REVIEW ARTICLE

Ataxias with Autosomal, X-Chromosomal or Maternal Inheritance

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ABSTRACT: Heredoataxias are a group of genetic disorders with a cerebellar syndrome as the leading clinical manifestation. The current classification distinguishes heredoataxias according to the trait of inheritance into autosomal dominant, autosomal recessive, X-linked, and maternally inherited heredoataxias. The autosomal dominant heredoataxias are separated into spinocerebellar ataxias (SCA1-8, 10-15, 17-23, 25-30, and dentato-rubro-pallido-luysian atrophy), episodic ataxias (EA1-7), and autosomal dominant mitochondrial heredoataxias (Leigh syndrome, MIRAS, ADOAD, and AD-CPEO). The autosomal recessive ataxias are separated into Friedreich ataxia, ataxia due to vitamin E deficiency, ataxia due to Abeta-lipoproteinemia, Refsum disease, late-onset Tay-Sachs disease, cerebrotendineous xanthomatosis, spinocerebellar ataxia with axonal neuropathy, ataxia telangiectasia, ataxia telangiectasia-like disorder, ataxia with oculomotor apraxia 1 and 2, spastic ataxia of Charlevoix-Saguenay, Cayman ataxia, Marinesco-Sjögren syndrome, and autosomal recessive mitochondrial ataxias (AR-CPEO, SANDO, SCAE, AHS, IOSCA, MEMSA, LBSL CoQ-deficiency, PDC-deficiency). Only two of the heredoataxias, fragile X/tremor/ataxia syndrome, and XLSA/A are transmitted via an X-linked trait. Maternally inherited heredoataxias are due to point mutations in genes encoding for tRNAs, rRNAs, respiratory chain subunits or single large scale deletions/duplications of the mitochondrial DNA and include MELAS, MERRF, KSS, PS, MILS, NARP, and non-syndromic mitochondrial disorders. Treatment of heredoataxias is symptomatic and supportive and may have a beneficial effect in single patients. **Please see page 424 for abbreviation list.

RÉSUMÉ: Ataxies dont l'hérédité est autosomique, liée à l'X ou maternelle. Les ataxies héréditaires regroupent des maladies génétiques dont la principale manifestation clinique est un syndrome cérébelleux. La classification actuelle de ces ataxies est basée sur le mode d'hérédité, soit autosomique dominant, autosomique récessif, lié à l'X et maternel. Les ataxies héréditaires autosomiques dominantes sont divisées en ataxies spinocérébelleuses (SCA1-8, 10-15, 17-23, 25-30 et atrophie dentato-rubro-pallido-luysienne), ataxies épisodiques (EA1-7) et ataxies héréditaires autosomiques dominantes mitochondriales (syndrome de Leigh, MIRAS, ADOAD et AD-CPEO). Les ataxies autosomiques récessives sont l'ataxie de Friedreich, l'ataxie due à un déficit en vitamine E, l'ataxie due à l'abêta-lipoprotéinémie, la maladie de Refsum, la maladie de Tay-Sachs à début tardif, la xanthomatose cérébrotendineuse, l'ataxie spinocérébelleuse avec neuropathie axonale, l'ataxie télangiectasie, l'ataxie ressemblant à l'ataxie télangiectasie, l'ataxie avec apraxie oculomotrice 1 et 2, l'ataxie spastique de Charlevoix-Saguenay, l'ataxie des îles Caïman, le syndrome de Marinesco-Sjögren et les ataxies mitochondriales autosomiques récessives (AR-CPEO, SANDO, SCAE, AHS, IOSCA, MEMSA, LBSL déficit en coenzyme Q, déficit en PDC). Seulement deux des ataxies héréditaires, le syndrome de l'X fragile/tremblement/ataxie et le XLSA/A ont un mode de transmission lié à l'X. Les ataxies héréditaires dont l'hérédité est maternelle sont dues à des mutations ponctuelles dans des gènes codant pour des ARNt, des ARNr, des sous-unités de la chaîne respiratoire ou des délétions/duplications uniques de grande taille de l'ADN mitochondrial dont MELAS, MERRF, KSS, PS, MILS, NARP et des maladies mitochondriales non syndromiques. Le traitement des ataxies héréditaires est un traitement symptomatique de soutien qui peut être bénéfique chez certains patients. **voir la page 424 pour la liste d'abrègement.

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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[1,2]. 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.

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History

The heredoataxia 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[3]. SCA3 was first described in 1972 in descendants of William Machado, a native of an Azore island[4]. The CAG-expansion responsible for SCA1 was detected in 1993[4]. The genetic cause of FA was first described in 1996[3].

Frequency

For all heredoataxias a prevalence of 6/100000 is reported[5] 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[6] or 0.9-3/100000[7]. The prevalence of SCAs in the Netherlands is reported to be 3/100000[8]. A much higher prevalence of SCAs of 18.5/100000 is reported from Japan[9]. The prevalence of SCA1 and 2 was 2.4/100000 in the province of Padua[10]. The prevalence of AR ataxias is estimated to be around 7/100000[11]. 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 the province of Padua[10]. Other studies found a prevalence of 2.2/100000 for autosomal recessive (AR) heredoataxias and of 3/100000 for AD heredoataxias[12]. 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 world-wide. 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[13]. In Japan SCA6, SCA3, and DRPLA are the three most frequent SCAs[14]. In China the most frequent SCAs were SCA3, SCA2, SCA1, SCA6, SCA7, SCA8, SCA10, SCA12, SCA14, SCA17, and DRPLA[15]. SCA2 is common in Korea. SCA3 is more common in Japan and Germany than in the UK [4]. FA is frequent in Germany but only a few cases with AOA or IOSCA (twinkle) have been diagnosed there[16]. Polyglutamine (poly-Q) SCAs are the most common of the AD heredoataxias and account together for 50% of these disorders[17].

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)[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[18]. 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[1], as in the following presentation.

Table 1: Classification of heredoataxias and non-hereditary ataxias

- Heredoataxias
  - Autosomal dominant
    - Spinocerebellar ataxias (SCA1-8, 10-15, 17-23, 25-30, dentato-rubro-pallido-luysian atrophy)
    - Episodic ataxias (EA1-7)
    - AD mitochondrial disorders with ataxia (LS, MIRAS, ADOAD, AD-CPEO)
  - Autosomal recessive
    - Friedreich ataxia-like phenotype
      - Friedreich ataxia
      - Ataxia due to vitamin E deficiency
      - Ataxia due to Abeta-lipoproteinemia
      - Refsum disease
    - Friedreich ataxia-like phenotype with cerebellar atrophy
      - Late-onset Tay-Sachs disease
      - Cerebrotendineous xanthomatosis
      - Spinocerebellar ataxia with axonal neuropathy
      - AR mitochondrial disorders with ataxia (AR-CPEO, SANDO, SCAE, AHS, IOSCA, MEMSA, LBSL CoQ-deficiency, PDC-deficiency)
    - Early-onset ataxia with cerebellar atrophy
      - Ataxia telangiectasia
      - Ataxia telangiectasia-like disorder
      - Ataxia with oculomotor apraxia 1 (AOA1)
      - Ataxia with oculomotor apraxia 2 (AOA2)
      - Spastic ataxia of Charlevoix-Saguenay
      - Cayman ataxia
      - Marinesco-Sjögren syndrome
  - X-chromosomal
    - Fragile X tremor/ataxia syndrome
    - X-linked mitochondrial disorders with ataxia (XLSA/A)
  - Maternally inherited heredoataxias
    - Point mutations (homoplasmic and heteroplasmic)
      - tRNAs or rRNA genes (MELAS, MERRF)
      - RC subunit genes (LHON, NARP, LS, MILS)
    - Single, large-scale deletions/duplications (sporadic, heteroplasmic)
      - CPEO, PS, KSS
- Non-hereditary ataxias
  - Acquired
    - Alcohol cerebellar degeneration
    - Lithium intoxication
    - Phenytoin intoxication
    - Intoxication with solvents
    - Paraneoplastic cerebellar degeneration
    - Gluten sensitivity
    - Superficial siderosis
  - Sporadic
    - Pure adult onset cerebellar ataxia
    - Olivopontocerebellar atrophy (OPCA)
    - Cerebellar type of multi-system atrophy

See abbreviations list on page 424.

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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)[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[18]. 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)[18].

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[20]. Longer expansions are associated with earlier onset and more severe disease[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[21]. Mutations causing AD SCAs segregate in a dominant manner because of their toxic gain-of-function characteristics[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[17]. Most likely, expanded RNA repeats sequester RNA-binding proteins, leading to aberrant RNA splicing[17]. This group includes SCA8, SCA10 and SCA12[6].

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[6,17]. Anticipation may be so extreme in some cases that affected children die long before the affected parent or grandparent becomes symptomatic[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[17]. Disease progression increases with increasing repeat size[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[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[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)[17,21,23]. Misfolding may then lead to assembly of the host proteins into insoluble beta-sheet-rich amyloid fibrillar aggregates ("exposed beta-sheet hypothesis")[23]. Inhibition of proteases that cleave elongated SCA proteins might have a therapeutic effect, by inhibiting poly-Q domains to aggregate[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[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 acetyl-transferases[17,21]. There are also indications that unstable CAG-repeats may secondarily cause mtDNA mutations[24].

5. Clinical presentation

SCAs are clinically characterized by a slowly progressive cerebellar syndrome with various oculomotor abnormalities, dysarthria, dysmetria, tremor, or ataxia[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[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[6]. In SCA20 the nucleus dentatus is typically calcified[6]. Quantification of the degree of atrophy is now possible by application of three-dimensional true volumetric methods[25]. Histopathologically, there is atrophy of the molecular, Purkinje cell and granular cell layers as well as the deep cerebellar nuclei[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[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[26].

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Table 2: AD spinocerebellar ataxias [2]

Disease	Gene	Locus	Mutation	Gene product	Additional manifestations	Age at onset
SCA1	ATXN1	6p23	CAG-expansion	Ataxin-1	Pyramidal signs, nystagmus, slow saccades, neuropathy, dementia, ophthalmoparesis	4-74
SCA2	ATXN2	12q24.1	CAG-expansion	Ataxin-2	Slow saccades, neuropathy, hyporeflexia, asymmetric wasting, myoclonus, dementia, ophthalmoparesis	6-67
SCA3	ATXN3	4q24.3-q31	CAG-expansion	Ataxin-3	Extrapyramidal signs, nystagmus, neuropathy, spasticity, diplopia, eye-lid retraction, ophthalmoparesis	5-65
SCA4	Puratrophin-1 (PLEKHG4)	16q22.1	Pm	Puratrophin-1 (PLEKHG4)	Pure cerebellar syndrome or additionally axonal sensory neuropathy	19-72
SCA5	-III Spectrin (SPTBN2)	11q13	Pm, Del	-III Spectrin (SPTBN2)	Pure cerebellar syndrome, slow progression, down-beat nystagmus	15-50
SCA6	CACNA1A	19p13	CAG-expansion	CACNA1A	Pure cerebellar syndrome, slow progression, allelic with EA2 and familial hemiplegic migraine	19-77
SCA7	ATXN7	3p14-p21.1	CAG-expansion	Ataxin-7	Pigmentary retinopathy, ophthalmoplegia, pyramidal signs	0.1-76
SCA8	ATXN8 (Kelch-like)	13q21	CTG-expansion	Ataxin-8 (Kelch-like)	Sensory neuropathy, slow progression	0-73
SCA10	ATXN10	22q13	ATTCT-expansion	Ataxin-10	Seizures, pyramidal signs, extrapyramidal signs	10-40
SCA11	TTBK2	5q14-21.3	Pm, Del, Ins	TTBK2	Pure cerebellar syndrome, slow progression	17-33
SCA12	PPP2R2B	5q31-q33	CAG-expansion	PPP2R2B	Upper extremity and head tremor, parkinsonism, hyperreflexia, dementia, neuropathy	8-55
SCA13	KCNC3	19q13.3-q13.4	Pm	KCNC3	Delayed motor development, mental retardation	4-60
SCA14	PRKCG	19q13.4-qter	Pm	PRKCG	Facial myokymia, rare myoclonus and focal dystonia, slow progression, incomplete penetrance	10-59
SCA15/16	ITPR1	3p26-p25	Del, Pm	ITPR1	Pure cerebellar syndrome or additionally head tremor, slow progression	10-66
SCA17	TBP	6q27	CAG-expansion	TBP	Dementia, choreatic movements, psychosis, behavioral changes, seizures, pyramidal signs, extrapyramidal signs	10-70
SCA18	Uk	7q22-q32	Uk	Uk	Axonal sensory neuropathy, limb weakness	13-27
SCA19	Uk	1p21-q21	Uk	Uk	Dementia	20-45
SCA20	Uk	11p13-q11	Uk	Uk	Dysphonia, dentate calcification, spasmodic cough, bradykinesia, palatal tremor	19-64
SCA21	Uk	7p21.3-p15.1	Uk	Uk	Extrapyramidal signs, cognitive impairment	6-30
SCA22	Uk	1p21-q23	Uk	Uk	Pure cerebellar syndrome	10-46
SCA23	Uk	20p13-12.3	Uk	Uk	Pure cerebellar syndrome or associated with sensory loss, pyramidal signs	43-56
SCA25	Uk	2p15-p21	Uk	Uk	Severe sensory neuropathy, FA-like	1.5-39
SCA26	Uk	19p13.3	Uk	Uk	Pure cerebellar syndrome, slowly progressive	26-60
SCA27	FGF14	13q34	Pm	FGF14	Slowly progressive, postural tremor, dyskinesia, cognitive impairment, behavioral abnormalities	12-40
SCA28	SCA28	18p11.22–q11.2	Pm	Uk	Ophthalmoparesis, nystagmus, hyperreflexia, ptosis slow progression	12-36
SCA29	Uk	3p26	Uk	Uk	Non progressive, highly variable phenotype	Congenital
SCA30	Uk	4q34.3-q35.1	Uk	Uk	Slowly progressive ataxia, mild pyramidal signs, hypermetric saccades, nystagmus	Mid-late life
DRPLA	DRPLA	12p13.31	CAG-expansion	Atrophin-1	Seizure, chorea, dementia, myoclonus	10-59

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[27]. Symptoms at onset include gait disturbance, double vision, dysarthria, impaired hand writing, or episodic vertigo[28]. Single patients may develop vocal cord abductor paralysis[29] or even psychosis[30]. 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 [28].

SCA2

SCA2 manifests as cerebellar syndrome with gait disturbance, double vision, dysarthria, impaired hand writing, episodic vertigo[28] or Parkinsonism[29,31]. There may be also saccade slowing, hyporeflexia, postural or action tremor, myoclonus, muscle cramps, or retinopathy[4,31]. In the later stages the thalamus, brainstem or spinal cord is involved[31]. There may be also involvement of the central somato-sensory system[32]. The disease course is slowly progressive but ultimately fatal[32]. Single patients may exclusively presented with Parkinsonism or MSA

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Table 3: Normal and expanded repeat-lengths in tri- and pentanucleotide repeat SCAs [4,21]

SCA-type	Mutated gene	NE	Normal size	Expanded	Anticipation
SCA1	ATXN1	CAG	6-39	40-91	+
SCA2	ATXN2	CAG	15-31	32-500	++
SCA3	ATXN3	CAG	13-36	61-84	++
SCA6*	CACNA1A	CAG	4-20	20-29	++
SCA7	ATXN7	CAG	4-35	37-306	+++
SCA8	ATXN8	CTG	15-50	71-800	+++
SCA10	ATXN10	ATTCT	10-22	280-4500	++
SCA12	PPP2R2B	CAG	7-31	51-78	-
SCA17	TBP	CAG	25-42	46-63	++
DRPLA	DRPLA	CAG	7-34	49-88	+++

NE: nucleotide expansion, *: channelopathy, inclusions not within the nucleus but cytoplasm. See abbreviations list on page 424.

Table 4: Manifestations in addition to the cerebellar syndrome in SCAs [6]

Slowing of saccades	SCA2, 3, 7
Ophthalmoplegia	SCA1, 2, 3, 28
Pigmentary retinopathy, degeneration	SCA2, 7, 14
Pyramidal signs	
Spasticity	SCA3, 8
Exaggerated tendon reflexes	SCA12, 28
Pyramidal signs positive	SCA7, 8, 10, 17, 30
Cognitive impairment	SCA7, 8, 10, 12, 13, 17, 27, DRPLA
Behavioral abnormalities	SCA10, 13, 17, 21, 27, DRPLA
Seizures	SCA10, 17, DRPLA
Dysphagia	SCA8
Incontinence	SCA8
Peripheral neuropathy	SCA1, 2, 3, 4, 8, 10, 12, 18, 22, 25
Extrapyramidal involvement	
Extrapyramidal signs	SCA1, 21
Parkinsonism	SCA2. 3, 7, 8, 12
Dyskinesias	SCA27
Dystonia	SCA3, 7, 14, 17, 27
Chorea	SCA3, 17, DRPLA
Postural tremor	SCA12,14, 15/16,17,19,27
Intracerebral calcifications	SCA20
Myoclonus	SCA2, 8, 14, 19, DRPLA
Vestibular dysfunction	SCA3
Sensory deficits	SCA3, 7
Nystagmus	SCA3, 6, 15/16, 28

with Parkinsonism[33]. Neuropathological investigations may also show subclinical involvement of the auditory brainstem system[34]. Histopathological investigations may reveal olivo-ponto-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[35]. Neuronal intranuclear inclusions are less frequent than in other poly-Q diseases[31]. The condition is caused by a CAG-repeat expansion in the ataxin-2 gene[31]. Only 67% of the onset variability is determined by CAG-repeat length, suggesting non-repeat factors to substantially influence disease onset[28]. Anticipation regarding onset and rapidity of disease progression is frequently present (Table 3)[31].

SCA3

SCA3 is the most prevalent SCA in nearly all countries world-wide[36,37]. Symptoms at onset are variable and include gait disturbance, double vision, dysarthria, impaired hand writing, and episodic vertigo[28]. Most frequently SCA3 starts with ataxic gait after age 40y[4]. 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[38,39]. Almost half of the patients complain about muscle cramps and a quarter develops fasciculations[40]. The disease course is slowly progressive and ultimately fatal[32]. Neuropathological investigations may show subclinical involvement of the auditory brainstem system[33]. SCA3 is due to a CAG-repeat expansion in a coding region of the ataxin-3 gene (Table 2). The phenotypic variability depends on the repeat-size[37]. Anticipation is most frequently associated with repeat expansions in paternal transmission (Table 3)[37]. Only 46% of the onset variability is determined by the CAG-repeat length, suggesting non-repeat factors to substantially influence disease onset[28]. Homocygosity may aggravate the phenotype[41].

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[42]. Neuropathologically, there is widespread cerebellar and brain degeneration with obvious demyelination and axonal fiber loss[42]. SCA4 is due to point mutations in the puratrophin-1 (PLEKHG4) gene on chromosome 16 q22.1.

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 sepctrin[17]. 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[17]. Anticipation may be extreme and is more pronounced with maternal than paternal transmission[4].

SCA6

SCA6 is clinically characterized by a severe form of late onset slowly progressive pure cerebellar ataxia, with nystagmus,

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reduced smooth pursuit, or cognitive dysfunction[43,44]. Early functional deficits may include impaired saccade velocity, saccade metrics, or pursuit gain[45]. Neuropsychological tests may reveal impaired visual memory, verbal fluency, or executive functions[46]. In accordance with these deficits SPECT may show prefrontal hypoperfusion[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[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[17].

SCA7

SCA7 presents clinically as severe cerebellar ataxia, achromatopsia with cone-rod retinal dystrophy degeneration, and macular degeneration[48,49]. It is the only SCA with pigmentary retinopathy[4]. Occasionally, spastic paraparesis may be the onset presentation of the disease[50]. Rarely, patients additionally develop cranio-cervical dystonia[49], dysarthria, dysphagia, pyramidal signs, parkinsonism, impaired writing, smooth pursuits, pupillary impairment, sensory deficits, hypoacusis, or cognitive impairment[51]. Neuropathological investigations may show subclinical involvement of the auditory brainstem system[34]. 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)[48]. The correlation between the repeat-length and the clinical severity is positive[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[48]. In a patient with 13 and 70 CAG repeats in the ataxin-7 gene the phenotype resembled that of KSS[52].

SCA8

SCA8 is clinically characterized by adult-onset, slowly progressive cerebellar ataxia, ataxic dysarthria, 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, visoperceptual, or visoconstructive functions[53], mood disturbance, parkinsonism[54], tremor, myoclonus, upper motor neuron signs, urinary incontinence, or dysphagia[55-59]. SCA8 shares several common clinical features with the cerebellar form of multiple system atrophy (MSA). MRI shows severe cerebellar atrophy and white matter hyperintensities[56,59]. Neuropathologically, degeneration of Purkinje cells, inferior olivary or nigral neurons, or periaqueductal gliosis is evident[60]. SCA8 is due to a heterozygous CTG/CAG[61] repeat expansion (100-152 repeats, normal: 15-91 repeats) in the Kelch-like-1 gene (KLHL1) (Tables 2 and 3)[57,62]. Expanded alleles mostly show repeat-size contraction and high instability in spermatogenesis[62]. Because of the dramatic repeat instability and strongly reduced penetrance anticipation is extreme (Table 3)[4]. Extremely large expansions (800 repeats), however, may be associated with absence of the disease[4]. Reduced penetrance is associated with CCG, CTA, CTC, CCA, or CTT interruptions preceding the repeat[4]. The CTG expansion could alter KLHL1 expression through a dominant RNA-based mechanism as in MD1 or be transcribed in the opposite direction and thus encode a toxic poly-Q fragment[17]. There are some indications that SCA8 transcripts downregulate the KLHL1 expression by an antisense mechanism[63]. Possibly, bidirectional expression across pathogenic microsatellite expansions occurs. Potential pathogenic effects of mutations from both strands are considered[64,65].

SCA10

SCA10 was first reported in a large Portugese ancestry family with pure cerebellar ataxia. Later on, SCA10 has been also described in Brazilian and Mexican families, which additionally presented with epilepsy[66,67], polyneuropathy, pyramidal signs, and cognitive and neuropsychiatric impairment [68]. MRI shows cerebellar atrophy[69]. SCA10 is due to an expansion of an ATTCT repeat of up to 4500 copies (normal: 10-22 copies) in intron 9 of the ataxin-10 gene[70,71], encoding for an approximately 55kD protein of unknown function, which belongs to the armadillo repeat proteins[72,73]. There are indications that instability of the ATTCT expansion results in aberrant replication origin activity[72]. SCA10 shows anticipation in some studies[74], which is rather associated with intergenerational retraction than expansion[75], but not in others[69]. There is an inverse relation between expansion size and age at onset in some studies[75].

SCA11

SCA11 has been first described in a Caucasian family with British ancestry[18]. SCA11 is clinically a type III SCA with "pure" cerebellar involvement, like SCA4, 5, 6, 14, 22, 23, 26 and 28[18]. Single cases may present with hyperreflexia. The progression of the disease is slow. Histopathologically, there is substantial cerebellar degeneration and tau deposition. SCA11 is due to mutations in the TTBK2 gene on chromosome 15q14-q21.3, encoding for the tau tubulin kinase 2[76]. Protein tau and tau kinases have been implicated in neurodegeneration.

SCA12

SCA12 is clinically characterized by a cerebellar syndrome and additionally postural tremor of the upper limbs, head tremor, parkinsonism, hyperreflexia, dementia, and neuropathy. SCA12 is caused by an unstable CAG repeat expansion in the non-coding region of the PPP2R2B gene. In affected individuals the CAG-repeat expansion ranges from 51-78[4], 21[77]. PPP2R2B encodes for Bbeta1 and Bbeta2, which are alternatively spliced and constitute neuron-specific regulatory subunits of the protein phosphatase 2a (PP2A) holoenzyme[78]. In cell cultures translocation of PP2A/Bbeta2 to mitochondria promotes apoptosis, whereas silencing of PP2A/Bbeta2 protects neurons against free radical-mediated, exotoxic, or ischemic alteration. Expression of Bbeta2 induces mitochondrial fragmentation, whereas Bbeta2 silencing or inhibition results in elongation of mitochondria[78].

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SCA13

SCA13 is a slowly progressive, relatively pure SCA with childhood onset, delayed motor development and mental disturbances[79]. SCA13 is due to point mutations in the KCNC3 gene, encoding for the voltage-gated potassium channel Kv3.3, highly enriched in the cerebellum[17]. Mutations are expected to change the output characteristics of fast-spiking cerebellar neurons, in which KCNC3 confers the capacity for high-frequency firing[17].

SCA14

Patients with SCA14 present with gait ataxia, cervical dystonia, positional vertigo, retinal degeneration, and facial muscle weakness[80]. Rare manifestations are executive dysfunction, axial myoclonus, myorhythmia, tremor, or decreased vibration sense[14,81]. SCA14 is due to missense mutations in the protein kinase Cgamma gene (PRKCG) encoding protein kinase Cy, highly expressed in Purkinje cells[17,82,83]. The majority of the mutations is located in the C1B subdomain of the gene[84]. These mutations lead to sustained Ca++ influx[85] and disturb the development of Purkinje cell dendrites and reduce synapse formation[83]. There is also aggregation of mutant PRKCG, which impairs the ubiquitin-proteasome system and induces endoplasmatic reticular stress, leading to apoptosis[83].

SCA15/16

SCA16 was first described in 2001 in an Anglo-Celtic family from Australia[86-88]. Affected individuals present with cerebellar ataxia, gaze-evoked horizontal nystagmus and tremor[88]. Later on Japanese patients with the same phenotype were described and designated as SCA15[89]. MRI shows cerebellar, particularly vermal atrophy exclusively[88]. 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[90].

SCA17

SCA17 is a typical poly-Q disease[91] and the third most frequent SCA genotype[92]. The phenotype of SCA17 is often severe with involvement of the cerebral cortex, the striatum and the cerebellum[93]. 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[92]. Onset is extremely variable but the phenotype less variable than in other SCAs[93]. The MRI may reveal atrophy of grey matter around mesial cerebellar structures, occipito-parietal structures, the anterior putamen, and the thalamus[94]. Oculography may reveal impaired smooth pursuit, defective saccade accuracy, hyperreflexive vestibulo-ocular reflexes[92]. As the causative mutation a CAG/CAA expansion of 46-63 repeats in the TATA-box binding protein has been identified (Table 3)[16,93,95]. SCA17 is unique in that the poly-Q tract is encoded by either long stretches of pure CAGs or a complex configuration containing CAA interruptions[91]. There are indications that CAA interruptions serve as limiting elements for further CAG expansion, which could explain the lack of anticipation in SCA17[91].

SCA18

SCA18 is clinically characterized by a cerebellar syndrome associated with axonal neuropathy and limb weakness. Onset of SCA18 is between 13-27y. The mutated gene responsible for this phenotype is so far unknown but linkage-studies localized the mutated gene to 7q22-q32[6].

SCA19

SCA19 was described in only a single family so far. Affected individuals display a late onset, slowly progressive mild cerebellar ataxia, hyporeflexia, and signs of frontal lobe dysfunction. A postural head tremor and myoclonic movements were observed occasionally[96,97]. The causative mutated gene has not been identified but linkage studies identified the locus at 1p21-q21[97].

SCA20

So far only a single pedigree with SCA20 has been reported[98]. Patients presented with palatal tremor, dysarthria, dysphonia, and hypermetric saccades[99]. An MRI shows pancerebellar atrophy, dentate calcification, and in some cases olivary pseudo-hypertrophy. The mutated gene responsible for SCA20 has not been identified yet, but the locus has been mapped to 11q12[98]. Recently, a 260kb duplication has been detected in this region, spanning ten known and two unknown genes[98].

SCA21

SCA21 is a slowly progressive, mild ataxia associated with extra-pyramidal signs[100]. Affected patients develop moderate gait and limb ataxia, associated with akinesia, tremor rigidity, hyporeflexia, and mild cognitive impairment[100,101]. The responsible mutation has been mapped to chromosome 7p in a single family from France but the responsible gene remains to be identified[100,102].

SCA22

Clinically, SCA22 patients present with dysarthria and hyporeflexia in addition to slowly progressive gait ataxia[103]. MRI shows atrophy of the cerebellum sparing the brain-stem[103]. The mutation shows anticipation. Linkage analysis mapped the suspected gene to a locus at 1p21-q23[103]. 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. However, 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[96].

SCA23

SCA23 is clinically characterized by late-onset (>40y), slowly progressive isolated cerebellar ataxia[104]. Neuro-pathological investigations show neuronal loss in the Purkinje cell layer, dentate nuclei, inferior olives, thinning of cerebello-pontine tracts, demyelination of posterior and lateral spinal cord

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columns, and intranuclear inclusions in nigral neurons[104]. The responsible mutated gene has been mapped to the locus 20p13-p12.3[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 intrafamilial 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 (Table 2).

SCA26

SCA26 was described only in a single Norwegian family so far[105]. Clinically, the affected members presented with pure cerebellar ataxia[105]. Age at onset ranged from 26 to 60y. MRI showed cerebellar atrophy exclusively[105]. By application of a genome-wide linkage scan with a new strategy a locus at 10p13.3 was identified[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[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[106]. MRI, however, exclusively showed moderate cerebellar atrophy in the two oldest patients[106]. SCA27 is caused by mutations in the FGF14 gene encoding for the fibroblast growth factor 14[106], which presumably regulates synaptic plasticity by controlling mobilization, trafficking or docking of synaptic vesicles to presynaptic zones[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[107,108]. Mean age at onset was 19.5y, starting with imbalanced standing, gaze-evoked nystagmus, and mild gait uncoordination[108]. Later on, slow saccades, CPEO, ptosis, and exaggerated deep tendon reflexes develop[108]. Meanwhile, SCA28 has been also described in a second Italian family[107]. SCA28 is caused by point mutations in the SCA28 gene located on chromosome 18p11.22[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[99]. As the most likely contenders TACSTD1 and ODZ3 were identified.

DRPLA

DRPLA is a neurodegenerative disorder first described in 1972[109]. DRPLS is highly prevalent in Japan. DRPLA is clinically characterized by myoclonus, epilepsy, mental deterioration, behavioural changes, or dementia, cerebellar ataxia, and choreoathetosis[109,110]. Neuropathologically, there is degeneration of the dentate-rubral and pallido-luysian 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[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)[111]. Some of them present with additional abnormalities during the attacks. The current classification is based on genetics and actually includes seven distinct subtypes[111]. It is quite likely, however, that the number of phenotypes and mutated genes will grow further[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[112]. Interictally, myokymia can be observed[111]. EA1 is caused by mutations in the KCNA1 gene on 12q13, encoding for the potassium channel gene Kv1.1[111].

Episodic ataxia 2

EA2 is the 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[111]. The attacks may be associated with vertigo, nausea, vomiting, migraine or other headache, fluctuating weakness, dystonia, or seizures[111]. Interictally, nystagmus may occur[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[111]. EA2 is allelic to SCA6 and familial hemiplegic migraine (FHM1), characterized by migraine, hemiplegia, interictal nystagmus, and progressive ataxia[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[114]. The exact genetic defect is unknown but linkage studies localized the mutated gene to the locus 1q42[115].

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Table 5: AD episodic ataxias

Disease	Gene	Locus	Mutation	Gene product	Additional manifestations during attack	Interictal manifestations	Duration of attacks	Age at onset(y)
EA1	KCNA 1	12q13	Pm, del	KCNA 1	None	Myokymia and jerking movements of face and limbs	Seconds, minutes	2-15
EA2	CACNA1A	19p13	Pm, del, TNR	CACN A1A	Down-beat nystagmus, migraine, vertigo, nausea, vomiting, weakness, dysarthria	Ataxia, nystagmus	Hours, days	2-20
EA3	Uk	1q42	Uk	Uk	Myokymia, migraine, tinnitus, vertigo, dysarthria	None	1 minute to 6 hours	1-42
EA4	Uk	Uk	Uk	Uk	Vertigo, diplopia. interictal nystagmus and abnormal smooth pursuit	Nystagmus	Brief	23-60
EA5	CACNB4β4	2q22-23	Pm	CACN B4β4	Vertigo	Nystagmus, ataxia, epilepsy	Hours	3-19
EA6	SLC1A3	5p13	Pm	EAAT1	Cognitive impairment	Epilepsy, migraine, ataxia, motor delayed milestones	Hours, days	<20
EA7	Uk	19q13	Uk	Uk	Vertigo, weakness, slurring, dysarthria	None	Hours, days	13-19

Uk: unknown, Pm: point mutation, Del: deletion, TNR: trinucleotid-expansion. See abbreviations list on page 424.

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[111,116]. Interictally, nystagmus can be observed[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[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[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[118]. The exact genetic defect is unknown but linkage studies localized the mutated gene to locus 19q13[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[119]. Later on, however, these patients develop severe encephalopathy with death in their twenties[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[120].

C. AD Transmitted MIDs

Syndromic and non-syndromic MIDs may present with cerebellar or sensory ataxia[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[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[1]. AR ataxias are generally associated with neuropathy and, contrary to AD ataxias, there is less involvement outside the nervous system[123]. The major forms can be distinguished on the basis of the phenotype, age at onset, biochemical parameters, the MRI, and the genotype[16]. AR ataxias usually start in childhood[5]. Additional neurological features include optic atrophy, extrapyramidal signs, pyramidal signs, peripheral neuropathy, cognitive impairment, or epilepsy. The pathogenesis of these

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Table 6: AR hereditary ataxias

Disease	Gene	Locus	Mutation	Gene product	Additional features	Age at onset
FA	FRDA1	9q13-q21.1	Trinuc; Pm	Frataxin	Neuropathy, Babinski sign, deep sensory loss, cardiomyopathy, diabetes, saccadic smooth pursuit, fixation instability, saccadic dysmetria	2-55
AVED	αTTP	8q13.1-q13.3	Del; Ins; Pm	α-tocopherol transfer protein	Head titubation, retinopathy, nystagmus, saccadic pursuit, low serum vitamin E	2-52
ABL	MTP	4q22–24	Pm	Large subunit of MTP	Steatorrhea, areflexia, sensory ataxia, retinal degeneration, dissociated nystagmus on lateral gaze, slow saccades, neuropathy, acanthocytes, low LDL	0-20
Refsum disease	PHYH, PEX7	10pter-11.2, 6q21-22.2	Pm, Del, Ins	Phytanoyl-CoA hydroxylase, peroxin 7 receptor protein	Neuropathy, deafness, retinitis pigmentosa, anosmia, skeletal abnormalities, ichthyosis, renal failure, cardiomyopathy	<20
Late-onset Tay-Sachs	HEXA	15q23-24	Pm, Del, Ins	Beta-hexosaminidase A	Areflexia, proximal muscle weakness, wasting, fasciculations, behavioral abnormalities	Childhood, adulthood
Cerebrotendineous xanthomatosis	CYP27	2	Pm, Del, Ins	Sterol-27-hydroxylase	Pyramidal signs, extrapyramidal signs, neuropathy, seizures, cognitive decline, dementia	20
SCA + axonal neuropathy	TDP1	14q31-32	Pm, Del	Tyrosyl-DNAphosphodiesterase 1	Neuropathy, distal wasting, pes cavus	Childhood
AT	ATM gene	11q22-q23	Del; Ins; Pm	ATM protein (Phospho-inositol-3-kinase type enzyme)	Telangiectasia, immune deficiency, predisposition to cancer, oculomotor apraxia, increased latency of saccades increased alpha-fetoprotein, chromosomal instability	1-4
ATLD	MRE11	11q21	Pm	MRE11	Similar to AT, milder course	1-7
AOA1	APTX	9p13	Ins; Del; Pm	Aprataxin	Oculomotor apraxia, fixation instability, saccadic pursuit, gaze-evoked nystagmus, hypometric saccades, neuropathy, choreoathetosis, mild mental retardation, hypercholesterolemia, hypoalbuminemia	1-29
AOA2	SETX-	9q34	Pm; Del	Senataxin	Oculomotor apraxia, saccadic pursuit, slow saccades, choreoathetosis, neuropathy	3-30
AR spastic ataxia	SACS	13q11	Pm	Sacsin	Pyramidal signs, neuropathy	1-5
Cayman ataxia	ATCAY	19p13.1	Pm	Caytaxin	Muscle hypotonia, mental retardation	Childhood
Marinesco-Sjögren	SIL1	5q31	Pm, Del	HSPA5	Cataract, mental retardation, short stature, hypogonadism, skeletal deformities, myopathy, neuropathy, epilepsy	Infancy

FA: Friedreich ataxia, AVED: ataxia with vitamin E deficiency, ABL: Abetalipoproteinemia, AOA1, 2: ataxia with oculomotor apraxia type 1 and 2, AT: ataxia-telangiectasia, ATLD: ataxia-telangiectasia-like disorder. See page 424 for any additional abbreviations.

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[124]. 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[125]. Hypertrophic cardiomyopathy is present in less than half of the patients[126]. Hypertrophic cardiomyopathy is due to altered cellular iron trafficking and thus iron accumulation[127]. However, also the myocardial microvasculature seems to be affected[128]. Axonal sensory neuropathy, distal wasting, sensori-neural deafness, optic atrophy, and diabetes are other common features. Two thirds of the patients develop scoliosis[129]. Rarely, patients develop head tremor[130]. During the disease course neurological and cardiac abnormalities worsen, despite antioxidant treatment with idebenone[131].

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Voxel-based morphometry demonstrates a significant loss of gray and white matter within the dorsal medulla, cerebellar hemispheres, rostral vermis, and the dentate region[132]. The main histopathological abnormalities of the brain in FA patients are neuronal atrophy and proliferation of synaptic terminals in the dentate nucleus, also known as "grumose degeneration"[124]. The dentate nucleus may be particularly affected because it contains abundant iron[124]. Iron is deposited within mitochondria in the form of ferrihydrite but only affected patients mineralize iron in the form of ferrition[133].

FA is caused by a GAA-trinucleotide-repeat expansion in intron 1 of the FRDA gene on chromosome 9q13-21[134]. Normal genes contain up to 40 GAA-triplets in an Alu sequence of intron 1[134]. FA patients carry 70 to 1700 repeats[134]. The expansion elicits transcriptional silencing of the FRDA gene by the formation of non-B DNA structures (sticky triplex DNA structure), by formation of a persistent DNA x RNA hybrid, or by heterochromatin formation[135]. The non-B DNA conformations decrease transcription and subsequently reduce levels of frataxin (loss-of-function mutation)[136]. The region adjacent to the repeat-expansion is hyper-methylated[137].

Over 90% of FA patients are homozygous for the GAA-expansion[138]. Only a few patients are compound heterozygous, harbouring point mutations or microdeletions on one allele, and the GAA expansion on the other allele. Extremely rarely (prevalence 1/100000) FA may also occur in patients heterozygous for the GAA-expansion[139]. In patients heterozygous for the GAA-expansion, the five coding exons of the frataxin gene should be sequenced for point mutations[134]. In 2-4% of the cases FA is due to point mutations in the FRDA gene[1]. The expansion size is inversely correlated with age of onset and age of confinement to wheel-chair, and directly correlated with the incidence of systemic manifestations, particularly cardiomyopathy[138]. The GAA-expansion increases with age and causes postnatal somatic instability and thus disease progression[140].

FRDA encodes for frataxin, a mitochondrial protein involved in iron handling, particularly iron-sulphur cluster biosynthesis[135]. Frataxin plays a crucial role in iron metabolism and iron detoxification and interacts with RC proteins[135]. Genetic studies in patients with onset after 25 years of age (late onset FA, LOFA) or with retained tendon reflexes (FARR) have proved that these variant forms are due to the same molecular defect as for the typical FRDA cases. FA should be considered in all patients with sporadic or AR ataxia[1].

Ataxia with vitamin E deficiency

Ataxia with vitamin E deficiency presents with a phenotype similar to FA[141,142] but impaired visual acuity or retinitis pigmentosa may be early findings[1]. Cardiomyopathy is the most common systemic finding but less common than in FA[1]. 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[142]. 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[1]. Only early supplementation with vitamin E may slow the progression of the disease[143].

Abeta-lipoproteinaemia

The phenotype resembles that of FA and vitamin E deficiency but is additionally associated with lipid malabsorption, hypocholesterolaemia, acanthocytosis, or retinitis pigmentosa[1]. Onset is before age 20y. Abeta-lipoproteinemia 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, phytanic acid, found in diary products, meat and fish, accumulates in the body fat[144].

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[1]. 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[1].

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-hydroxilase is part of the bile-acid synthesis pathway and if mutated results in elevation of cholesterol and bile alcohols[1].

Spinocerebellar ataxia with axonal neuropathy

Spinocerebellar ataxia with axonal neuropathy is a rare, childhood onset ataxia, so far described only in Saudi Arabia[1]. 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[1].

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AR transmitted MIDs presenting with ataxia

Syndromic and non-syndromic AR transmitted MIDs may present with cerebellar or sensory ataxia[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[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[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[146]. High concentrations of serum alpha-fetoprotein are a typical laboratory finding. MRI may show extensive, diffuse white matter demyelination, T1 and T2-hypointense lesions, T1 hypointense and T2 hyperintense lesions, or numerous telangiectasia upon gadolinium enhancement in single patients[147].

The disease is caused by mutations in the AT-mutated gene (ATM), resulting in loss or inactivation of the gene product[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[146]. The phenotype can vary in severity depending on whether the ATM protein is completely absent or not[148]. 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[145].

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[149]. 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 (SETX), 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[150]. 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[151]. The MRI 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[151].

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,

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Table 7: AD, AR, Xl, and maternally transmitted mitochondrial ataxias

MID	Frequency of ataxia	MI	Mutated gene(s)	mtDNA	nDNA
mtDNA genes					
1. Point mutations in genes encoding for tRNAs or rRNAs (homoplasmic or heteroplasmic)					
MELAS	rare	mat	tRNAs, rRNAs	PM (homplasmic or heteroplasmic)	n
MERRF	frequent	mat	tRNAs, rRNAs	PM (homplasmic or heteroplasmic)	n
MSL	rare	mat	tRNAs	PM (homplasmic or heteroplasmic)	n
MIDD	rare	mat	tRNAs	PM (homplasmic or heteroplasmic)	n
2. Point mutations in genes encoding for RC subunits (homoplasmic or heteroplasmic)					
LHON	rare	mat	RC subunits	PM	n
NARP	frequent	mat	RC subunits	PM	n
MILS	frequent	mat	RC subunits	PM	n
3. Single deletions/duplications (sporadic, heteroplasmic)					
PS	rare	mat	multiple RC subunits, RNAs	Single deletion/duplication	n
KSS	frequent	mat	multiple RC subunits, RNAs	Single deletion/duplication	n
nDNA genes					
Encoding for RC subunits					
LS	frequent	AD, AR	RC subunits, assembly factors	n	PM, deletion
Intergenomic signaling					
AD-CPEO	rare	AD	POLG1, ANT1, twinkle	mtDNA breakage syndrome	PM
AR-CPEO	rare	AR	POLG1	mtDNA breakage syndrome	PM
SANDO	frequent	AR	POLG1	mtDNA breakage syndrome	PM
SCAE	frequent	AR	16q21-q23	mtDNA breakage syndrome	Uk
AHS	frequent	AR	POLG1	mtDNA depletion syndrome	PM
MNGIE	rare	AR	Thymidine phsophorylase	mtDNA breakage syndrome	PM
IOSCA	frequent	AR	C10orf2 (twinkle)	mtDNA depletion syndrome	PM
MIRAS	frequent	AD	POLG1	multiple mtDNA deletions	PM
MEMSA	frequent	Uk	POLG1	n	PM
ADOAD	rare	AD	OPA1	multiple mtDNA deletions	PM
CoQ production					
LS	rare	AR	CoQ pathway	Uk	Uk
Mitochondrial transport machinery					
XLSA	frequent	XL	ABC7	n	PM
Other					
LBSL	frequent	AR	DARS2	n	PM
DIDMOAD	rare	AR	WFS1, WFS2	multiple mtDNA deletions	PM

PM: point mutations, del: deletion, dupl: duplication, uk: unknown, n: normal. MI: mode of inheritance. See abbreviations list on page 424.

starting in the sixth decade of life[152,153]. Only 4% of the patients exhibit all three features, 20% two features and half of the patients all three features[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[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.

XLSA/A

X-linked sideroblastic anemia with ataxia (XLSA/A) is a rare syndromic MID, characterized by mild sideroblastic anemia with hypochromia and microcytosis and cerebellar ataxia[155,156]. Cerebral imaging shows severe cerebellar atrophy. XLSA/A is due to mutations in the mitochondrial ATP-binding cassette transporter ABC7 on chromosome Xq13[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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with ataxia, are the MERRF, NARP, MILS, and KSS syndrome. Though more rarely, ataxia may be also 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)[111].

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, cholesterin (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

Type 1. Spinal atrophy	FA
Type 2. Olivo-ponto-cerebellar atrophy	SCA1, 2, 3, 7, 13, DRPLA, EOCA, MSA-C
Type 3. Cortico-cerebellar atrophy	SCA 4-6, 8, 10. 12, 14-19, 21-22, 25, EOCA, AT, ILOCA

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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[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[160].

Effective measures

Severity and frequency of the unsteadiness of attacks in EAs may be reduced by acetazolamide[111]. Particularly, patients with EA2 can be dramatically responsive to acetazolamide, resulting in a decrease of frequency, duration, and severity of attacks[111]. Acetazolamide is usually started at 125-250mg/d and then increased up to 1000mg/d if needed and tolerated[111]. Side effects, such as tingling, numbness, decreased appetite, altered taste, impaired concentration and memory, or kidney stones have to be encountered[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[161]. In a four-year trial CoQ and vitamin E improved cardiac function and various neurological manifestations[1].

Vitamin E substitution can be highly effective in AR SCA with vitamin E deficiency if given early. Treatment of Abetalipoproteinemia includes dietary modification and vitamin E replacement, which may prevent neurological complications if applied early[1]. Recombinant human erythropoetin administered subcutaneously three times a week in 12 FA patients resulted in persistent, significant increase in frataxin after eight weeks[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[163]. In a preliminary trial D-cycloserine, an NMDA allosteric agonist, relieved some of the symptoms[160]. Some efficacy has been also reported for thyreotropin-releasing hormone, D-cycloserine, and azetazolamide in SCA6, but well designed studies are lacking[160]. Parkinsonism and tremor in SCA2 may temporarily respond to levodopa and muscle cramps to magnesium[31]. Orthopedic shoes improve gait, stability, speed of walking, and step length in FA[164]. Scoliosis in FA may require surgical stabilization of the spine[129].

Ineffective agents

Though physostigmin was helpful in single patients for ataxia, it did not improve ataxia in a double-blind cross-over trial[160]. 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[160]. Serotoninergic agents have been tried for ataxia but were largely ineffective[160]. Ineffective were also choline and derivatives in FA[160]. Generally, serotoninergic and cholinergic drugs seem to be ineffective in heredoataxias[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 transplantation[166]. A promising option could be the administration of histone deacetylase (HDAC) inhibitors, like phenylbutyrate in HD[17]. The effect is based on the fact that poly-Q proteins inhibit the histone acetyl-transferase activity and thus suppress transcription[17]. Another future option might be CoQ, which has been insignificantly beneficial in HD (HD-Care study)[17]. Another beneficial agent may be creatine-monohydrate[17]. In ataxias associated with a deficiency of GABA or glutamine in the brain the use of GABA-ergic respectively glutaminergic drugs could be helpful[165]. Misfolding of poly-Q proteins may be accessible to molecular chaperones, intrabodies, peptides, or small chemical compounds[23]. There is also extensive screening in progress to identify poly-Q aggregate inhibitors[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 heterogenous. Heredoataxias may be best classified according to their trait of inheritence. 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 heredoataxoas 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 cytaxin
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 Tranebjaerg syndrome)
DIMOAD (WFS)	Diabetes insipidus, diabetes mellitus, optic atrophy, deafness syndrome (Wolfram syndrome)
DNA	Desoxy-ribunucleic 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	Leucencephalopathy with brainstem and spinal cord involvement and lactacidosis
LHON	Leber's hereditary optic neuropathy
LOFA	Late-onset Friedreich ataxia
LS	Leigh syndrome
MDS	Mitochondrial depletion syndrome
MELAS	Mitochondrial encephalomyopathy, lactacidosis, 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
PPP2R2B	Gene encoding for the Bbeta-2 subunit of the protein phosphatase 2a (PP2A)
PRKCG	Proetein-kinase gamma gene
PS	Pearson syndrome
RC	Respiratory chain
RNA	Ribonucleic acid
SANDO	Sensory ataxic neuropathy, dysarthria, ophthalmoplegia
SARA	Scale for the Assessment and Rating of Ataxia
SCA	Spinocerebellar ataxia
SCAE	Juvenile-onset spino-cerebellar ataxia and epilepsy
SCAFI	SCA functional index
SETX	Gene encoding for senataxin
SIL1	Gene encoding for HSPA5 (nucleoside exchange factor)
SPECT	Single photon emission computed tomography
SPTBN2	Gene encoding for beta-III sepctrin
SSEPs	Somato-sensory evoked potentials
TTBK2	Gene encoding for tau tubulin kinase 2
XLSA/A	X-linked sideroblastic anemia with ataxia

References

1. Fogel BL, Perlman S. Clinical features and molecular genetics of autosomal recessive cerebellar ataxias. Lancet Neurol. 2007;6: 245-57.
2. Duenas AM, Goold R, Giunti P. Molecular pathogenesis of spinocerebellar ataxias. Brain. 2006:129:1357-70.
3. Pandolfo M. Friedreich ataxia. Arch Neurol. 2008;65:1296-303.
4. Honti V, Vécsei L. Genetic and molecular aspects of spinocerebellar ataxias. Neuropsychiatr Dis Treat. 2005;1:125-33.
5. Tallaksen CM. Hereditary ataxias. Tidsskr Nor Laegeforen. 2008;128:1977-80.
6. Manto MU. The wide spectrum of spinocerebellar ataxias (SCAs). Cerebellum. 2005;4:2-6.
7. Klockgether T. The clinical diagnosis of autosomal dominant spinocerebellar ataxias. Cerebellum. 2008;7:101-5.
8. van de Warrenburg BP, Sinke RJ, Verschuuren-Bemelmans CC, Scheffer H, Brunt ER, Ippel PF, et al. Spinocerebellar ataxias in the Netherlands: prevalence and age at onset variance analysis. Neurology. 2002;58:702-8.
9. Tsuji S, Onodera O, Goto J, Nishizawa M: Study Group on Ataxic Diseases. Sporadic ataxias in Japan - a population-based epidemiological study. Cerebellum. 2008;7:189-97.
10. Zortea M, Armani M, Pastorello E, Nunez GF, Lombardi S, Tonello S, et al. Prevalence of inherited ataxias in the province of Padua, Italy. Neuroepidemiology. 2004;23:275-80.

11. Espinós-Armero C, González-Cabo P, Palau-Martínez F. Autosomal recessive cerebellar ataxias. Their classification, genetic features and pathophysiology. Rev Neurol. 2005;41:409-22.
12. Koht J, Tallaksen CM. Cerebellar ataxia in the eastern and southern parts of Norway. Acta Neurol Scand Suppl. 2007;187:76-9.
13. Brusco A, Gellera C, Cagnoli C, Saluto A, Castucci A, Michielotto C et al. Molecular genetics of hereditary spinocerebellar ataxia: mutation analysis of spinocerebellar ataxia genes and CAG/CTG repeat expansion detection in 225 Italian families. Arch Neurol. 2004;61:727-33.
14. Sasaki H, Yabe I, Tashiro K. The hereditary spinocerebellar ataxias in Japan. Cytogenet Genome Res. 2003;100:198-205.
15. Jiang H, Tang BS, Xu B, Zhao GH, Shen L, Tang JG, et al. Frequency analysis of autosomal dominant spinocerebellar ataxias in mainland Chinese patients and clinical and molecular characterization of spinocerebellar ataxia type 6. Chin Med J (Engl). 2005;118:837-43.
16. Zühlke C, Bernard V, Gillessen-Kaesbach G. Investigation of recessive ataxia loci in patients with young age of onset. Neuropediatrics. 2007;38:207-9.
17. Soong BW, Paulson HL. Spinocerebellar ataxias: an update. Curr Opin Neurol. 2007;20:438-46.
18. Johnson J, Wood N, Giunti P, Houlden H. Clinical and genetic analysis of spinocerebellar ataxia type 11. Cerebellum. 2008;7:159-64.
19. Storey E, Bahlo M, Fahey MC, Sisson O, Lueck CJ, Gardner RM. A new dominantly-inherited pure cerebellar ataxia, SCA 30. J Neurol Neurosurg Psychiatry. 2008,(in press)
20. Liu CS, Cheng WL, Kuo SJ, Li JY, Soong BW, Wei YH. Depletion of mitochondrial DNA in leukocytes of patients with poly-Q diseases. J Neurol Sci. 2008;264:18-21.
21. Shao J, Diamond MI. Polyglutamine diseases: emerging concepts in pathogenesis and therapy. Hum Mol Genet. 2007;16(spec No. 2):R115-23.
22. Netravathi M, Pal PK, Purushottam M, Thennarasu K, Mukherjee M, Jain S. Spinocerebellar ataxias types 1, 2 and 3: age adjusted clinical severity of disease at presentation correlates with size of CAG repeat lengths. J Neurol Sci. 2009;277:83-6.
23. Nagai Y, Popiel HA, Fujikake N, Toda T. Therapeutic strategies for the polyglutamine diseases. Brain Nerve. 2007;59:393-404.
24. Safaei S, Houshmand M, Banoei MM, Panahi MS, Nafisi S, Parivar K et al. Mitochondrial tRNALeu/Lys and ATPase 6/8 gene variations in spinocerebellar ataxias. Neurodegener Dis. 2009;6:16-22.
25. Döhlinger S, Hauser TK, Borkert J, Luft AR, Schulz JB. Magnetic resonance imaging in spinocerebellar ataxias. Cerebellum. 2008;7:204-14.
26. Garrard P, Martin NH, Giunti P, Cipolotti L. Cognitive and social cognitive functioning in spinocerebellar ataxia: a preliminary characterization. J Neurol. 2008;255:398-405.
27. Matilla-Dueñas A, Goold R, Giunti P. Clinical, genetic, molecular, and pathophysiological insights into spinocerebellar ataxia type 1. Cerebellum. 2008;7:106-14.
28. Globas C, du Montcel ST, Baliko L, Boesch S, Depondt C, DiDonato S, et al. Early symptoms in spinocerebellar ataxia type 1, 2, 3, and 6. Mov Disord. 2008;23:2232-8.
29. Sasaki H. Clinical feature and molecular genetics of hereditary spinocerebellar ataxia. Rinsho Shinkeigaku. 2007;47:795-800.
30. Rottnek M, Riggio S, Byne W, Sano M, Margolis RL, Walker RH. Schizophrenia in a patient with spinocerebellar ataxia 2: coincidence of two disorders or a neurodegenerative disease presenting with psychosis? Am J Psychiatry. 2008;165:964-7.
31. Lastres-Becker I, Rüb U, Auburger G. Spinocerebellar ataxia 2 (SCA2). Cerebellum. 2008;7:115-24.
32. Rüb U, Seidel K, Ozerden I, Gierga K, Brunt ER, Schöls L, et al. Consistent affection of the central somatosensory system in spinocerebellar ataxia type 2 and type 3 and its significance for clinical symptoms and rehabilitative therapy. Brain Res Rev. 2007;53:235-49.
33. Kim JM, Hong S, Kim GP, Choi YJ, Kim YK, Park SS, et al. Importance of low-range CAG expansion and CAA interruption in SCA2 Parkinsonism. Arch Neurol. 2007;64:1510-8.
34. Hoche F, Seidel K, Brunt ER, Auburger G, Schöls L, Bürk K, et al. Involvement of the auditory brainstem system in spinocerebellar ataxia type 2 (SCA2), type 3 (SCA3) and type 7 (SCA7). Neuropathol Appl Neurobiol. 2008;34:479-91.
35. Armstrong J, Bonaventura I, Rojo A, González G, Corral J, Nadal N, et al. Spinocerebellar ataxia type 2 (SCA2) with white matter involvement. Neurosci Lett. 2005;381:247-51.
36. Paulson HL. Dominantly inherited ataxias: lessons learned from Machado-Joseph disease/spinocerebellar ataxia type 3. Semin Neurol. 2007;27:133-42.
37. Riess O, Rüb U, Pastore A, Bauer P, Schöls L. SCA3: neurological features, pathogenesis and animal models. Cerebellum. 2008;7: 125-37.
38. Alves S, Nascimento-Ferreira I, Auregan G, Hassig R, Dufour N, Brouillet E, et al. Allele-specific RNA silencing of mutant ataxin-3 mediates neuroprotection in a rat model of Machado-Joseph disease. PLoS ONE. 2008;3:e3341.
39. Timmann D, Gerwig M, Frings M, Maschke M, Kolb FP. Eyeblink conditioning in patients with hereditary ataxia: a one-year follow-up study. Exp Brain Res. 2005;162:332-45.
40. França MC Jr, D'Abreu A, Nucci A, Lopes-Cendes I. Muscle excitability abnormalities in Machado-Joseph disease. Arch Neurol. 2008;65:525-9.
41. Carvalho DR, La Rocque-Ferreira A, Rizzo IM, Imamura EU, Speck-Martins CE. Homozygosity enhances severity in spinocerebellar ataxia type 3. Pediatr Neurol. 2008;38:296-9.
42. Hellenbroich Y, Gierga K, Reusche E, Schwinger E, Deller T, de Vos RA, et al. Spinocerebellar ataxia type 4 (SCA4): initial pathoanatomical study reveals widespread cerebellar and brainstem degeneration. J Neural Transm. 2006;113:829-43.
43. Bour LJ, van Rootselaar AF, Koelman JH, Tijssen MA. Oculomotor abnormalities in myoclonic tremor: a comparison with spinocerebellar ataxia type 6. Brain. 2008;131:2295-303.
44. Teive HA, Munhoz RP, Raskin S, Werneck LC. Spinocerebellar ataxia type 6 in Brazil. Arq Neuropsiquiatr. 2008;66:691-4.
45. Christova P, Anderson JH, Gomez CM. Impaired eye movements in presymptomatic spinocerebellar ataxia type 6. Arch Neurol. 2008;65:530-6.
46. Kawai Y, Suenaga M, Watanabe H, Ito M, Kato K, Kato T, et al. Prefrontal hypoperfusion and cognitive dysfunction correlates in spinocerebellar ataxia type 6. J Neurol Sci. 2008;271:68-74.
47. Kordasiewicz HB, Gomez CM. Molecular pathogenesis of spinocerebellar ataxia type 6. Neurotherapeutics. 2007;4:285-94.
48. Garden GA, La Spada AR. Molecular pathogenesis and cellular pathology of spinocerebellar ataxia type 7 neurodegeneration. Cerebellum. 2008;7:138-49.
49. Lin Y, Zheng JY, Jin YH, Xie YC, Jin ZB. Trinucleotide expansions in the SCA7 gene in a large family with spinocerebellar ataxia and craniocervical dystonia. Neurosci Lett. 2008;434:230-3.
50. Linhares Sda C, Horta WG, Cunha FM, Castro JD, Santos AC, Marques W Jr. Spastic paraparesis as the onset manifestation of spinocerebellar ataxia type 7. Arq Neuropsiquiatr. 2008;66: 246-8.
51. Rüb U, Brunt ER, Seidel K, Gierga K, Mooy CM, Kettner M, et al. Spinocerebellar ataxia type 7 (SCA7): widespread brain damage in an adult-onset patient with progressive visual impairments in comparison with an adult-onset patient without visual impairments. Neuropathol Appl Neurobiol. 2008;34:155-68.
52. Gupta SN, Marks HG. Spinocerebellar ataxia type 7 mimicking Kearns-Sayre syndrome: a clinical diagnosis is desirable. J Neurol Sci. 2008;264:173-6.
53. Lilja A, Hämäläinen P, Kaitaranta E, Rinne R. Cognitive impairment in spinocerebellar ataxia type 8. J Neurol Sci. 2005;237:31-8.
54. Wu YR, Lin HY, Chen CM, Gwinn-Hardy K, Ro LS, Wang YC, et al. Genetic testing in spinocerebellar ataxia in Taiwan: expansions of trinucleotide repeats in SCA8 and SCA17 are associated with typical Parkinson's disease. Clin Genet. 2004;65:209-14.
55. He Y, Zu T, Benzow KA, Orr HT, Clark HB, Koob MD. Targeted deletion of a single Sca8 ataxia locus allele in mice causes abnormal gait, progressive loss of motor coordination, and Purkinje cell dendritic deficits. J Neurosci. 2006;26:9975-82.

56. Kumar N, Miller GM. White matter hyperintense lesions in genetically proven spinocerebellar ataxia 8. Clin Neurol Neurosurg. 2008;110:65-8.
57. Munhoz RP, Teive HA, Raskin S, Werneck LC. CTA/CTG expansions at the SCA 8 locus in multiple system atrophy. Clin Neurol Neurosurg. 2009;111:208-10.
58. Ohnari K, Aoki M, Uozumi T, Tsuji S. Severe symptoms of 16q-ADCA coexisting with SCA8 repeat expansion. J Neurol Sci. 2008;273:15-8.
59. Torrens L, Burns E, Stone J, Graham C, Wright H, Summers D, et al. Spinocerebellar ataxia type 8 in Scotland: frequency, neurological, neuropsychological and neuropsychiatric findings. Acta Neurol Scand. 2008;11741-8.
60. Ito H, Kawakami H, Wate R, Matsumoto S, Imai T, Hirano A, et al. Clinicopathologic investigation of a family with expanded SCA8 CTA/CTG repeats. Neurology. 2006;67:1479-81.
61. Mutsuddi M, Rebay I. Molecular genetics of spinocerebellar ataxia type 8 (SCA8). RNA Biol. 2005;2:49-52.
62. Silveira I, Alonso I, Guimarães L, Mendonça P, Santos C, Maciel P, et al. High germinal instability of the (CTG)n at the SCA8 locus of both expanded and normal alleles. Am J Hum Genet. 2000; 66:830-40.
63. Chen WL, Lin JW, Huang HJ, Wang SM, Su MT, Lee-Chen GJ, et al. SCA8 mRNA expression suggests an antisense regulation of KLHL1 and correlates to SCA8 pathology. Brain Res. 2008; 1233:176-84.
64. Ikeda Y, Daughters RS, Ranum LP. Bidirectional expression of the SCA8 expansion mutation: One mutation, two genes. Cerebellum. 2008;7:150-8.
65. Moseley ML, Zu T, Ikeda Y, Gao W, Mosemiller AK, Daughters RS, et al. Bidirectional expression of CUG and CAG expansion transcripts and intranuclear polyglutamine inclusions in spinocerebellar ataxia type 8. Nat Genet. 2006;38:758-69.
66. Raskin S, Ashizawa T, Teive HA, Arruda WO, Fang P, Gao R, et al. Reduced penetrance in a Brazilian family with spinocerebellar ataxia type 10. Arch Neurol. 2007;64:591-4.
67. Teive HA, Arruda WO, Raskin S, Ashizawa T, Werneck LC. The history of spinocerebellar ataxia type 10 in Brazil: travels of a gene. Arq Neuropsiquiatr. 2007;65:965-8.
68. Lin X, Ashizawa T. Recent progress in spinocerebellar ataxia type-10 (SCA10). Cerebellum. 2005;4:37-42.
69. Rasmussen A, Matsuura T, Ruano L, Yescas P, Ochoa A, Ashizawa T, et al. Clinical and genetic analysis of four Mexican families with spinocerebellar ataxia type 10. Ann Neurol. 2001;50:234-9.
70. Matsuura T, Yamagata T, Burgess DL, Rasmussen A, Grewal RP, Watase K et al. Large expansion of the ATTCT pentanucleotide repeat in spinocerebellar ataxia type 10. Nat Genet. 2000;26:191-4.
71. Potaman VN, Bissler JJ, Hashem VI, Oussatcheva EA, Lu L, Shlyakhtenko LS, et al. Unpaired structures in SCA10 (ATTCT)n.(AGAAT)n repeats. J Mol Biol. 2003;326:1095-111.
72. Liu G, Bissler JJ, Sinden RR, Leffak M. Unstable spinocerebellar ataxia type 10 (ATTCT*(AGAAT) repeats are associated with aberrant replication at the ATX10 locus and replication origin-dependent expansion at an ectopic site in human cells. Mol Cell Biol. 2007;27:7828-38.
73. März P, Probst A, Lang S, Schwager M, Rose-John S, Otten U, et al. Ataxin-10, the spinocerebellar ataxia type 10 neurodegenerative disorder protein, is essential for survival of cerebellar neurons. J Biol Chem. 2004;279:35542-50.
74. Matsuura T, Fang P, Pearson CE, Jayakar P, Ashizawa T, Roa BB, et al. Interruptions in the expanded ATTCT repeat of spinocerebellar ataxia type 10: repeat purity as a disease modifier? Am J Hum Genet. 2006;78:125-9.
75. Matsuura T, Fang P, Lin X, Khajavi M, Tsuji K, Rasmussen A, et al. Somatic and germline instability of the ATTCT repeat in spinocerebellar ataxia type 10. Am J Hum Genet. 2004;74: 1216-24.
76. Houlden H, Johnson J, Gardner-Thorpe C, Lashley T, Hernandez D, Worth P, et al. Mutations in TTBK2, encoding a kinase implicated in tau phosphorylation, segregate with spinocerebellar ataxia type 11. Nat Genet. 2007;39:1434-6.
77. Bahl S, Virdi K, Mittal U, Sachdeva MP, Kalla AK, Holmes SE, et al. Evidence of a common founder for SCA12 in the Indian population. Ann Hum Genet. 2005;69:528-34.
78. Dagda RK, Merrill RA, Cribbs JT, Chen Y, Hell JW, Usachev YM, et al. The spinocerebellar ataxia 12 gene product and protein phosphatase 2A regulatory subunit B(beta)2 antagonizes neuronal survival by promoting mitochondrial fission. J Biol Chem. 2008;283:36241-8.
79. Stevanin G, Durr A, Benammar N, Brice A. Spinocerebellar ataxia with mental retardation (SCA13). Cerebellum. 2005;4:43-6.
80. Miura S, Nakagawara H, Kaida H, Sugita M, Noda K, Motomura K, et al. Expansion of the phenotypic spectrum of SCA14 caused by the Gly128Asp mutation in PRKCG. Clin Neurol Neurosurg. 2009;111:211-5.
81. Klebe S, Durr A, Rentschler A, Hahn-Barma V, Abele M, Bouslam N, et al. New mutations in protein kinase Cgamma associated with spinocerebellar ataxia type 14. Ann Neurol. 2005;58:720-9.
82. Morita H, Yoshida K, Suzuki K, Ikeda S. A Japanese case of SCA14 with the Gly128Asp mutation. J Hum Genet. 2006;51:1118-21.
83. Seki T, Shimahara T, Yamamoto K, Abe N, Amano T, Adachi N, et al. Mutant gammaPKC found in spinocerebellar ataxia type 14 induces aggregate-independent maldevelopment of dendrites in primary cultured Purkinje cells. Neurobiol Dis. 2009;33:260-73.
84. Verbeek DS, Goedhart J, Bruinsma L, Sinke RJ, Reits EA. PKC gamma mutations in spinocerebellar ataxia type 14 affect C1 domain accessibility and kinase activity leading to aberrant MAPK signaling. J Cell Sci. 2008;121:2339-49.
85. Adachi N, Kobayashi T, Takahashi H, Kawasaki T, Shirai Y, Ueyama T, et al. Enzymological analysis of mutant protein kinase Cgamma causing spinocerebellar ataxia type 14 and dysfunction in Ca2+ homeostasis. J Biol Chem. 2008;283: 19854-63.
86. Knight MA, Kennerson ML, Anney RJ, Matsuura T, Nicholson GA, Salimi-Tari P, et al. Spinocerebellar ataxia type 15 (sca15) maps to 3p24.2-3pter: exclusion of the ITPR1 gene, the human orthologue of an ataxic mouse mutant. Neurobiol Dis. 2003;13:147-57.
87. Gardner RJ, Knight MA, Hara K, Tsuji S, Forrest SM, Storey E. Spinocerebellar ataxia type 15. Cerebellum. 2005;4:47-50.
88. Miyoshi Y, Yamada T, Tanimura M, Taniwaki T, Arakawa K, Ohyagi Y, et al. A novel autosomal dominant spinocerebellar ataxia (SCA16) linked to chromosome 8q22.1-24.1. Neurology. 2001;57:96-100.
89. Hara K, Shiga A, Nozaki H, Mitsui J, Takahashi Y, Ishiguro H, et al. Total deletion and a missense mutation of ITPR1 in Japanese SCA15 families. Neurology. 2008;71:547-51.
90. Iwaki A, Kawano Y, Miura S, Shibata H, Matsuse D, Li W, et al. Heterozygous deletion of ITPR1, but not SUMF1, in spinocerebellar ataxia type 16. J Med Genet. 2008;45:32-5.
91. Gao R, Matsuura T, Coolbaugh M, Zühlke C, Nakamura K, Rasmussen A, et al. Instability of expanded CAG/CAA repeats in spinocerebellar ataxia type 17. Eur J Hum Genet. 2008;16: 215-22.
92. Mariotti C, Alpini D, Fancellu R, Soliveri P, Grisoli M, Ravaglia S, et al. Spinocerebellar ataxia type 17 (SCA17): oculomotor phenotype and clinical characterization of 15 Italian patients. J Neurol. 2007;254:1538-46.
93. Stevanin G, Brice A. Spinocerebellar ataxia 17 (SCA17) and Huntington's disease-like 4 (HDL4). Cerebellum. 2008;7:170-8.
94. Lasek K, Lencer R, Gaser C, Hagenah J, Walter U, Wolters A et al. Morphological basis for the spectrum of clinical deficits in spinocerebellar ataxia 17 (SCA17). Brain. 2006;129:2341-52.
95. Lee LC, Chen CM, Chen FL, Lin PY, Hsiao YC, Wang Pr, et al. Altered expression of HSPA5, HSPA8 and PARK7 in spinocerebellar ataxia type 17 identified by 2-dimensional fluorescence difference in gel electrophoresis. Clin Chim Acta. 2009;400:56-62.
96. Schelhaas HJ, van de Warrenburg BP. Clinical, psychological, and genetic characteristics of spinocerebellar ataxia type 19 (SCA19). Cerebellum. 2005;4:51-4.
97. Verbeek DS, Schelhaas JH, Ippel EF, Beemer FA, Pearson PL, Sinke RJ. Identification of a novel SCA locus (SCA19) in a Dutch autosomal dominant cerebellar ataxia family on chromosome region 1p21-q21. Hum Genet. 2002;111:388-93.

98. Knight MA, Hernandez D, Diede SJ, Dauwerse HG, Rafferty I, van de Leemput J, et al. A duplication at chromosome 11q12.2-11q12.3 is associated with spinocerebellar ataxia type 20. Hum Mol Genet. 2008;17:3847-53.
99. Storey E, Knight MA, Forrest SM, Gardner RJ. Spinocerebellar ataxia type 20. Cerebellum. 2005;4:55-7.
100. Delplanque J, Devos D, Vuillaume I, De Becdelievre A, Vangelder E, Maurage CA, et al. Slowly progressive spinocerebellar ataxia with extrapyramidal signs and mild cognitive impairment (SCA21). Cerebellum. 2008;7:179-83.
101. Knight MA, Gardner RJ, Bahlo M, Matsuura T, Dixon JA, Forrest SM, et al. Dominantly inherited ataxia and dysphonia with dentate calcification: spinocerebellar ataxia type 20. Brain. 2004;127:1172-81.
102. Vuillaume I, Devos D, Schraen-Maschke S, Dina C, Lemainque A, Vasseur F, et al. A new locus for spinocerebellar ataxia (SCA21) maps to chromosome 7p21.3-p15.1. Ann Neurol. 2002;52: 666-70.
103. Chung MY, Lu YC, Cheng NC, Soong BW. A novel autosomal dominant spinocerebellar ataxia (SCA22) linked to chromosome 1p21-q23. Brain. 2003;126:1293-9.
104. Verbeek DS, van de Warrenburg BP, Wesseling P, Pearson PL, Kremer HP, Sinke RJ. Mapping of the SCA23 locus involved in autosomal dominant cerebellar ataxia to chromosome region 20p13-12.3. Brain. 2004;127:2551-7.
105. Yu GY, Howell MJ, Roller MJ, Xie TD, Gomez CM. Spinocerebellar ataxia type 26 maps to chromosome 19p13.3 adjacent to SCA6. Ann Neurol. 2005;57:349-54.
106. Brusse E, de Koning I, Maat-Kievit A, Oostra BA, Heutink P, van Swieten JC. Spinocerebellar ataxia associated with a mutation in the fibroblast growth factor 14 gene (SCA27): A new phenotype. Mov Disord. 2006;21:396-401.
107. Mariotti C, Brusco A, Di Bella D, Cagnoli C, Seri M, Gellera C, et al. Spinocerebellar ataxia type 28: A novel autosomal dominant cerebellar ataxia characterized by slow progression and ophthalmoparesis. Cerebellum. 2008;7:184-8.
108. Cagnoli C, Mariotti C, Taroni F, Seri M, Brussino A, Michielotto C, et al. SCA28, a novel form of autosomal dominant cerebellar ataxia on chromosome 18p11.22-q11.2. Brain. 2006;129:235-42
109. Oyanagi S. Hereditary dentatorubral-pallidoluysian atrophy. Neuropathology. 2000;20 suppl:S42-6.
110. Garcia Ruiz PJ, Mayo D, Hernandez J, Cantarero S, Ayuso C. Movement disorders in hereditary ataxias. J Neurol Sci. 2002; 202:59-64.
111. Jen JC. Hereditary episodic ataxias. Ann N Y Acad Sci. 2008;1142: 250-3.
112. Klockgether T. Recent advances in degenerative ataxias. Curr Opin Neurol. 2000;13:451-5.
113. Riant F, Mourtada R, Saugier-Veber P, Tournier-Lasserve E. Large CACNA1A deletion in a family with episodic ataxia type 2. Arch Neurol. 2008;65:817-20.
114. Steckley JL, Ebers GC, Cader MZ, McLachlan RS. An autosomal dominant disorder with episodic ataxia, vertigo, and tinnitus. Neurology. 2001;57:1499-502.
115. Cader MZ, Steckley JL, Dyment DA, McLachlan RS, Ebers GC. A genome-wide screen and linkage mapping for a large pedigree with episodic ataxia. Neurology. 2005;65:156-8.
116. Damji KF, Allingham RR, Pollock SC, Small K, Lewis KE, Stajich JM, et al. Periodic vestibulocerebellar ataxia, an autosomal dominant ataxia with defective smooth pursuit, is genetically distinct from other autosomal dominant ataxias. Arch Neurol. 1996;53:338-44.
117. Escayg A, De Waard M, Lee DD, Bichet D, Wolf P, Mayer T, et al. Coding and noncoding variation of the human calcium-channel beta4-subunit gene CACNB4 in patients with idiopathic generalized epilepsy and episodic ataxia. Am J Hum Genet. 2000;66:1531-9.
118. Kerber KA, Jen JC, Lee H, Nelson SF, Baloh RW. A new episodic ataxia syndrome with linkage to chromosome 19q13. Arch Neurol. 2007;64:749-52.
119. Debray FG, Lambert M, Gagne R, Maranda B, Laframboise R, MacKay N, et al. Pyruvate dehydrogenase deficiency presenting as intermittent isolated acute ataxia. Neuropediatrics. 2008;39: 20-3.
120. Craig K, Elliott HR, Keers SM, Lambert C, Pyle A, Graves TD, et al. Episodic ataxia and hemiplegia caused by the 8993T>C mitochondrial DNA mutation. J Med Genet. 2007;44:797-9.
121. Finsterer J. Mitochondrial ataxias. Eur J Neurol. In Press 2009.
122. Finsterer J. Leigh and Leigh-like syndrome in children and adults. Pediatr Neurol. 2008;39:223-35
123. Di Donato S, Gellera C, Mariotti C. The complex clinical and genetic classification of inherited ataxias. II. Autosomal recessive ataxias. Neurol Sci. 2001;22:219-28.
124. Koeppen AH, Michael SC, Knutson MD, Haile DJ, Qian J, Levi S, et al. The dentate nucleus in Friedreich's ataxia: the role of iron-responsive proteins. Acta Neuropathol. 2007;114:163-73.
125. Hirai T, Suzuki M, Kurita A, Inoue K. Neurological findings, neurophysiological examinations, and sural nerve biopsy in a case of Friedreich ataxia. Rinsho Shinkeigaku. 2006;46:485-90.
126. Fayssoil A, Nardi O, Orlikowski D, Annane D. Hypertrophic cardiomyopathy in Friedreich's ataxia. Int J Cardiol. 2008;127:e122-3.
127. Whitnall M, Rahmanto YS, Sutak R, Xu X, Becker EM, Mikhael MR, et al. The MCK mouse heart model of Friedreich's ataxia: Alterations in iron-regulated proteins and cardiac hypertrophy are limited by iron chelation. Proc Natl Acad Sci USA. 2008;105:9757-62.
128. Raman SV, Dickerson JA, Al-Dahhak R. Myocardial ischemia in the absence of epicardial coronary artery disease in Friedreich's ataxia. J Cardiovasc Magn Reson. 2008;10:15.
129. Milbrandt TA, Kunes JR, Karol LA. Friedreich's ataxia and scoliosis: the experience at two institutions. J Pediatr Orthop. 2008;28:234-8.
130. Galimanis A, Glutz L, Spiegel R, Burgunder JM, Kaelin-Lang A. Very-late-onset Friedreich ataxia with disturbing head tremor and without spinal atrophy--a case report. Mov Disord. 2008;23:1058-9.
131. Ribaï P, Pousset F, Tanguy ML, Rivaud-Pechoux S, Le Ber I, Gasparini F, et al. Neurological, cardiological, and oculomotor progression in 104 patients with Friedreich ataxia during long-term follow-up. Arch Neurol. 2007;64:558-64.
132. Della Nave R, Ginestroni A, Tessa C, Salvatore E, Bartolomei I, Salvi F, et al. Brain white matter tracts degeneration in Friedreich ataxia. An in vivo MRI study using tract-based spatial statistics and voxel-based morphometry. Neuroimage. 2008;40:19-25.
133. Popescu BF, Pickering IJ, George GN, Nichol H. The chemical form of mitochondrial iron in Friedreich's ataxia. J Inorg Biochem. 2007;101:957-66.
134. Pandolfo M. Friedreich ataxia: Detection of GAA repeat expansions and frataxin point mutations. Methods Mol Med. 2006;126: 197-216.
135. Wells RD. DNA triplexes and Friedreich ataxia. FASEB J. 2008;22:1625-34.
136. Hebert MD. Targeting the gene in Friedreich ataxia. Biochimie. 2008;90:1131-9.
137. Greene E, Mahishi L, Entezam A, Kumari D, Usdin K. Repeat-induced epigenetic changes in intron 1 of the frataxin gene and its consequences in Friedreich ataxia. Nucleic Acids Res. 2007;35:3383-90.
138. Gellera C, Castellotti B, Mariotti C, Mineri R, Seveso V, Didonato S, et al. Frataxin gene point mutations in Italian Friedreich ataxia patients. Neurogenetics. 2007;8:289-99.
139. Reddy PL, Grewal RP. Friedreich's ataxia: a clinical and genetic analysis. Clin Neurol Neurosurg. 2007;109:200-2.
140. De Biase I, Rasmussen A, Monticelli A, Al-Mahdawi S, Pook M, Cocozza S, et al. Somatic instability of the expanded GAA triplet-repeat sequence in Friedreich ataxia progresses throughout life. Genomics. 2007;90:1-5.
141. Federico A. Ataxia with isolated vitamin E deficiency: a treatable neurologic disorder resembling Friedreich's ataxia. Neurol Sci. 2004;25:119-21.
142. Marzouki N, Benomar A, Yahyaoui M, Birouk N, Elouazzani M, Chkili T, et al. Vitamin E deficiency ataxia with (744 del A) mutation on alpha-TTP gene: genetic and clinical peculiarities in Moroccan patients. Eur J Med Genet. 2005;48:21-8.

143. Gabsi S, Gouider-Khouja N, Belal S, Fki M, Kefi M, Turki I, et al. Effect of vitamin E supplementation in patients with ataxia with vitamin E deficiency. Eur J Neurol. 2001;8:477-81.
144. Finsterer J, Regelsberger G, Voigtländer T. Refsum disease due to the splice-site mutation c.135-2A>G before exon 3 of the PHYH gene, diagnosed eight years after detection of retinitis pigmentosa. J Neurol Sci. 2008;266:182-186.
145. Staples ER, McDermott EM, Reiman A, Byrd PJ, Ritchie S, Taylor AM, et al. Immunodeficiency in ataxia telangiectasia is correlated strongly with the presence of two null mutations in the ataxia telangiectasia mutated gene. Clin Exp Immunol. 2008; 153:214-20.
146. Biton S, Barzilai A, Shiloh Y. The neurological phenotype of ataxia-telangiectasia: solving a persistent puzzle. DNA Repair (Amst). 2008;7:1028-38.
147. Habek M, Brinar VV, Rados M, Zadro I, Zarković K. Brain MRI abnormalities in ataxia-telangiectasia. Neurologist. 2008;14: 192-5.
148. Taylor AM, Byrd PJ. Molecular pathology of ataxia telangiectasia. J Clin Pathol. 2005;58:1009-15.
149. Le B, I, Brice A, Durr A. New autosomal recessive cerebellar ataxias with oculomotor apraxia. Curr Neurol Neurosci Rep. 2005;5:411-7.
150. Engert JC, Bérubé P, Mercier J, Doré C, Lepage P, Ge B, et al. ARSACS, a spastic ataxia common in northeastern Québec, is caused by mutations in a new gene encoding an 11.5-kb ORF. Nat Genet. 2000;24:120-5.
151. Senderek J, Krieger M, Stendel C, Bergmann C, Moser M, Breitbach-Faller N, et al. Mutations in SIL1 cause Marinesco-Sjögren syndrome, a cerebellar ataxia with cataract and myopathy. Nat Genet. 2005;37:1312-4.
152. Adams SA, Steenblock KJ, Thibodeau SN, Lindor NM. Premutations in the FMR1 gene are uncommon in men undergoing genetic testing for spinocerebellar ataxia. J Neurogenet. 2008;22:77-92.
153. Berry-Kravis E, Abrams L, Coffey SM, Hall DA, Greco C, Gane LW, et al. Fragile X-associated tremor/ataxia syndrome: clinical features, genetics, and testing guidelines. Mov Disord. 2007;22:2018-30.
154. Mascalchi M. Spinocerebellar ataxias. Neurol Sci. 2008;29 suppl 3:311-3.
155. Allikmets R, Raskind WH, Hutchinson A, Schueck ND, Dean M, Koeller DM. Mutation of a putative mitochondrial iron transporter gene (ABC7) in X-linked sideroblastic anemia and ataxia (XLSA/A). Hum Mol Genet. 1999;8:743-9.
156. Hellier KD, Hatchwell E, Duncombe AS, Kew J, Hammans SR. X-linked sideroblastic anaemia with ataxia: another mitochondrial disease? J Neurol Neurosurg Psychiatry. 2001;70:65-9.
157. Maguire A, Hellier K, Hammans S, May A. X-linked cerebellar ataxia and sideroblastic anaemia associated with a missense mutation in the ABC7 gene predicting V411L. Br J Haematol. 2001;115:910-7.
158. Schmitz-Hübsch T, Klockgether T. An update on inherited ataxias. Curr Neurol Neurosci Rep. 2008;8:310-9.
159. Schöls L, Arning L, Schüle R, Epplen JT, Timmann D. "Pseudodominant inheritance" of ataxia with ocular apraxia type 2 (AOA2). J Neurol. 2008;255:495-501.
160. Ogawa M. Pharmacological treatments of cerebellar ataxia. Cerebellum. 2004;3:107-11.
161. Di Prospero NA, Baker A, Jeffries N, Fischbeck KH. Neurological effects of high-dose idebenone in patients with Friedreich's ataxia: a randomised, placebo-controlled trial. Lancet Neurol. 2007;6:878-86.
162. Boesch S, Sturm B, Hering S, Goldenberg H, Poewe W, Scheiber-Mojdehkar B. Friedreich's ataxia: clinical pilot trial with recombinant human erythropoietin. Ann Neurol. 2007;62:521-4.
163. Boddaert N, Le Quan Sang KH, Rötig A, Leroy-Willig A, Gallet S, Brunelle F, et al. Selective iron chelation in Friedreich ataxia: biologic and clinical implications. Blood. 2007;110:401-8.
164. Goulipian C, Bensoussan L, Viton JM, Milhe-De Bovis V, Ramon J, Delarque A. Orthopedic shoes improve gait in Friedreich's ataxia: a clinical and quantified case study. Eur J Phys Rehabil Med. 2008;44:93-8.
165. Gazulla J, Modrego P. Buspirone and serotonin in spinocerebellar ataxia. J Neurol Sci. 2008;268:199-200.
166. Underwood BR, Rubinsztein DC. Spinocerebellar ataxias caused by polyglutamine expansions: a review of therapeutic strategies. Cerebellum. 2008;7:215-21.