detected in this region, spanning ten known and two unknown genes.

SCA21

SCA21 is a slowly progressive, mild ataxia associated with extra-pyramidal signs. Affected patients develop moderate gait and limb ataxia, associated with akinesia, tremor rigidity, hyporeflexia, and mild cognitive impairment. The responsible mutation has been mapped to chromosome 7p in a single family from France but the responsible gene remains to be identified.

SCA22

Clinically, SCA22 patients present with dysarthria and hyporeflexia in addition to slowly progressive gait ataxia. MRI shows atrophy of the cerebellum sparing the brain-stem. The mutation shows anticipation. Linkage analysis mapped the suspected gene to a locus at 1p21-q23. Unfortunately, the mutated gene could not be identified yet. Though both SCA19 and SCA22 are linked to 1p21-q21, the clinical features are slightly different. It cannot be excluded that the mutated genes lie in close approximation and it is quite likely that the same gene is mutated in both types and that SCA19 and SCA22 represent the same condition.

SCA23

SCA23 is clinically characterized by late-onset (>40y), slowly progressive isolated cerebellar ataxia. Neuro-pathological investigations show neuronal loss in the Purkinje cell layer, dentate nuclei, inferior olives, thinning of cerebellar pontine tracts, demyelination of posterior and lateral spinal cord...
columns, and intranuclear inclusions in nigral neurons\textsuperscript{104}. The responsible mutated gene has been mapped to the locus 20p13-p12.3\textsuperscript{104}.

**SCA25**

SCA25 has been described only in a single, large French kindred so far and was clinically characterized by cerebellar ataxia and sensory neuropathy. There was large intranuclear phenotypic variability regarding age at onset, and severity, ranging from pure sensory neuropathy to a Friedreich-like picture. Linkage studies mapped the suspected mutated gene to the locus 2p\textsuperscript{105}.

**SCA26**

SCA26 was described only in a single Norwegian family so far\textsuperscript{105}. Clinically, the affected members presented with pure cerebellar ataxia\textsuperscript{105}. Age at onset ranged from 26 to 60y. MRI showed cerebellar atrophy exclusively\textsuperscript{105}. By application of a genome-wide linkage scan with a new strategy a locus at 10p13.3 was identified\textsuperscript{105}.

**SCA27**

SCA27 was reported only in a single Dutch family with 14 patients, who presented with childhood-onset postural tremor and slowly progressing ataxia evolving from young adulthood\textsuperscript{106}. In several of these patients dystonia, suggesting basal ganglia affection, was present. Neuropsychological testing additionally revealed intellectual decline, behavioural problems, and deficit memory and executive functions\textsuperscript{106}. MRI, however, exclusively showed moderate cerebellar atrophy in the two oldest patients\textsuperscript{106}. SCA27 is caused by mutations in the FGF14 gene encoding for the fibroblast growth factor 14\textsuperscript{106}, which presumably regulates synaptic plasticity by controlling mobilization, trafficking or docking of synaptic vesicles to presynaptic zones\textsuperscript{17}.

**SCA28**

SCA28 was first described in a four generation Italian family presenting with juvenile-onset, and slowly progressive gait and limb ataxia, dysarthria, hyperreflexia at lower limbs, nystagmus and ophthalmoparesis\textsuperscript{107,108}. Mean age at onset was 19.5y, starting with imbalanced standing, gaze-evoked nystagmus, and mild gait uncoordination\textsuperscript{108}. Later on, slow saccades, CPEO, ptosis, and exaggerated deep tendon reflexes develop\textsuperscript{108}. Meanwhile, SCA28 has been also described in a second Italian family\textsuperscript{107}. SCA28 is caused by point mutations in the SCA28 gene located on chromosome 18p11.22\textsuperscript{107}.

**SCA29**

SCA29 is a congenital disorder, clinically characterized by a cerebellar syndrome with a number of highly varying features. The responsible mutated gene has not been detected yet but linkage studies located the mutated gene to 3p26.

**SCA30**

Recently a new SCA has been described phenotypically presenting with slowly-evolving ataxia developing in mid or late life, minor pyramidal signs, and hypermetric saccades. The MRI showed cerebellar atrophy. Genome-wide linkage analysis detected a locus at 4q34.3-q35.1\textsuperscript{15}. As the most likely contenders TACSTD1 and ODZ3 were identified.

**DRPLA**

DRPLA is a neurodegenerative disorder first described in 1972\textsuperscript{109}. DRPLS is highly prevalent in Japan. DRPLA is clinically characterized by myoclonus, epilepsy, mental deterioration, behavioural changes, or dementia, cerebellar ataxia, and choreoathetosis\textsuperscript{109,110}. Neuropathologically, there is degeneration of the dentate-rubral and pallido-putamen pathway, supratentorial white matter lesions, and degenerative lesions in the putamen, Goll’s nucleus of the medulla oblongata, and the lateral corticospinal and Goll’s tract of the spinal cord\textsuperscript{109}. The mutated gene was mapped to the locus H-DRPL on chromosome 12p13.31 in 1994 and was identified as atrophin-1.

**B. Episodic Ataxias**

Episodic ataxias (EAs) are a group of rare AD diseases characterized by recurrent, discrete episodes of ataxia, giddiness, and vertigo (Table 5)\textsuperscript{111}. Some of them present with additional abnormalities during the attacks. The current classification is based on genetics and actually includes seven distinct subtypes\textsuperscript{111}. It is quite likely, however, that the number of phenotypes and mutated genes will grow further\textsuperscript{111}.

**Episodic ataxia 1**

EA1 is the second most common of the EAs, and clinically characterized by early childhood-onset brief attacks of ataxia lasting seconds to minutes, typically triggered by exercise, emotional stress, or startle\textsuperscript{112}. Interictally, myokymia can be observed\textsuperscript{111}. EA1 is caused by mutations in the KCNA1 gene on 12q13, encoding for the potassium channel gene Kv1.1\textsuperscript{111}.

**Episodic ataxia 2**

EA2 is the second most common of the EAs and clinically characterized by childhood or adolescent-onset attacks of ataxia lasting hours to days, commonly triggered by exercise, stress, or alcohol\textsuperscript{111}. The attacks may be associated with vertigo, nausea, vomiting, migraine or other headache, fluctuating weakness, dystonia, or seizures\textsuperscript{111}. Interictally, nystagmus may occur\textsuperscript{111,113}. EA2 is caused by mutations in the CACNA1A gene on 19p13, encoding for the pore-forming and voltage-sensing subunit of the voltage-gated Ca-channel Cav2.1\textsuperscript{111}. EA2 is allelic to SCA6 and familial hemiplegic migraine (FHM1), characterized by migraine, hemiplegia, interictal nystagmus, and progressive ataxia\textsuperscript{111}. Due to the large size of the gene and the recognition of only few mutations so far, molecular diagnosis for EA1 and EA2 is available only in specialized or research laboratories.

**Episodic ataxia 3**

EA3 has been described only in a single family so far and is clinically characterized by episodic vertigo, tinnitus and ataxia\textsuperscript{114}. The exact genetic defect is unknown but linkage studies localized the mutated gene to the locus 1q42\textsuperscript{115}. 
Episodic ataxia 4

EA4, also known as periodic vestibulo-cerebellar ataxia, has been described in two kindreds so far and is clinically characterized by late-onset episodic vertigo and ataxia\(^\text{111,116}\). Interictally, nystagmus can be observed\(^\text{111}\). The underlying genetic defect is unknown and no locus has been detected so far.

Episodic ataxia 5

EA5 presents clinically similar as EA2 and is due to mutations in the CACNB4 gene on chromosome 2q22-23, encoding for the beta4-subunit of the Ca-channel Cav2.1. So far, mutations were found in two families, of which one did not exhibit ataxia but generalized epilepsy\(^\text{117}\).

Episodic ataxia 6

EA6 is clinically similar to EA2 but due to mutations in the SLC1A3 gene, which encodes for the glial glutamate transporter EAAT1\(^\text{111}\).

Episodic ataxia 7

EA7 is clinically characterized by adulthood-onset episodic ataxia, weakness, slurred speech, and vertigo, which can be triggered by exertion and excitement and lasts for hours or days\(^\text{118}\). The exact genetic defect is unknown but linkage studies localized the mutated gene to locus 19q13\(^\text{118}\).

Episodic ataxia at infancy may be caused by mutations in the PDH1 gene causing intermittent, isolated, infantile ataxia as a manifestation of PDH deficiency\(^\text{119}\). Later on, however, these patients develop severe encephalopathy with death in their twenties\(^\text{119}\). Episodic ataxia has been also described in a member of a family with a MID due to the 8993T>C mutation in the mtDNA ATP6 gene, who reported intermittent speech and gait disturbance and hemiplegic migraine\(^\text{120}\).

### C. AD Transmitted MIDs

Syndromic and non-syndromic MIDs may present with cerebellar or sensory ataxia\(^\text{121}\). Syndromic AD transmitted MIDs with ataxia include the LS, MIRAS, ADOAD, and AD chronic progressive external ophthalmoplegia. Ataxia is most prevalent in LS and MIRAS. LS is the MID with the widest genetic heterogeneity of all MIDs and due to mutations in the SURF1, NDUFS1-8, or NDUFV1-2 genes\(^\text{122}\). Other mutated genes include the POLG1 (MIRAS, AD-CPEO), OPA1 (ADOAD), ANT1 (AD-CPEO) or C10orf2 (AD-CPEO) genes.

### Autosomal recessive heredoataxias

AR ataxias are a heterogeneous group of genetic diseases, clinically characterized by an early onset cerebellar syndrome with poor balance, falls, imprecise hand coordination, postural or kinetic tremor, dysarthria, dysphagia, vertigo, or diplopia\(^\text{1}\). AR ataxias are generally associated with neuropathy and, contrary to AD ataxias, there is less involvement outside the nervous system\(^\text{123}\). The major forms can be distinguished on the basis of the phenotype, age at onset, biochemical parameters, the MRI, and the genotype\(^\text{16}\). AR ataxias usually start in childhood\(^\text{5}\). Additional neurological features include optic atrophy, extrapyramidal signs, pyramidal signs, peripheral neuropathy, cognitive impairment, or epilepsy. The pathogenesis of these
forms was shown to be associated with a “loss-of-function” of specific cellular proteins involved in metabolic homeostasis, cell-cycle, or DNA-repair/protection. In Europe the most frequent forms are FA, ataxia telangiectasia (AT), and ataxia with oculomotor apraxia (AOA). So far, 14 loci have been mapped in addition to the AR MIDs with ataxia and mutations in 14 genes have been detected (Table 6).

**A. Friedreich ataxia-like phenotype**

**Friedreich ataxia**

Friedreich ataxia is the most common heredoataxia in Caucasian populations and characterized by nervous system, cardiac and endocrine manifestations. The essential clinical features are progressive gait, trunk and limb ataxia, dysarthria, muscle hypotonia, absent deep tendon reflexes, sensory loss, positive pyramidal signs, muscle weakness, and onset before age 25. Hypertrophic cardiomyopathy is present in less than half of the patients. Hypertrophic cardiomyopathy is due to altered cellular iron trafficking and thus iron accumulation. However, also the myocardial microvasculature seems to be affected. Axonal sensory neuropathy, distal wasting, sensori-neural deafness, optic atrophy, and diabetes are other common features. Two thirds of the patients develop scoliosis. Rarely, patients develop head tremor. During the disease course neurological and cardiac abnormalities worsen, despite antioxidant treatment with idebenone.

### Table 6: AR hereditary ataxias

<table>
<thead>
<tr>
<th>Disease</th>
<th>Gene</th>
<th>Locus</th>
<th>Mutation</th>
<th>Gene product</th>
<th>Additional features</th>
<th>Age at onset</th>
</tr>
</thead>
<tbody>
<tr>
<td>FA</td>
<td>FRDA</td>
<td>9q13-q21.1</td>
<td>Trinuc; Pm</td>
<td>Frataxin</td>
<td>Neuropathy, Babinski sign, deep sensory loss, cardiomyopathy, diabetes, saccadic smooth pursuit, fixation instability, saccadic dysmetria</td>
<td>2-55</td>
</tr>
<tr>
<td>AVED</td>
<td>αTTP</td>
<td>8q13.1-q13.3</td>
<td>Del; Ins; Pm</td>
<td>α-tocopherol transfer protein</td>
<td>Head titubation, retinopathy, nystagmus, saccadic pursuit, low serum vitamin E</td>
<td>2-52</td>
</tr>
<tr>
<td>ABL</td>
<td>MTP</td>
<td>4q22-24</td>
<td>Pm</td>
<td>Large subunit of MTP</td>
<td>Steatorrhea, areflexia, sensory ataxia, retinal degeneration, dissociated nystagmus on lateral gaze, slow saccades, neuropathy, acanthocytes, low LDL</td>
<td>0-20</td>
</tr>
<tr>
<td>Refsum disease</td>
<td>PHYH, PEX7 10pter-11.2, 6q21-22.2</td>
<td>Pm, Del, Ins</td>
<td>Phytanoyl-CoA hydroxylase, peroxin 7 receptor protein</td>
<td></td>
<td>Neupropathy, deafness, retinitis pigmentosa, anosmia, skeletal abnormalities, ichthyosis, renal failure, cardiomyopathy</td>
<td>&lt;20</td>
</tr>
<tr>
<td>Late-onset Tay-Sachs</td>
<td>HEXA</td>
<td>15q23-24</td>
<td>Pm, Del, Ins</td>
<td>Beta-hexosaminidase A</td>
<td>Areflexia, proximal muscle weakness, wasting, fasciculations, behavioral abnormalities</td>
<td>Childhood, adulthood</td>
</tr>
<tr>
<td>Cerebrotubular xanthomatosis</td>
<td>CYP27</td>
<td>2</td>
<td>Pm, Del, Ins</td>
<td>Sterol-27-hydroxylase</td>
<td>Pyramidal signs, extrapyramidal signs, neuropathy, seizures, cognitive decline, dementia</td>
<td>20</td>
</tr>
<tr>
<td>SCA + Axonal neuropathy</td>
<td>TDP1</td>
<td>14q31-32</td>
<td>Pm, Del</td>
<td>Tyrosyl-DNAphosphodiesterase 1</td>
<td>Neuropathy, distal wasting, pes cavus</td>
<td>Childhood</td>
</tr>
<tr>
<td>AT</td>
<td>ATM gene</td>
<td>11q22-q23</td>
<td>Del; Ins; Pm</td>
<td>ATM protein (Phospho-inositol-3-kinase type enzyme)</td>
<td>Telangiectasia, immune deficiency, predisposition to cancer, oculomotor apraxia, increased latency of saccades increased alpha-fetoprotein, chromosomal instability</td>
<td>1-4</td>
</tr>
<tr>
<td>ATLD</td>
<td>MRE1</td>
<td>11q21</td>
<td>Pm</td>
<td>MRE11</td>
<td>Similar to AT, milder course</td>
<td>1-7</td>
</tr>
<tr>
<td>AOA1</td>
<td>APTX</td>
<td>9p13</td>
<td>Ins; Del; Pm</td>
<td>Aprataxin</td>
<td>Oculomotor apraxia, fixation instability, saccadic pursuit, gaze-evoked nystagmus, hypometric saccades, neuropathy, choreoathetosis, mild mental retardation, hypercholesterolemia, hypoalphalipoproteinemia</td>
<td>1-29</td>
</tr>
<tr>
<td>AOA2</td>
<td>SETX</td>
<td>9q34</td>
<td>Pm; Del</td>
<td>Senataxin</td>
<td>Oculomotor apraxia, saccadic pursuit, slow saccades, choreoathetosis, neuropathy</td>
<td>3-30</td>
</tr>
<tr>
<td>AR spastic ataxia</td>
<td>SACS</td>
<td>13q11</td>
<td>Pm</td>
<td>Sacsin</td>
<td>Pyramidal signs, neuropathy</td>
<td>1-5</td>
</tr>
<tr>
<td>Cayman ataxia</td>
<td>ATCA</td>
<td>19p13.1</td>
<td>Pm</td>
<td>Caytatin</td>
<td>Muscle hypotonia, mental retardation</td>
<td>Childhood</td>
</tr>
<tr>
<td>Marinesco-Sjögren</td>
<td>SIL1</td>
<td>5q31</td>
<td>Pm, Del</td>
<td>HSPA5</td>
<td>Cataract, mental retardation, short stature, hypogonadism, skeletal deformities, myopathy, neuropathy, epilepsy</td>
<td>Infancy</td>
</tr>
</tbody>
</table>

Ataxia with vitamin E deficiency

Ataxia with vitamin E deficiency presents with a phenotype similar to FA but impaired visual acuity or retinitis pigmentosa may be early findings. Cardiomyopathy is the most common systemic finding but less common than in FA. Typically, serum concentrations of vitamin E are reduced. Most patients are from the Mediterranean area. Age at onset is before 20. There is great phenotypic variability. The disease is caused by mutations in the α-tocopherol transfer protein gene on chromosome 8q13. The alpha-tocopherol transfer protein mediates the incorporation of vitamin E into circulating lipoproteins, and mutations presumably reduce vitamin availability to the nervous system. The mechanism underlying the pathogenesis appears to be oxidative stress. Only early supplementation with vitamin E may slow the progression of the disease.

Abeta-lipoproteinaemia

The phenotype resembles that of FA and vitamin E deficiency but is additionally associated with lipid malabsorption, hypcholesterolaemia, acanthocytosis, or retinitis pigmentosa. Onset is before age 20y. Abeta-lipoproteinaemia is caused by mutations in the gene for the large subunit of microsomal triglyceride transfer protein, located on chromosome 4q22-24, which functions in the assembly of apolipoprotein-B containing very low-density lipoproteins and chylomicrons.

Refsum disease

Refsum disease is clinically characterized by cerebellar ataxia, retinitis pigmentosa, deafness, anosmia, cardiomyopathy, renal insufficiency, skeletal abnormalities, and ichthyosis. The disease is either due to mutations in the PHYH gene, encoding for the peroxisomal enzyme peroxisomal phytanoyl-CoA hydroxylase or due to mutations in the PEX7 gene, which encodes for the peroxin 7 protein receptor required to import proteins with a type 2 peroxisomal signal into peroxisomes. Because of the impaired alpha-oxidation of branched chain fatty acids, phytic acid, found in diary products, meat and fish, accumulates in the body fat.

B. Friedreich ataxia-like with cerebellar atrophy

Late-onset Tay-Sachs disease

Contrary to infantile-onset Tay Sachs disease, the adult form is clinically characterized by cognitive decline, cerebellar dysfunction, areflexia, proximal muscle weakness, wasting, and fasciculations. There is notable cerebellar atrophy on MRI. It is due to mutations in the HEXA gene, encoding for beta-hexosaminidase. The late-onset form results from one inactive allele and one with a less severe mutation and residual enzyme activity.

Cerebrotendineous xanthomatosis

Cerebrotendineous xanthomatosis presents for the first time around 20 years of age with cerebellar ataxia, pyramidal signs, extra-pyramidal signs, neuropathy, seizures, psychiatric abnormalities, and dementia. Cerebrotendineous xanthomatosis is caused by mutations in the CYP27 gene, which encodes for the mitochondrial sterol 27-hydroxylase. The sterol 27-hydroxylase is part of the bile-acid synthesis pathway and if mutated results in elevation of cholesterol and bile alcohols.

Spinocerebellar ataxia with axonal neuropathy

Spinocerebellar ataxia with axonal neuropathy is a rare, childhood onset ataxia, so far described only in Saudi Arabia. In addition to cerebellar atrophy it presents with axonal sensorimotor neuropathy, distal wasting, and pes cavus. It is caused by mutations in the TDP1 gene, which encodes for the tyrosyl-DNA phosphodiesterase 1. This enzyme is likely involved in the repair of DNA-topoisomerase 1 complexes during transcription and replication and of topoisomerase 1-related single-strand breaks in postmitotic neurons.
AR transmitted MIDs presenting with ataxia

Syndromic and non-syndromic AR transmitted MIDs may present with cerebellar or sensory ataxia\(^1\)\(^{121}\). Among the syndromic AR transmitted MIDs which frequently present with ataxia are the Leigh syndrome, AR-CPEO, SANDO, SCAE, AHS, IOSCA, MEMSA, and LBSL. More rarely ataxia occurs in AR-CPEO, MNGIE, DIDMOAD (Wolfram syndrome), CoQ deficiency, or PDC-deficiency\(^1\)\(^{121}\). Genes mutated in AR-MIDs with ataxia are the SURF1, NDUFS1-8, or NDUFV1-2 genes (LS), POLG1 (SANDO, AHS, MEMSA, AR-CPEO), C10orf2/twinkle (IOSCA), DARS2 (LBSL), thymidine phosphorylase (MNGIE), or WFS genes (DIDMOAD).

C. Early-onset ataxia with cerebellar atrophy

Ataxia telangiectasia (AT)

AT is a rare AR disorder, clinically characterized by cerebellar ataxia, ocular apraxia, telangiectasias, immune defects in about half of the cases, and a predisposition to malignancy\(^1\)\(^{145}\). Patients present in early childhood with progressive cerebellar ataxia and later develop ubiquitous telangiectasia and progressive neurological degeneration. Choreoathetosis and/or dystonia occur in 90% of the patients. A prospectively important feature is the susceptibility to cancer. About 40% of the patients are at risk to develop a malignoma. The most frequent malignancies found are T-cell or B-cell lymphoma. There may be acute sensitivity to ionizing radiation or radiomimetic chemicals\(^1\)\(^{146}\). High concentrations of serum alpha-fetoprotein are a typical laboratory finding. MRI may show extensive, diffuse white matter demyelination, TI and T2-hypointense lesions, TI hypointense and T2 hyperintense lesions, or numerous telangiectasia upon gadolinium enhancement in single patients\(^1\)\(^{47}\).

The disease is caused by mutations in the AT-mutated gene (ATM), resulting in loss or inactivation of the gene product\(^1\)\(^{146}\). The protein is a serine/threonine protein kinase, which mobilizes the complex, multi-branched cellular response to DNA double strand breaks by phosphorylating numerous DNA damage response players\(^1\)\(^{146}\). The phenotype can vary in severity depending on whether the ATM protein is completely absent or not\(^1\)\(^{48}\). Patients with no ATM activity develop a markedly more severe phenotype with more frequent sinopulmonary infections, lower immunoglobulin levels, greater need for prophylactic antibiotics, and a higher prevalence of B-cell lymphoma than patients with residual ATM activity\(^1\)\(^{45}\).

Ataxia telangiectasia-like disease (ATLD)

Ataxia telangiectasia-like disease is similar to ataxia telangiectasia, but has a later onset and a slower progression. Patients lack telangiectasias and immunodeficits, and have normal concentrations of serum alpha fetoprotein. The disease is caused by mutations in the meiotic recombination 11 gene MRE11\(^1\).

Ataxia with oculomotor apraxia type 1 (AOA1)

The disease is similar to AT and characterized by cerebellar gait and limb ataxia, oculomotor apraxia, sensorimotor neuropathy, nystagmus, and choreoathetosis\(^1\)\(^{49}\). AOA1 has an early age at onset and is clinically characterized by variable oculomotor apraxia, extrapyramidal signs, and mild cognitive impairment. Patients have hypoalbuminemia, hypercholesterolemia, and normal serum alpha-fetoprotein. There is marked cerebellar atrophy on MRI. The disease is caused by mutations in the aprataxin gene, APTX, on chromosome 9p13. The protein likely plays a role in DNA repair. AOA1 is most prevalent in Europe, Japan, and North Africa\(^1\).

Ataxia with oculomotor apraxia type 2 (AOA2)

Ataxia with oculomotor apraxia type 2 (AOA2) is the second most frequent AR ataxia and presents with a similar phenotype as AOA1, but age at onset is in the early teens and there are less oculomotor apraxia, extrapyramidal signs, or cognitive changes than in AOA1\(^1\). Laboratory studies show normal albumin but high serum alpha-fetoprotein. MRI shows particularly vermal atrophy. The disease is caused by mutations in the senataxin gene (SEXT), on chromosome 9q34. Although the functional role of human senataxin is unknown, its yeast orthologue, Sen1p, is implicated in DNA transcription, repair, and processing.

AR spastic ataxia of Charlevoix-Saguenay

This disorder presents with cerebellar dysfunction, pyramidal signs, sensorimotor neuropathy and wasting and was first described in North-East Canada\(^1\). Recently the disorder was also described in Europe, Asia, and North Africa. MRI shows atrophy of the vermis. The disease is due to mutations in the SACS gene, which encodes for sacsin, which is assumed to have a chaperone role in protein-folding\(^1\)\(^{50}\). The exact pathogenesis, however, is unknown.

Cayman ataxia

Cayman ataxia has been so far described only in an inbred population from Grand Cayman island and is clinically characterized by cerebellar ataxia, muscle hypotonia, and psychomotor retardation. There is cerebellar atrophy on MRI. The disorder is due mutations in the ATCAY gene, which encodes for caytaxin, of which the function is so far unknown\(^1\).

Marinesco-Sjögren syndrome

Marinesco-Sjögren syndrome is a rare infantile-onset cerebellar ataxia associated with mental retardation, epilepsy, cataract, short stature, hypogonadism, myopathy, wasting, neuropathy, and skeletal deformities\(^1\)\(^{51}\). The MRS shows cerebellar atrophy. The syndrome is caused by mutations in the SIL1 gene, encoding for HSPA5, a nucleotide exchange factor for the heat-shock protein 70 family. HSPA5 functions as a molecular chaperone during nascent protein protein folding and transport\(^1\)\(^{51}\).

X-LINKED ATAXIAS

Fragile X tremor/ataxia syndrome

Fragile X tremor/ataxia syndrome (FXTAS) affects only men and is clinically characterized by three cardinal clinical features: progressive intention tremor, ataxia, and cognitive decline.
starting in the sixth decade of life\textsuperscript{152,153}. Only 4\% of the patients exhibit all three features, 20\% two features and half of the patients all three features\textsuperscript{152}. During the disease course parkinsonism or peripheral neuropathy may additionally develop. FXTAS presents with typical findings on MRI showing symmetric regions of T2-hyperintensities in the middle cerebellar peduncles and adjacent cerebellar white matter (peridentate white matter) and non-specific symmetric signal changes in the cerebral white matter but normal pons and basal ganglia\textsuperscript{154}. FXTAS is caused by an expanded CGG-repeat in the intron of the FMR1 gene. Depending on the site of the expansion premutations (55 to 200 repeats) and full repeat expansions (>200 repeats) are differentiated. Only patients with the premutation exhibit FXTAS. Males with >200 repeats develop fragile X mental retardation syndrome (no transcription of FMR1). Prevalence of the syndrome is not known, but testing is recommended when there is a clinical suspicion as it is readily available in many laboratories.

**XL SA/A**

X-linked sideroblastic anemia with ataxia (XL SA/A) is a rare syndromic MID, characterized by mild sideroblastic anemia with hypochromia and microcytosis and cerebellar ataxia\textsuperscript{155,156}. Cerebral imaging shows severe cerebellar atrophy, XL SA/A is due to mutations in the mitochondrial ATP-binding cassette transporter ABC7 on chromosome Xq13\textsuperscript{157}.

**Maternally inherited ataxias**

Maternally inherited MIDs often present with ataxia as the single or dominant manifestation or as a sign among various others. Maternally inherited MIDs, which go frequently along

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### Table 7: AD, AR, XL, and maternally transmitted mitochondrial ataxias

<table>
<thead>
<tr>
<th>MID</th>
<th>Frequency of ataxia</th>
<th>MI</th>
<th>Mutated gene(s)</th>
<th>mtDNA</th>
<th>nDNA</th>
</tr>
</thead>
<tbody>
<tr>
<td>mtDNA genes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Point mutations in genes encoding for tRNAs or rRNAs (homoplasmic or heteroplasmic)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MELAS</td>
<td>rare</td>
<td>mat</td>
<td>tRNAs, rRNAs</td>
<td>PM (homoplasmic or heteroplasmic)</td>
<td>n</td>
</tr>
<tr>
<td>MERRF</td>
<td>frequent</td>
<td>mat</td>
<td>tRNAs, rRNAs</td>
<td>PM (homoplasmic or heteroplasmic)</td>
<td>n</td>
</tr>
<tr>
<td>MSL</td>
<td>rare</td>
<td>mat</td>
<td>tRNAs</td>
<td>PM (homoplasmic or heteroplasmic)</td>
<td>n</td>
</tr>
<tr>
<td>MIDD</td>
<td>rare</td>
<td>mat</td>
<td>tRNAs</td>
<td>PM (homoplasmic or heteroplasmic)</td>
<td>n</td>
</tr>
<tr>
<td>2. Point mutations in genes encoding for RC subunits (homoplasmic or heteroplasmic)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LHON</td>
<td>rare</td>
<td>mat</td>
<td>RC subunits</td>
<td>PM</td>
<td>n</td>
</tr>
<tr>
<td>NARP</td>
<td>frequent</td>
<td>mat</td>
<td>RC subunits</td>
<td>PM</td>
<td>n</td>
</tr>
<tr>
<td>MILS</td>
<td>frequent</td>
<td>mat</td>
<td>RC subunits</td>
<td>PM</td>
<td>n</td>
</tr>
<tr>
<td>3. Single deletions/duplications (sporadic, heteroplasmic)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PS</td>
<td>rare</td>
<td>mat</td>
<td>multiple RC subunits, RNAs</td>
<td>Single deletion/duplication</td>
<td>n</td>
</tr>
<tr>
<td>KSS</td>
<td>frequent</td>
<td>mat</td>
<td>multiple RC subunits, RNAs</td>
<td>Single deletion/duplication</td>
<td>n</td>
</tr>
<tr>
<td>nDNA genes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Encoding for RC subunits</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LS</td>
<td>frequent</td>
<td>AD, AR</td>
<td>RC subunits, assembly factors</td>
<td>n</td>
<td>PM, deletion</td>
</tr>
<tr>
<td>Intergenomic signaling</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AD-CPEO</td>
<td>rare</td>
<td>AD</td>
<td>POLG1, ANT1, twinkle</td>
<td>mtDNA breakage syndrome</td>
<td>PM</td>
</tr>
<tr>
<td>AR-CPEO</td>
<td>rare</td>
<td>AR</td>
<td>POLG1</td>
<td>mtDNA breakage syndrome</td>
<td>PM</td>
</tr>
<tr>
<td>SANDO</td>
<td>frequent</td>
<td>AR</td>
<td>POLG1</td>
<td>mtDNA breakage syndrome</td>
<td>PM</td>
</tr>
<tr>
<td>SCAE</td>
<td>frequent</td>
<td>AR</td>
<td>16q21-q23</td>
<td>mtDNA breakage syndrome</td>
<td>Uk</td>
</tr>
<tr>
<td>AHS</td>
<td>frequent</td>
<td>AR</td>
<td>POLG1</td>
<td>mtDNA depletion syndrome</td>
<td>PM</td>
</tr>
<tr>
<td>MNGIE</td>
<td>rare</td>
<td>AR</td>
<td>Thymidine phosphorylase</td>
<td>mtDNA breakage syndrome</td>
<td>PM</td>
</tr>
<tr>
<td>IOSCA</td>
<td>frequent</td>
<td>AR</td>
<td>C10orf2 (twinkle)</td>
<td>mtDNA depletion syndrome</td>
<td>PM</td>
</tr>
<tr>
<td>MIRAS</td>
<td>frequent</td>
<td>AD</td>
<td>POLG1</td>
<td>multiple mtDNA deletions</td>
<td>PM</td>
</tr>
<tr>
<td>MEMSA</td>
<td>frequent</td>
<td>Uk</td>
<td>POLG1</td>
<td>n</td>
<td>PM</td>
</tr>
<tr>
<td>ADOAD</td>
<td>rare</td>
<td>AD</td>
<td>POLG1</td>
<td>multiple mtDNA deletions</td>
<td>PM</td>
</tr>
<tr>
<td>CoQ production</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LS</td>
<td>rare</td>
<td>AR</td>
<td>CoQ pathway</td>
<td>Uk</td>
<td>Uk</td>
</tr>
<tr>
<td>Mitochondrial transport machinery</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>XLSA</td>
<td>frequent</td>
<td>XL</td>
<td>ABC7</td>
<td>n</td>
<td>PM</td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LBSSL</td>
<td>frequent</td>
<td>AR</td>
<td>DARS2</td>
<td>n</td>
<td>PM</td>
</tr>
<tr>
<td>DIDMOAD</td>
<td>rare</td>
<td>AR</td>
<td>WFS1, WFS2</td>
<td>multiple mtDNA deletions</td>
<td>PM</td>
</tr>
</tbody>
</table>

with ataxia, are the MERRF, NARP, MILS, and KSS syndrome. Though more rarely, ataxia may also be a feature of MELAS, LHON, PS, MSL, or MIDD syndrome. Maternally inherited ataxias may be due to tRNA mutations (MERRF, MELAS, MSL, MIDD), single mtDNA deletions (KSS, PS), or mutations in genes encoding for subunits of the RC complexes (NARP, MILS, LHON) (Table 7).

**DIAGNOSIS**

The basis of diagnosing heredoataxias is the detailed individual and family history and clinical neurologic examination. The family history should be particularly directed towards the number of family members affected, their sex and phenotype, to construct a family tree for assessing the trait of inheritance. For SCAs it is important to find out which features, other than that of the cerebellar syndrome, the phenotype includes. For EAs it is important to confirm that the attacks occur without impairment of consciousness. One feature, which delineates EAs from other heredoataxias is the clear onset and end of an attack, without waxing or waning of symptoms (Table 8).

### Table 8: Diagnosis of heredoataxias

| Individual and family history (assessment of phenotype and hereditary trait (family tree)) |
| Clinical neurologic investigation (SARA-, INAS-, ICARS-, SCAF1-score) |
| Blood chemical investigations (vitamin E, cholesterol (AOA1), albumin (AOA1)) |
| Electrophysiology |
| Nerve conduction studies (if neuropathy is a feature of the phenotype) |
| Motor evoked potentials |
| Visually evoked potentials |
| Somato-sensory evoked potentials (to confirm dorsal column affection) |
| Nystagmography |
| Retinography |
| Polysomnography |
| MRI, MRS, DTI |
| Nerve biopsy |
| Genetics |

Clinical neurologic examination should assess the degree of cerebellar impairment, which can be quantified by the “Scale for the Assessment and Rating of Ataxia” (SARA)\(^{158}\). Additional non-ataxia abnormalities can be assessed by the “Inventory of Non-ataxia Symptoms” (INAS)\(^{158}\). Severity of ataxia may be also scored by the International Ataxia Cooperative Rating Scale (ICARS)\(^{39}\). Another scale to assess functionality in ataxia patients is the SCA functional index (SCAFI) (Table 8)\(^{158}\).

Of additional help, particularly in forms with neurological or extra-neurological abnormalities, are blood chemical investigations, such as determination of vitamin E, neuroimaging, nerve conduction studies, electromyography, evoked potentials, cerebral, or spinal MRI, occasionally nerve biopsy, cardiac investigations, and genetic investigations. All these investigations are particularly helpful to rule out differentials of heredoataxias (Table 1). Nerve conduction studies may be helpful in phenotypes, which also include motor or sensory neuropathy\(^{159}\). Visually evoked potentials may be prolonged in case of optic nerve involvement, particularly in SCA7\(^{159}\). Tibial SSEPs may show slowing of the impulse conduction along the spinal sensory tracts\(^{125}\). Motor evoked potentials may show prolonged central motor conduction time, most frequently in SCA1, even without clinical pyramidal affection\(^{159}\). Polysomnography may detect brainstem involvement and particularly periodic leg movements during sleep\(^{159}\). Nystagmography may reveal vertical nystagmus particularly in SCA3 and 6 (Table 4)\(^{159}\). Sural nerve biopsy may show marked decrease in large myelinated fibers, and a moderate decrease in small myelinated fibers with normal density of unmyelinated fibers\(^{125}\). Carbon dioxide laser stimulation and skin biopsy may confirm that unmyelinated fibers are not involved (Table 8)\(^{125}\).

Cerebral MRI is particularly helpful since it is non-invasive, relatively cost-neutral, and widely available. The main finding in heredoataxias on MRI is atrophy. Three main patterns can be differentiated: 1. pure atrophy of the medulla and the spinal cord with symmetric changes in the white matter tracts of the lateral and posterior columns, as in FA, 2. olivo-ponto-cerebellar atrophy with atrophy of the cerebellum, brainstem, and cervical spinal cord and characteristic diffuse changes of the pons, middle cerebellar peduncle, and cerebellum, and 3. cortico-cerebellar atrophy with atrophy of the cerebellar folia without any signal change and normal bulk of the brainstem and spinal cord (Table 9)\(^{154}\). Diffusion MRI may typically show increased ADC maps and diffusivity and reduced fractional anisotropy in the brainstem and cerebellum\(^{154}\). MRS may show a decreased NAA peak or decreased NAA/PCr ratio in the cerebellum or pons\(^{154}\).

Genetic testing is the key cornerstone of diagnosing heredoataxias, although it is actually successful in only 50-75%\(^{5,6}\) of the cases. Genetic testing for SCA1, 2, 3, 6, 7, 17, and

### Table 9: Types of Atrophy on cerebral MRI in heredoataxias

<table>
<thead>
<tr>
<th>Type 1. Spinal atrophy</th>
<th>FA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 2. Olivo-ponto-cerebellar atrophy</td>
<td>SCA1, 2, 3, 7, 13, DRPLA, EOCA, MSA-C</td>
</tr>
<tr>
<td>Type 3. Cortico-cerebellar atrophy</td>
<td>SCA 4-6, 8, 10, 12, 14-19, 21-22, 25, EOCA, AT, ILOCA</td>
</tr>
</tbody>
</table>
DRPLA has become customary in front of a hereditary ataxia, as testing is technically easy. Priority for molecular testing may take into account the main associated symptoms (Table 4) and the geographical origin of the family, since some SCA genotypes have been demonstrated to be more frequent in certain regions\textsuperscript{159}. No routine test is yet available for the other SCAs and diagnosis will have to be made in collaboration with specialized or research laboratories.

**TREATMENT**

Curative treatment is not available for heredoataxias but application of symptomatic treatment may contribute to substantial relief of symptoms. Repeatedly attempts have been made to relieve ataxia but no confirmed pharmacological treatment is yet available\textsuperscript{160}.

**Effective measures**

Severity and frequency of the unsteadiness of attacks in EAs may be reduced by acetazolamide\textsuperscript{111}. Particularly, patients with EA2 can be dramatically responsive to acetazolamide, resulting in a decrease of frequency, duration, and severity of attacks\textsuperscript{111}. Acetazolamide is usually started at 125-250mg/d and then increased up to 1000mg/d if needed and tolerated\textsuperscript{111}. Side effects, such as tingling, numbness, decreased appetite, altered taste, impaired concentration and memory, or kidney stones have to be encountered\textsuperscript{111}.

Idebenone (0.5mg/kgBW) over three months improved muscle force, tolerability of workload, motility, speech coordination, and reduction of fatigue in FA. High dose idebenone (up to 75mg/kgBW/d) is also well tolerated\textsuperscript{161}. In a four-year trial CoQ and vitamin E improved cardiac function and various neurological manifestations\textsuperscript{1}.

Vitamin E substitution can be highly effective in AR SCA with vitamin E deficiency if given early. Treatment of Abeta- lipoproteinemia includes dietary modification and vitamin E replacement, which may prevent neurological complications if applied early\textsuperscript{1}. Recombinant human erythropoetin administered subcutaneously three times a week in 12 FA patients resulted in persistent, significant increase in frataxin after eight weeks\textsuperscript{162}. Six-months treatment with the membrane permeant chelator deferiprone in nine patients with FA removed intracellular iron accumulations and improved polyneuropathy and ataxic gait\textsuperscript{163}. In a preliminary trial D-cycloserine, an NMDA allosteric inhibitor, showed some efficacy in a subject with low E vitamin or a FA-like phenotype, when FRDA has been excluded\textsuperscript{164}.

Ineffective agents

Though physostigmine was helpful in single patients for ataxia, it did not improve ataxia in a double-blind cross-over trial\textsuperscript{165}. Sulfamethoxazole/trimethoprim was thought to be effective for spasticity and rigidity rather than ataxia in SCA3 but this effect was not confirmed in a double-blind placebo-controlled trial\textsuperscript{160}. Serotoninergic agents have been tried for ataxia but were largely ineffective\textsuperscript{160}. Ineffective were also choline and derivatives in FA\textsuperscript{160}. Generally, serotoninergic and cholinergic drugs seem to be ineffective in heredoataxias\textsuperscript{165}.

**Future options**

Data from animal and cell models show that future therapeutic strategies may rely on silencing gene expression, increasing the protein clearance, reducing the toxicity of the mutated protein, or influence downstream pathways activated by the mutant protein or translocation\textsuperscript{166}. A promising option could be the administration of histone deacetylase (HDAC) inhibitors, like phenylbutyrate in HD\textsuperscript{17}. The effect is based on the fact that poly-Q proteins inhibit the histone acetyl-transferase activity and thus suppress transcription\textsuperscript{11}. Another future option might be CoQ, which has been insignificantly beneficial in HD (HD-Care study)\textsuperscript{17}. Another beneficial agent may be creatine-monohydrate\textsuperscript{17}. In ataxias associated with a deficiency of GABA or glutamine in the brain the use of GABA-ergic respectively glutamnergic drugs could be helpful\textsuperscript{165}. Misfolding of poly-Q proteins may be accessible to molecular chaperones, intrabodies, peptides, or small chemical compounds\textsuperscript{23}. There is also extensive screening in progress to identify poly-Q aggregate inhibitors\textsuperscript{23}.

Because of the availability of symptomatic and supportive treatment it is important to try and confirm the genetic diagnosis in a subject with low E vitamin or a FA-like phenotype, when FRDA has been excluded.

**CONCLUSIONS**

In the case of a family history compatible with AD, inheritance testing for mutations causing SCA1, 2, 3, 6, 7, 17, or DRPLA should be initially carried out. For these forms mutational screening is available in most laboratories. If an AR ataxia is suspected, FRDA mutations must always be excluded. Diagnosis of other recessive forms may be guided by biochemical findings, such as reduced levels of vitamin E or albumin, and increased levels of cholesterol, or alpha-fetoprotein (AOA2). For these latter forms genetic diagnosis can only be done in specialized laboratories. An X-linked phenotype with onset >60y is highly suspect of FXTAS. Maternal inheritance suggests a MID as a cause of ataxia. AD, AR, XL-inherited MIDs are more difficult to diagnose and usually require a broad range of diagnostic effort.

Overall, heredoataxias are a group of neurodegenerative disorders, which are phenotypically and genotypically quite heterogeneous. Heredoataxias may be best classified according to their trait of inheritance. In case of AD, AR, or XL transmission the investigating physician should always consider a MID if the presenting phenotype does not fit into one of the non-mitochondrial ataxias. To guide the geneticist and approach the correct diagnosis, additional CNS and non-neurological features and the presentation on MRI need to be considered and the presenting phenotype needs to be classified. In each case it should be intended to clarify the genetic background, which is a pre-requisite for sufficient genetic counseling and for assessing the prognosis. Since a number of trials are still ongoing, therapeutic options for heredoataxias are limited to symptomatic treatment. However, perspectives for future effective therapies are promising.
LIST OF ABBREVIATIONS

AD Autosomal dominant
ADOAD Autosomal dominant optic atrophy and deafness
AHS Alpers Huttenlocher syndrome
ANT1 Adenosine-nucleotide-transferase 1
AOA Ataxia with optomotoric apraxia
AR Autosomal recessive
AT Ataxia telangiectasia
ATCAY Gene encoding for cytactin
ATP Adenosine tri-phosphate
CACNA1A Alpha 1-subunit of the neuronal calcium channel
CAG Cytosin-Adenosin-Guanin
CoQ Coenzyme Q
CPEO Chronic external ophthalmoplegia
CYP27 Gene encoding for the sterol 27-hydroxylase
DDS (MTS) Deafness dystonia syndrome (Mohr Tranebaerg syndrome)
DIMOAD (WFS) Diabetes insipidus, diabetes mellitus, optic atrophy, deafness syndrome (Wolfram syndrome)
DNA Desoxy-ribonucleic acid
DRPLA Dentato-rubro-pallido-luysian atrophy
DTI Diffusion tensor imaging
EA Episodic ataxia
EAAT1 Glial glutamate transporter
FA Friedreich ataxia
FARR Friedreich ataxia with retained reflexes
FHM Familial hemiplegic migraine
FGF14 Fibroblast growth factor 14 gene
FRDA Friedreich ataxia gene
FXTAS Fragile X tremor ataxia syndrome
HD Huntington’s disease
HEXA Gene encoding for beta-hexosaminidase
ICARS International Ataxia Cooperative Rating Scale
INAS Inventory of Non-ataxia Symptoms
IOSCA Infantile-onset spinocerebellar ataxia
KCNC3 Gene encoding for the neuronal potassium channel Kv3.3
KLHL1 Kelch-like 1 gene
KSS Kearns Sayre syndrome
LBSL Leber’s hereditary optic neuropathy
LOFA Late-onset Friedreich ataxia
LS Leigh syndrome
MDS Mitochondrial depletion syndrome
MELAS Mitochondrial encephalomyopathy, lactic acidosis, stroke-like episodes
MEMSA Myoclonus epilepsy, myopathy and sensory ataxia
MERRF Myoclonic epilepsy and ragged red fibers
MID Mitochondrial disorder
MIDD Mitochondrial diabetes and deafness syndrome
MILS Maternally inherited Leigh syndrome
MIRAS Mitochondrial recessive ataxia syndrome
MLASA Autosomal recessive sideroblastic anemia with mitochondrial myopathy and lactic acidosis
MNGIE Mitochondrial neuro-gastro-intestinal encephalomyopathy
MRI Magnetic resonance imaging
MRS Magnetic resonance spectroscopy
MSA Multisystem atrophy
MSL Multiple systemic lipomatosis
NAA N-acetyl aspartate
NARP Neurogenic muscle weakness, ataxia, and retinitis pigmentosa
OPA Optic atrophy
PDC Pyruvat-dehydrogenase complex
PDH Pyruvat-dehydrogenase
PEX7 Gene encoding for the peroxin 7 protein receptor
PHYH Gene encoding for peroxisomal phytanoyl-CoA hydroxylase
PLEKHG4 Gene encoding for puratrophin-1
POLG1 Polymerase-gamma gene
PPP2RB Gene encoding for the Bbeta-2 subunit of the protein phosphatase 2a (PP2A)
PRKCG Proetien-kinase gamma gene
PS Pearson syndrome
RC Respiratory chain
RNA Ribonucleic acid
SANDO Sensory ataxic neuropathy, dystarthis, ophthalmoplegia
SARA Scale for the Assessment and Rating of Ataxia
SCA Spinocerebellar ataxia
SCAE Juvenile-onset spinocerebellar ataxia and epilepsy
SCAFII SCA functional index
SETX Gene encoding for sematrin
SIL1 Gene encoding for HSPA5 (nucleoside exchange factor)
SPECT Single photon emission computed tomography
SPTBN2 Gene encoding for beta-III spectrin
SSEP’s Somato-sensory evoked potentials
TTBK2 Gene encoding for tau tubulin kinase 2
XLSA/A X-linked sideroblastic anemia with ataxia

REFERENCES


