

**National consensus on the diagnosis, treatment and prevention of
hereditary cerebellar ataxias**

Under the editorship of

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Bulgarian Society of Neurology

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**Bulgarian Society of Child Neurology, Psychiatry and Developmental
Psychology**

**National consensus on diagnosis, treatment and prevention of hereditary
cerebellar ataxias**

On this day, 19.06.2025, we, the undersigned specialists, reached a consensus on the
diagnosis, treatment and prevention of hereditary cerebellar ataxias:

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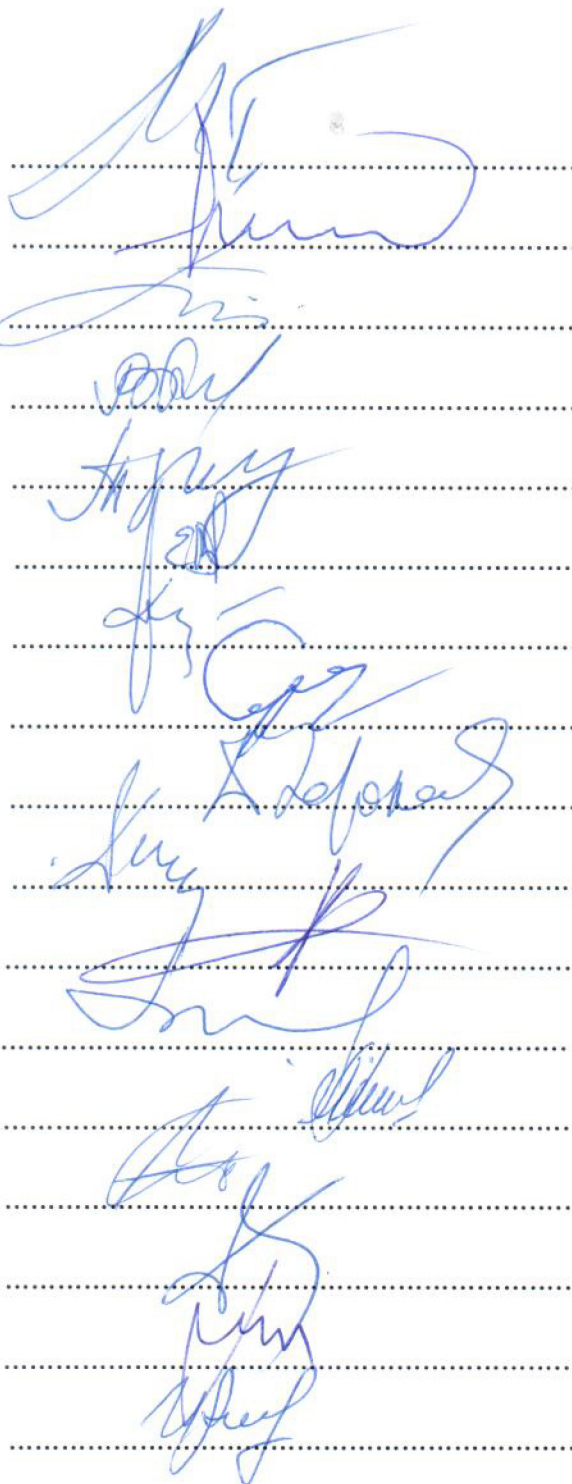


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Abbreviations used

AA- Amino acids
AFP - Alpha-fetoprotein
ALS - Amyotrophic lateral sclerosis
ATP- Adenosine triphosphate
GTCS - Generalized tonic-clonic seizures
CAEPs - Cortical auditory-evoked potentials
CP - Cerebral palsy
CT scan - Computed tomography scan
CTX - Cerebrotendinous xanthomatosis
DNA - Deoxyribonucleic acids
DOPA – Dopamine
DRPLA - Dentatorubral-pallidoluysian atrophy
EF - Ejection fraction
EMG - Electromyography
ERG – Electroretinography
HCA - Hereditary cerebellar ataxias
HDL - High-density lipoproteins
HJ - Hip joint
MEPs - Motor evoked potentials
MJD - Machado-Joseph disease
MS - Multiple sclerosis
MRI - Magnetic resonance imaging
MSA - Multisystem atrophy
NCS- Nerve conduction studies
NPA - Niemann-Pick Disease Type A
NPB - Niemann-Pick Disease Type B
NPC - Niemann-Pick Disease Type C
NGS - Next-generation sequencing
NPD - Neuropsychological development
ncRNA - Non-coding ribonucleic acids
OCT - Optical coherence tomography
PFTs - Pulmonary function tests
PET- Positron emission tomography

RNA- Ribonucleic acids

SSEPs - Somatosensory evoked potentials

SCA - Spinocerebellar ataxia

TR - Tendon reflexes

tRNA - Transfer ribonucleic acids

VEPs - Visual evoked potentials

WES - Whole exome sequencing

WGS - Whole genome sequencing

Hereditary cerebellar ataxias (HCAs) represent a large group of disorders that are heterogeneous in clinical and genetic context. In some forms an isolated pan-cerebellar syndrome is present, while in others extracerebellar manifestations are observed, such as retinal pigmentary degeneration, extrapyramidal movement disorders, pyramidal manifestations, cortical involvement (epileptic seizures, cognitive and behavioural disorders), neuropathy and involvement of other organs and systems.

In the last 20 years, with the rapid development of genetics and the expansion of molecular and genetic methods of diagnosis, the knowledge about HCA has significantly expanded, and more specifically the knowledge about their underlying gene defects and pathogenetic mechanisms which could be the basis for future therapeutic strategies.

1. Epidemiology of hereditary cerebellar ataxias

The overall incidence of cerebellar degeneration is about 1-5/100 000.

The incidence of autosomal dominant (AD) forms (SCA) is about 1/35,000, with SCA type 3 (Machado-Joseph Disease) being the most common AD form, followed by SCA type 2 and SCA type 6. Some forms occur with higher frequency in certain populations - SCA type 3 in Portugal and Brazil, SCA type 2 is most common in Spain, Italy, Norway, Cuba and Singapore. SCA type 6 is the second most common in the Netherlands and Japan, while SCA type 7 in Mexico and SCA type 10 among American Indians. Dentatorubral-pallidoluysian atrophy (DRPLA) is typical in Asia but also in Portugal. Despite advances in molecular genetic research in recent decades, between 20% and 33% of families with ataxia of AD inheritance type remain without an accurate genetic diagnosis.

The incidence of autosomal recessive (AR) cerebellar degeneration is about 1-7.2/100,000, with Friedreich's ataxia being the most common, followed by ataxia with oculomotor apraxia type 1 (AOA1) and ataxia-telangiectasia (AT). In Norway, by exception, AT is the most common form with an incidence of 18%, and AOA1 is the second most common in Portugal and France. In this type of inheritance, between 37% and 60% of patients have not undergone genetic verification.

In Bulgaria, SCA1 followed by SCA2 are the most common forms of autosomal dominant cerebellar ataxias, while Friedreich's ataxia followed by AT are the most common of the group of AR cerebellar ataxias.

2. Pathophysiology of cerebellar involvement

Recent research on the cerebellum - basal ganglia- thalamus - cerebral cortex connections makes it possible to clarify the functions of the cerebellum and its afferent and efferent connections. The cerebellum is involved not only in motor control but also in cognitive and behavioural processes.

Clinically, pancerebellar syndrome is divided into cerebellar motor syndrome, vestibulocerebellar syndrome, and cerebellar cognitive-affective syndrome (CCAS) based on anatomical testing and functional neuroimaging.

The classical topographic classification: vermis associated with *nucl. fastigii*, middle zone associated with *nucl. globosus* and *nucl. emboliformis*, and lateral zone associated with *nucl. dentatus* has been replaced by a new approach based on functional anatomy and the associated syndromes:

- Cerebellar motor syndrome (CMS) includes dynamic ataxia, dysdiadochokinesia (DDK), intense tremor, and hypotonia. The primary sensorimotor area is located in the frontal lobe and adjacent to lobule VI. A second sensorimotor area is located in lobule VIII. These areas are connected to the caudal part of the pons and thence to the contralateral *lobus ant.* which in turn is connected to the motor cortex via the thalamus.
- Vestibulocerebellar syndrome (VCS) manifests with gaze fixation deficits - nystagmus, saccadic eye movements, opsoclonus, dizziness, static and locomotor ataxia in an indeterminate direction. *Lobulus flocculonodularis* is connected with the vestibular nuclei, and three subzones have been identified: flocculo-parafloccular, *nodulus-uvula ventralis* (lobules IX and X), and dorsal oculomotor vermis (lobules V-VII). The vestibulocerebellar system and the vestibulospinal system are closely connected.
- Cerebellar cognitive-affective syndrome (CCAS) is found in patients with lesions in the posterior cerebellar lobe, the so-called cognitive cerebellum lobules VI, VII and most probably lobus IX. Cognitive impairments are found in a number of cerebellar diseases, and the severity of these manifestations ranges from discrete to severe pseudo-psychiatric disorders. Executive functions, visuospatial skills, and verbal memory are affected. Language processing and affect are impaired in some patients. A severe form of impairment is the posterior fossa syndrome (PFS), or the so-called cerebellar mutism syndrome (CMS), seen in children operated for midline tumours, such as medulloblastomas.

3. Classification and forms of hereditary cerebellar ataxias

They are classified into four groups based on their mode of inheritance:

- Autosomal dominant ataxias and episodic ataxias
- Autosomal recessive ataxias
- X-linked ataxias
- Mitochondrial ataxias

3.1. Autosomal dominant spinocerebellar ataxias

Forty-eight subtypes of SCA have been identified, determined by mutations in 35 genes. The most frequent forms are due to pathological trinucleotide expansions (polyQ - most frequently CAG; but also CTA/CTG) in various genes, (*ATXN1/SCA1*, *ATXN2/SCA2*, *ATXN3/SCA3*, *CACNA1A/SCA6*, *ATXN7/SCA7*, *TBP/SCA17*, *ATN1/DRPLA*). There are also forms with pathologically elevated penta- and hexanucleotide repeats, such as in SCA 10, 37 and 36. Point mutations, deletions, insertions and duplications are found in the remaining forms.

Many of the forms cannot be differentiated on the basis of their clinical manifestations alone, necessitating subsequent genetic verification.

The pathogenetic mechanisms underlying neurodegeneration in AD SCA are complex and include: pathologically increased trinucleotide repeat expansion (TNR expansion) associated with RNA toxicity, mitochondrial dysfunction, disturbances in the function of certain ion channels, autophagy disorders, etc. The well expressed clinical heterogeneity in AD SCA in terms of age of onset, rate of progression and severity of disease also suggests the influence of modifier genes.

The onset in SCA determined by pathological trinucleotide expansions is most often between 20 and 40 years of age, with an inverse correlation with the magnitude of the expansion. Static, locomotor, and dynamic ataxia are the first manifestations that progress over time and lead to loss of independent gait after varying periods of time. Pancerebellar syndrome is most often combined with extracerebellar manifestations, such as quadripylaridal syndrome, extrapyramidal syndrome, retinal degeneration, dementia, and epileptic seizures (Table 1).

AD SCAs, regardless of the underlying pathogenetic mechanisms, are divided into three types taking into account the presence or absence of extracerebellar involvement based on Harding's classification of 1982. In Type I, cerebellar ataxia is

associated with other neurological manifestations, whereas in type III, pure cerebellar ataxia is present. Retinal pigmentary degeneration is also found in Type II or SCA7 (Figure 1).

Figure 1. Clinical classification of AD SCA.

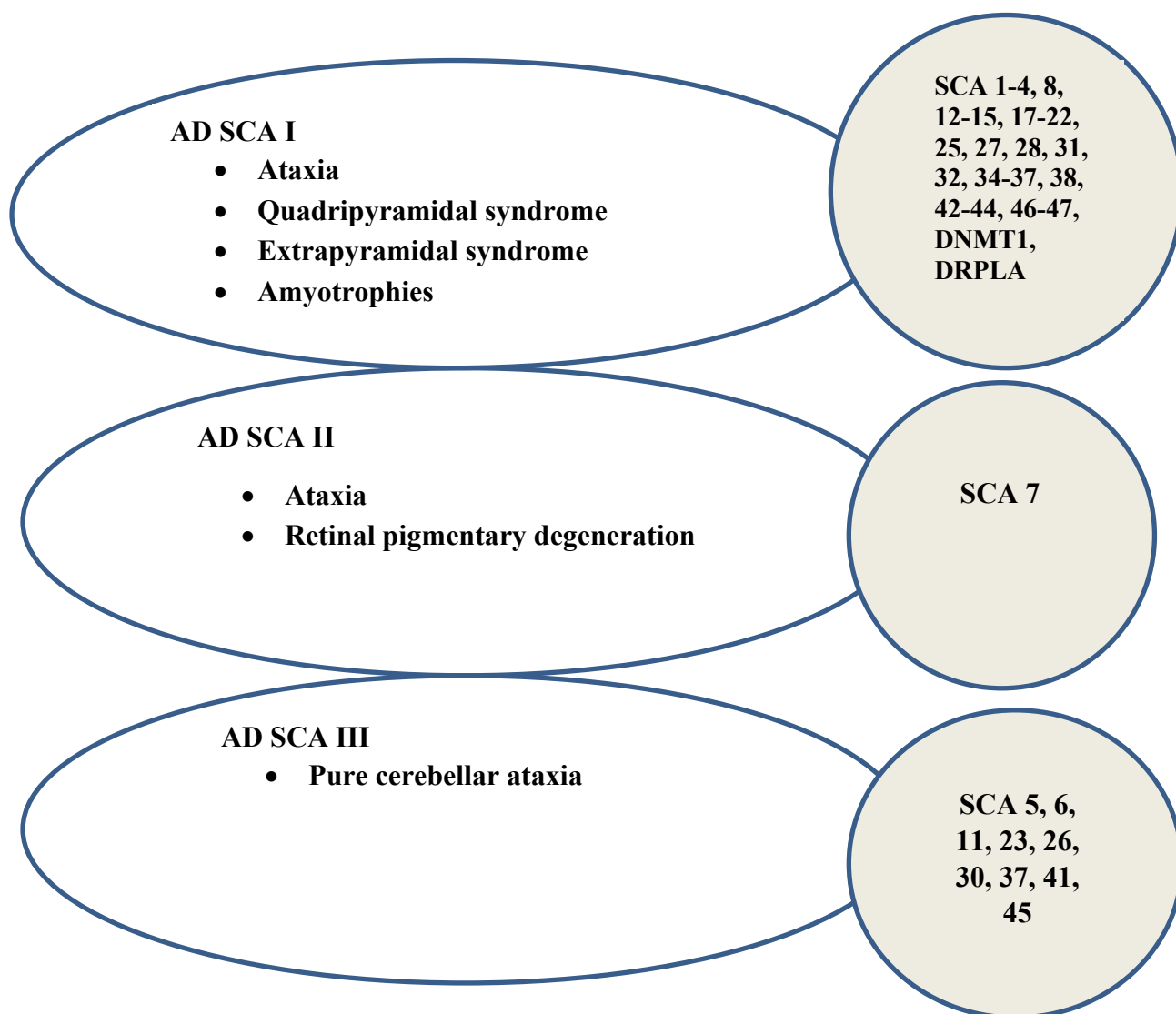


Table 1. Types of AD SCA and ataxia-associated extracerebellar manifestations.

Clinical manifestations associated with ataxia	AD type SCA
Neuropathy	1, 2, 3, 4, 18, 25, 38, 43, 46
Pyramidal signs	1, 3, 7, 8, 10, 14, 15, 17, 35, 40, 43
Dystonia	3, 14, 17, 20, 35
Myoclonus	14
Parkinson's syndrome	2, 3, 10, 14, 17, 19/22, 21
Tremor	12, 15, 27
Chorea	17, 27, DRPLA
Cognitive impairments	2, 8, 13, 17, 19/22, 21, 36, 44, DRPLA
Mental manifestations	2, 17
Ophthalmoplegia	2, 3, 28, 40
Visual disturbances	7
Fasciculations of the facial muscles and tongue	36
Ichthyosis	34
Epileptic seizures	10, 19/22, ATN1
Narcolepsy	DNMT1
Hearing disorder	31, 36, DNMT1

3.1.1. AD SCAs , due to pathologically increased trinucleotide repeats

Table 2. AD SCAs , due to pathologically increased nucleotide repeats.

Gene	Mutation	Disease	Clinical manifestations complementary to ataxia	Comment
<i>ATN1</i>	CAG (Gln) in exon 5, over 48 copies	DRPLA (Dentatorubral -pallidoluysian atrophy)	Chorea, dementia, myoclonus, epileptic seizures	- Expressed anticipation - The most common SCA in Japan - Diff. diagnosis with Huntington's chorea
<i>ATXN1</i>	CAG (Gln) In exon 8, over 39 copies	SCA1	Peripheral neuropathy, pyramidal signs, bulbar syndrome, cognitive impairment	More pronounced anticipation in parental inheritance
<i>ATXN2</i>	CAG (Gln) in exon 1, over 33 copies	SCA2	↓ T-reflexes, dementia, neuropathy, delayed eye saccades	- More pronounced anticipation in parental inheritance - Founder effect in Cuba
<i>ATXN3</i>	CAG (Gln) in Exon 8, 60-87 copies	SCA3	Amyotrophy, fasciculations, sensory deficits, nystagmus, delayed saccadic eye movements, quadripylamidal syndrome, extrapyramidal syndrome, reduced life expectancy	- More pronounced anticipation in parental inheritance - Founder effect in Portugal - Also known as Machado-Joseph disease

<i>ATXN7</i>	CAG (Gln) in exon 1, over 36 copies	SCA7	Vision loss/ retinopathy, rapid progression, reduced life expectancy	• More pronounced anticipation in parental inheritance
<i>ATXN8</i>	CAG (Gln) in exon 1	SCA8	Slow progression, pathologically lively T-reflexes, reduced vibratory sense, early-onset cognitive impairments	• More pronounced anticipation in maternal inheritance
<i>ATXN8OS</i>	CAG (Gln) 3' UTR, 71-1300 copies			
<i>ATXN10</i>	ATTCT at intron 9, over 800 copies	SCA10	Epileptic seizures in some families	• More pronounced anticipation in parental inheritance • Ancestor effect in Mexico
<i>CACNA1A</i>	CAG (Gln) at Exon 7, 20-33 copies	SCA6	May begin as episodic ataxia, with slow progression, onset after 50, normal life expectancy	• Without anticipation
<i>TBP</i>	CAG or CAA (Gln) in exon 3, over 49 copies	SCA17	Cognitive impairments, chorea, dystonia, myoclonus, epileptic seizures	• Anticipation is common
BEAN1	TGGAA in intron 6	CZA31 (OMIM 117210)		• Common in Japan

NOP56	GGCCTG in intron 1, over 650 copies	SCA36	Tendon hyperreflexia, fasciculations, atrophy of the tongue	No definitive data on anticipation
PPP2R2B	CAG, 51- 78	SCA12 (OMIM 604326)	Action tremor in the fourth decade of life, cognitive/mental impairments, hyperreflexia, Parkinson's syndrome	No definitive data on anticipation

3.1.1.1. SCA1

It affects about 6% of AD SCA, with a higher relative incidence of 39-41% reported in Serbia, Russia and South Africa. It is also the most common form of SCA with AD type of inheritance in Bulgaria.

SCA type 1 is a neurodegenerative disorder caused by a pathologically increased CAG trinucleotide expansion in the coding region of the *ATXN1* gene localized in 6p22-p23. The normal number of trinucleotide CAG repeats is 6-42. Clinical manifestations are observed at CAG counts between 39 and 84. *ATXN1* is supposed to be involved in suppressing transcription and regulation of Notch and Capicua-controlled developmental processes. Penetrance is considered to be 100% by the age of 52 years. (Genis D. et al. 1995).

Clinical manifestations include progressive static, locomotor and dynamic ataxia, dysarthria, quadripylamidal syndrome and cognitive deficits. Oculomotor disorders include hypermetric saccades and nystagmus seen in the early stages of the disease. As the disease progresses, the saccades slow down and vertical gaze palsy develops, followed by horizontal gaze palsy. Dysphagia and swallowing disorders progress and may lead to aspiration pneumonia. Sensory disturbances of the paresthesia type are rarer, but about 50% of patients develop a disturbed vibratory sensation with preserved sensation of pain and temperature. Sphincter disturbances are mild and include urge urination and urinary incontinence. Cognitive impairments are mild and occur in about 20-30% of cases. Verbal memory and executive functions

are predominantly affected, which is more pronounced in comparison to SCA2 and SCA3. Mental retardation is only seen in major expansions and clinical onset before 15 years of age. Bulbar weakness, amyotrophies, and ophthalmoplegia are found in these early forms. Progression is more rapid in these patients. Very rarely diplopia, optic atrophy, choreic and dystonic hyperkinesias may be present and are seen in the advanced stages of the disease.

The time between onset of clinical manifestations and loss of independent gait averaged 6.0 years, which was faster compared with SCA2 and SCA3. Gender did not play a determinant role in the rate of progression.

In some of the patients the ENG showed evidence of sensory axonal polyneuropathy. In patients with SCA, MEPs showed evidence of central and peripheral conduction time prolongation. On the other hand, VEPs and CAEPs in rare cases showed nonspecific changes.

MRI of the brain showed evidence of atrophy of the cerebellar vermis, hemispheres, pons, medulla oblongata, and cervical spinal cord in a large proportion of patients, which correlated with the results of neuropathological examinations in which the main structures affected by neurodegeneration were Purkinje cells, *nucleus dentatus*, brainstem nuclei, *oliva inferior*, and *tractus spinocerebellaris*.

3.1.1.2. SCA2

Spinocerebellar ataxia type 2 is one of the most common polyglutamine (polyQ) diseases. This form accounts for about 15% of AD SCA and is the second most common form of AD SCA in the Bulgarian population.

It is due to a dominant overexpansion (over 32-33) of the trinucleotide CAG in the *ATXN2* gene. The normal number of CAG repeats in *ATXN2* is considered to be 13-31, with 22 being the most common number in healthy humans. When the expansion is greater than 31 CAG triplets, SCA 2 develops. In case of 32-33 triplets, ataxia with very late onset develops, as the most frequent number of repeats in patients is in the range 37-39. Very severe multisystem infantile forms of the disease are found in cases with CAG expansion greater than 200.

Moderately elevated numbers of these trinucleotide repeats - up to 34 - are also associated with the development of amyotrophic lateral sclerosis (ALS).

It is assumed that the ATXN2 protein is involved in iRNA processing, translation, calcium release from the endoplasmic reticulum, intracellular transport of the epidermal growth factor receptor, and neuronal homeostasis maintenance. Ataxin-2 is predominantly expressed in Purkinje cells, mesencephalon, *medulla oblongata*, *substantia nigra* neurons, and is localized in the Golgi apparatus/ endoplasmic reticulum. The mutant protein aggregates in the endoplasmic reticulum in the form of pathological inclusions.

Olivopontocerebellar atrophy is a typical feature of patients with SCA 2 in the setting of other AD ataxias, being detected early in the course of the disease. Significant atrophy of the cerebellum, pons and frontal cortex is present in autopsied patients.

Greater instability of CAG expansion in subsequent generations is found in the cases of paternal inheritance.

The disease onset is in adulthood, and the clinical presentation is not homogeneous. The main clinical manifestations include static, locomotor and dynamic ataxia and dysarthria. Pronounced delayed ocular saccades and sensorimotor polyneuropathy are seen in more than 50% of patients. Other clinical manifestations that may be seen in this form of the disease are pyramidal signs, extrapyramidal manifestations (dystonic hyperkinesias and Parkinsonian syndrome), peripheral motor neuron involvement, cognitive regression, and others.

ENG examination found a reduction of SNAP amplitudes, more pronounced in the upper extremities. SSEPs are absent or have prolonged latency times in a large proportion of patients. CAEPs are abnormal in more than 50% of patients with SCA2.

MRI of the brain reveals early olivopontocerebellar atrophy. PET shows evidence of glucose hypometabolism with pontocerebellar localization. Voxel-based morphometry demonstrates marked atrophy of the cerebellar hemispheres, vermis, pons, mesencephalon, and thalamus. Of the supratentorial structures, atrophic changes were found in the orbitofrontal, temporomesial, and insular cortex, as well as in primary somatosensory cortex.

3.1.1.3. SCA3

Also known as Machado-Joseph disease (MJD), SCA3 is the most common SCA worldwide, accounting for about 20% of patients with AD inheritance in the United

States and about 50% of those in Germany, Japan, Portugal, and Taiwan. There are no genetically verified patients in Bulgaria at this stage.

The disease is caused by a pathologically elevated number of CAG repeats in the coding region of the *MJD1* gene. Ataxin-3 is a small soluble protein that moves between the nucleus and cytoplasm. Normally, it is predominantly localized in the cytoplasm, whereas in injured neurons Ataxin-3 is localized in the nucleus. Its role is that of an enzyme that deubiquitinates the long chain of ubiquitin.

The disease onset age is highly variable from 5 to 70 years of age, and its manifestations include progressive ataxia, dysarthria, nystagmus, saccadic and delayed eye movements, and ophthalmoplegia. Facial atrophy, dystonic hyperkinesias, spastically increased muscle tone, and amyotrophies may also be present. Mild cognitive impairment is found without reaching moderate or severe dementia.

Survival averages 20-25 years after clinical onset.

MJD is classified into the following subtypes based on clinical manifestations: (Sequeiros J et al. 1993; Matsumura R et al. 1996):

"Type I" - with onset around 25 years of age, with most pronounced manifestation - spastically increased muscle tone, including rigidity, bradykinesia and mild ataxia

"Type II" - with ataxia and central motor neuron involvement.

"Type III" - with late onset ataxia, amyotrophy and areflexia

According to some authors, "Type IV" could also be differentiated, in which Parkinson syndrome is present.

This classification highlights the clinical heterogeneity of SCA3. In some cases, Parkinson syndrome is a most prominent manifestation and is responsive to DOPA therapy. Spastically increased muscle tone and neuropathy are more common, as compared to other AD SCA. Axonal neuropathy, associated with amyotrophy and fasciculations, is more typical in late onset. The severity of polyneuropathy correlates more with patients' age than with the number of repeats. Sleep problems are also very characteristic of the disease: behavioural disturbances during REM sleep, central sleep apnoea, excessive daytime sleepiness and restless legs syndrome.

MRI of the brain showed evidence of pontocerebellar atrophy and a dilated fourth ventricle. Basal ganglia lesions were also present, predominantly in patients with

marked extrapyramidal syndrome. The severity of MRI established changes correlates with the magnitude of CAG expansion.

3.1.1.4. SCA6

From an etiopathogenetic point of view this form of ataxia is channelopathy. The mutations are pathological expansions of 20-33 CAG repeats on chromosome 19p13.2-p13.1, where the *CACNA1A* gene, which encodes the $\alpha 1A$ subunit of the P/Q-type voltage-dependent calcium channel, is localized. This channel is highly expressed in the cytoplasm and nucleus of Purkinje cells, but also in the nuclei of neurons in cases of other degenerative diseases with pathological expansions. Mutations in this gene are also associated with episodic ataxia type 2 and familial hemiplegic migraine.

This form is considered to be milder than SCA 1-3 and 7, having its onset between 16 and 72 years of age with ataxia of stance and gait. According to some authors, the initial symptoms are diplopia, dysarthria, vertigo and lower limb pain. The disease is slowly progressive, mainly in terms of locomotor ataxia, dysmetria and dysarthria, with rare episodic exacerbations. Other manifestations are dysphagia, diplopia, nystagmus, abnormal vestibulo-ocular reflex, hyperreflexia, neuropathy, extrapyramidal manifestations (Parkinsonian syndrome, dystonia and blepharospasm, myoclonias), cognitive impairment, depression and fatigue. MRI was consistent with cerebellar atrophy.

3.1.1.5. SCA7

SCA7 accounts for between 1% and 11.7% of dominant forms of ataxia, with a higher prevalence in Scandinavian countries.

The disease is caused by a pathological expansion in the *ATXN7* gene, in which the normal number of repeats is 4 to 18. The anticipation is more pronounced in cases of paternal inheritance.

ATXN7 is a transcription factor with a critical role in chromatin remodeling at the level of acetylation and deubiquitination of histones.

Clinical onset is most often between the second and fourth decade of life, but can reach up to age 70.

Forms with onset in infancy are extremely severe, most often beginning between 3 months and 3 years of age, and the number of CAG repeats is over 100-150. Progression is rapid and fatal outcome occurs within a few months or years. Apart from ataxia, other manifestations include severe hypotonia, epileptic seizures,

myoclonus, dysphagia, cardiac involvement with structural abnormalities, mainly of the atrial septum, *ductus arteriosus*, heart failure, and hepatomegaly.

The classic phenotype, due to 50-55 CAG repeats, has onset predominantly in adolescence, combining visual disturbances with ataxia. Most commonly, the disease begins with a colour vision disturbance (blue-yellow dyschromatopsia), followed by a decrease in visual acuity (central vision involvement). Cerebellar dysfunction and pyramidal signs appear later in the course of the disease. The ocular fundi show pigmentary changes in the macular area - cone-rod dystrophy. Angiofluorography reveals hypopigmentations in the form of halo in the macula, also known as bull's-eye, are present in the setting of cone-rod dystrophy that disappear with disease progression. Macular atrophy and a white optic disc could also be present.

Cerebellar ataxia is associated with pyramidal signs, dysphagia, dysarthria, tongue atrophy, delayed eye saccades, external ophthalmoplegia, and in rare cases, hypoacusis. In a 1998 study, Benton et al. described psychoses, auditory hallucinations, delusions, and behavioural disturbances in association with extrapyramidal manifestations (orofacial dyskinesias, upper limb choreoathetosis, and dystonia). In case of repeat count between 36 and 43, the disease has late onset with ataxia being the most prominent manifestation and with very few or no retinal abnormalities.

When making the diagnosis, it is important to perform a detailed ophthalmologic evaluation, including fundoscopy, ERG, and fluorescein angiography to confirm cone-rod dystrophy. ENG and EMG revealed peripheral motor neuron involvement, which was also established by neuropathological studies. MRI was suggestive of atrophy of cerebellar atrophy and cervical myelopathy.

Due to progressive bulbar weakness, aspiration pneumonia is a frequent cause of lethal outcome.

3.1.1.6. SCA8

It is caused by bidirectional transcription at a locus on chromosome 13q21, involving a CTG expansion in the *ATXN8OS* gene and a complementary CAG expansion in the *ATXN8* gene. These variations lead to toxic effect at RNA and protein level.

Clinically, it develops as a slowly progressive ataxia with onset between 13 and 65 years of age, and the need to use mobility aids occurs around 20 years after onset.

Eye movement disorders are seen in moderately to severely affected patients. Quadripyramidal syndrome, myoclonus and athetosis in the upper limbs are also present. Vibratory sense is also disturbed in a small proportion of patients. Neuropsychological examinations reveal disturbances in attention and executive functions, as well as psychiatric disorders. Mental retardation is present with onset in childhood. Brain MRI showed evidence of atrophy of cerebellar hemispheres and vermis, with relatively preserved brainstem and cerebrum.

3.1.1.7. SCA10

It is differentiated in three aspects from other AD SCA: clinically it is a combination of ataxia and epilepsy; it is mainly prevalent in the Americas and genetically it is determined by a pathological pentanucleotide expansion (ATTCT) in the *ATXN10* gene.

The age of onset ranges from 10 to 49 years, with anticipation in subsequent generations. It begins with static, locomotor ataxia, dysarthria, the full expression of pancerebellar syndrome developing for a period of 5-10 years. Nystagmus, saccadic eye movements, pyramidal signs, and polyneuropathy are present. Initially, epilepsy was considered non-progressive and responsive to standard antiepileptic medications, but in some patients with progressive disease, the epileptic syndrome is difficult to control by and requires antiepileptic polytherapy in combination with vagus nerve stimulation or epileptic surgery.

3.1.1.8. SCA12

It is very common in North India, where it accounts for about 16% of all AD forms. It is caused by pathological trinucleotide expansion of CAG/CTG on chromosome 5q32, where the *PPP2R2B* gene is localized. It encodes multiple regulatory subunits of the trimeric phosphatase PP2A. The normal triplet length is 4-32, as more than 46 repeats is considered to indicate the development of a disease.

The first clinical manifestations are seen around 30 years of age with tremor in the upper limbs and head that increase with disease progression. In some patients, mild locomotor ataxia and dysarthria may be present at the onset of clinical manifestations. In some cases, mild neuropathy, facial myokymias, dystonias, Parkinsonian syndrome, pyramidal signs, dementia and dysphagia are seen alongside the ataxia and oculomotor manifestations of cerebellar involvement. In late stages,

manifestations of autonomic dysfunction are also present. MRI show evidence of cerebellar and cerebral atrophy. Diffusion tensor imaging (DTI) reveals microstructural changes in the cerebellar nuclei, cerebellar pathways, vestibular nuclei, and diffuse white matter injury.

3.1.1.9. SCA17

The disease has a complex and variable phenotype, in some cases overlapping with that of Huntington's chorea. This form is caused by abnormal CAG/CAA expansion in the TATA-box binding protein (*TBP*) gene on 6q. In contrast to other AD SCAs with pathological expansions, here the specific structure of the *TBP* gene does not lead to anticipation. SCA17 sometimes presents a diagnostic problem due to incomplete penetrance.

The age of onset is highly variable - between 3 and 60 years. The main clinical manifestations include ataxia and/or dementia, seen in about 73% of cases. Psychiatric disorders such as aggression, paranoia, euphoria and depression are also frequently reported. Choreic hyperkinesias are typical in this form of ataxia and because of the combination with psychiatric and cognitive impairments, SCA is included in the differential diagnosis of Huntington's chorea. SCA17 is also called Huntington's disease-like 4. Less frequently reported manifestations include epilepsy (20%), autonomic disorders (9%), apraxia (7%), and neuropathy (3%).

The main neuroradiological findings in SCA17 include: cerebral atrophy, cerebellar atrophy, linear hyperintense lesions in the putamen. Fluorodeoxyglucose PET detects reduction of glucose metabolism in the basal ganglia region in patients with SCA17.

3.1.1.10. SCA31

This disease has a high incidence in Japan, where it accounts for 8-42% of AD SCA. It is due to an insertion containing a pentanucleotide expansion (TGGAA)_n in the region of the overlapping introns of the *BEAN* gene and the *TK2* gene on 16q21-q22.

Clinically, it presents as a late-onset and pure form of ataxia with MRI evidence of cerebellar atrophy. Extrapyrmidal manifestations - facial dystonias and blepharospasm are rarely reported.

3.1.1.11. SCA36

The disease is caused by a GGCCTG hexanucleotide expansion (650-2,500) in the nucleolar protein 56 gene (*NOP56*). It is considered an RNA-mediated neurodegenerative disease due to RNA toxicity.

Apart from the slowly progressive pancerebellar syndrome, another major manifestation is peripheral motor neuron involvement. Well-expressed variations between different populations have been reported: atrophy and fasciculations of the limbs and tongue are found in 12% of French patients and 63% of Japanese patients, as the incidence increases with disease progression. Other manifestations are pyramidal signs, sensorineural hearing loss and mild cognitive impairment with predominant involvement of executive functions. MRI is suggestive of cerebellar atrophy.

3.1.1.12. Dentatorubral-pallidoluysian atrophy (DRPLA)

It is due to a pathological CAG expansion in the *ATN1* gene, which encodes atrophin-1, known as a member of a family of transcriptional corepressors involved in nuclear signaling.

DRPLA is an AD form clinically characterized by a combination of cerebellar ataxia, choreoathetosis, myoclonia, epilepsy, dementia, and mental disorders. The term was coined by Smith et al. when describing neuropathological changes involving marked neuronal loss within the dentatorubral-pallidoluysian systems in a sporadic patient.

It is characterized by pronounced clinical variability determined by the size of the expansion. In case of onset in adolescence, the main manifestations are as in progressive myoclonic epilepsy (ataxia, myoclonia, epilepsy and cognitive decline). Absences and myoclonic seizures are also found in this form. In case of onset after age 40, epileptic seizures are much rarer, but progressive ataxia, choreic hyperkinesias, and dementia place DRPLA in the differential diagnostic group of Huntington's chorea. In patients with small expansions (49-55), the clinical presentation includes pure pancerebellar syndrome. MRI reveals cerebellar atrophy and brainstem atrophy, with marked involvement of the pontine tegmentum.

3.1.2. AD forms not caused by pathological expansions

Table 3. AD SCA not caused by pathological expansions. In some of the genes there is also an autosomal recessive (AR) type of inheritance.

Gene	Mode of inheritance	Phenotype		Other clinical characteristics / Comments	Gene Review / OMIM
		Ataxia	Spasticity		
<i>AFG3L2</i>	AD	+	+	Ophthalmoparesis, ptosis, delayed eye saccades	SCA28 (OMIM 610246)
	AR				SCAR5 (OMIM 614487)
<i>CACNA1A</i>	AD	+	-		Episodic ataxia type 2 (OMIM 108500)
<i>ITPR1</i>	AD	+	-	Onset in adulthood, slow progression	SCA15/16 (OMIM 606658)
	AD	+	-	Congenital, non-progressive	SCA29 (OMIM 117360)
<i>KCNC3</i>	AD	+	-	Onset in adulthood, slow progression	SCA13
				Congenital, non-progressive	
<i>KCND3</i>	AD	+	-		SCA19/22 (OMIM 605411)
<i>PRKCG</i>	AD	+	-		SCA14
<i>TTBK2</i>	AD	+	+	Quadripyramidal syndrome, nystagmus and saccadic eye movements	SCA11
<i>TMEM240</i>	AD	+	-	Cognitive deficit	SCA21

<i>SPTBN2</i>	AD	+	-		SCA5 (OMIM 600224)
	AR				SCAR14 (OMIM 615386)
<i>PDYN</i>	AD	+	-	Dysarthria, delayed ocular saccades, positive pathological Babinski reflex and disturbed proprioception	SCA23
<i>EEF2</i>	AD	+	-	Dysarthria, nystagmus	SCA26
<i>FGF14</i>	AD	+	-	Orofacial dyskinesias, eye movement manifestations (nystagmus, dysmetric saccades, strabismus), psychiatric manifestations and cognitive impairment	SCA27
<i>ELOVL4</i>	AD	+	-	Erythrokeratoderma	SCA34
<i>TGM6</i>	AD	+	+	Nystagmus, delayed ocular saccades, central motor neuron involvement	SCA35

				(pseudobulbar paresis and lively T-reflexes).	
<i>ELOVL5</i>	AD	+	-		SCA38
<i>CCDC88C</i>	AD	+	-	Pathologically lively T-reflexes	SCA40
<i>TRPC3</i>	AD	+	-		SCA41
<i>MME</i>	AD	+	-	Sensorimotor polyneuropathy	SCA43
<i>FAT2</i>	AD	+	-		SCA45
<i>PLD3</i>	AD	+	-	Axonal sensory polyneuropathy	SCA46
<i>STUB1</i>	AD	+		Dysarthria, cognitive decline, depression and anxiety.	SCA48

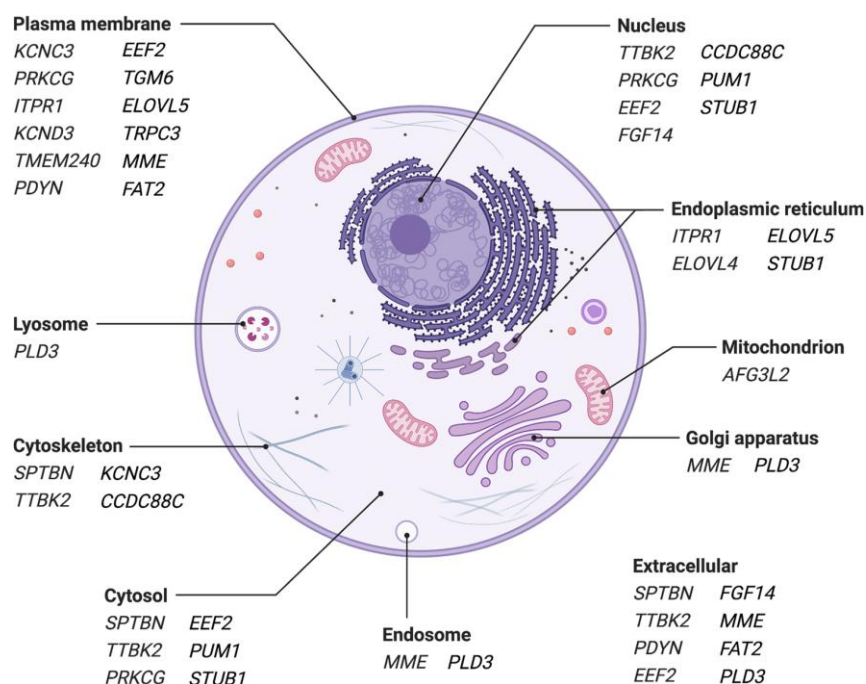


Figure 2. Localization of proteins whose dysfunction leads to the development of AD SCAs unrelated to pathological expansions.

3.1.2.1. SCA5

This form of AD SCA results from mutations in the *SPTBN2* gene encoding β -III-spectrin, which is expressed in Purkinje cells and cerebellar cortex. β -III spectrin binds to the Golgi apparatus and cytoplasmic vesicles and regulates glutamate signaling.

The main clinical manifestations of the disease include ataxia, dysarthria and nystagmus with onset in childhood and very slow progression, allowing patients to retain their ability to move independently. MRI of the brain shows evidence of cerebellar atrophy.

3.1.2.2. SCA11

The disease is caused by mutations in the *TTBK2* gene, which encodes a kinase that phosphorylates microtubule-associated tau protein, microtubule-associated protein 2 (MAP2), β -tubulin, CEP164, and the atypical kinesin KIF2A with localization in microtubules. It is also suggested that it is involved in the formation of primary cilia during embryogenesis. The mutant TTBK2 interferes with the normal protein with a dominant negative effect, leading to dysregulation of the processes described above.

TTBK2 is also expressed in other organs (bronchi, lung, smooth muscle, testes, fallopian tubes).

SCA 11 is a relatively benign form with late onset and slow progression associated with quadripyramidal syndrome, nystagmus and saccadic eye movements. MRI is suggestive of cerebellar atrophy.

3.1.2.3. SCA13

It is a relatively benign form, caused by mutations in the *KCNC3* gene located on chromosome 19. It encodes a potassium ion channel required for rapid repolarization of neurons. Kv3.3 binds to actin and stabilizes the cortical actin network. Mutations in this gene result in dysregulation of the duration and frequency of action potential generation and reorganization of Ca^{2+} ion channel function and calcium homeostasis of Purkinje cells.

The age of onset and severity of clinical manifestations are highly variable, even within one and the same family. Additional manifestations of the clinical phenotype include nystagmus, mild to moderate intellectual deficit, myoclonia, dysphagia, bradykinesia, and pathologically lively T-reflexes. The life expectancy of these patients is not limited. Neuroimaging examinations are suggestive of cerebellar atrophy and pons atrophy.

3.1.2.4. SCA14

SCA14 is the result of mutations in the *PRKCG* gene, which encodes protein kinase C γ (PKC γ), a member of the serine/threonine family of specific protein kinases that are activated by Ca^{2+} and diacylglycerol. This kinase is expressed in cerebellar and spinal cord neurons. One of the functions of *PRKCG* is phosphorylation of GRIN1/NMDAR receptors which makes it very important for synaptogenesis, synaptic plasticity, excitotoxicity and brain functions. This kinase is also involved in Purkinje cell maturation. Mutations in the *PRKCG* gene lead to increased Ca^{2+} entry into cells and impaired calcium homeostasis. Subsequently, this leads to disturbance in synaptic differentiation, neuronal degeneration, and abnormal Purkinje cell functions.

This form of ataxia has a slow progression and is associated with dysarthria and nystagmus. Myoclonus, tremor, dystonia, depression and cognitive impairment may be present in some cases. Neuroimaging examinations show evidence of marked cerebellar atrophy.

3.1.2.5. SCA15

The disease is caused by mutations in the *ITPR1* gene, which encodes a receptor known as inositol 1,4,5-trisphosphate receptor type 1. It is localized on the surface of intracellular membranes such as that of the endoplasmic reticulum and mediates calcium release following stimulation by inositol 1,4,5-trisphosphate. High calcium concentrations determined by mutations in *ITPR1* are cytotoxic and lead to Purkinje cell degeneration.

SCA15 (former name SCA15/16) is a slowly progressive form in which ataxia is associated with nystagmus, saccadic eye movements, dysarthria and dysphagia. In some patients a mild cognitive impairment is also found. The age of onset is variable, with MRI evidence of cerebellar atrophy with more severe involvement of the vermis, however, with no changes in the region of the brainstem.

3.1.2.6. SCA18

It was described in a Dutch family as a slowly progressive sensorimotor polyneuropathy with ataxia. Locus 7q22-q32 was identified by linkage analysis, but no specific gene has yet been identified.

3.1.2.7. SCA19

The disease is caused by mutations in the *KCND3* gene, encoding the Kv4.3 potassium ion channel expressed in the heart, the brain and a number of other tissues. Mutations in the gene disrupt the function of the channel, but how this leads to neurodegeneration is not yet clear.

SCA19 is a mild and slowly progressive ataxia associated with myoclonus, tremor, dysarthria and oculomotor disorders. In the more severe phenotype, Parkinson syndrome, epilepsy and cognitive impairment are present. Neurodegeneration is found in the vermis and Purkinje cells.

3.1.2.8. SCA20

SCA20 is only clinically defined, manifesting as slowly progressive ataxia and dysarthria that could precede ataxia and be combined with palatal tremor and dysphonia. CT scan shows no findings of calcifications in the region of *nucl. dentatus*. MRI of the brain shows findings of cerebellar atrophy without involvement. A 260-kb

duplication in 11p13-q11 is considered to cause the disease, but the exact gene has not yet been identified.

3.1.2.9. SCA21

It is caused by mutations in the *TMEM240* gene, encoding transmembrane protein 240, highly expressed in the frontal cortex and the cerebellum. The exact function of the protein is still under investigation. SCA21 is a slowly progressive ataxia combined with cognitive impairment, dysarthria, and akinesia with clinical onset in childhood. Neuroimaging examinations show findings of cerebellar atrophy.

3.1.2.10. SCA23

The disease is caused by mutations in the *PDYN* gene, which encodes proto-dynorphin, which after proteolysis leads to the formation of the opioid peptides β -neo-endorphins, dynorphin A and dynorphin B, enkephalins, and rimorphins. Dynorphin A and dynorphin C are localized predominantly in Purkinje cells. Dynorphin A (DynA) is neurotoxic and stimulates neurodegeneration via glutamate receptors. SCA23 is a late form of ataxia with slow progression associated with dysarthria, delayed ocular saccades, positive pathological Babinski reflex and disturbed proprioception. Neuropathologic examinations demonstrated neurodegeneration of Purkinje cells, *nucleus dentatus*, and *olivae inferiores*, as well as demyelination of the posterior and the lateral spinal cord columns.

3.1.2.11. SCA25

It has been described in one family, being inherited in the AD pattern with incomplete penetrance. The main clinical manifestations include ataxia, nystagmus, saccadic eye movements, muscle hypotonia and sensory neuropathy. The age of onset is highly variable from 17 months to 39 years, and patients have MRI findings of cerebellar atrophy. Linkage analysis linked this form to 2p21-p13, with no specific gene.

3.1.2.12. SCA26

The locus identified in SCA26 is on 19p13.3, where the *EEF2* gene is located. It encodes translation elongation factor 2 (eEF2), which facilitates GTP-dependent translocation of retinoid-tRNA from the A-(aminoacyl-) portion to the P-(peptidyl)-

portion of ribosomes. This form is late-onset one, where ataxia is associated with nystagmus, dysarthria, and cerebellar atrophy, according to MRI findings.

3.1.2.13. SCA27

It is due to mutations in the *FGF14* gene, which encodes a fibroblast growth factor highly expressed in cerebellar cells. In addition to its role as a growth factor, this protein is involved in the development of the nervous system, the regulation of the activity of voltage-dependent calcium channels, and synaptic plasticity. SCA27 is an early-onset, slow-progressing form with orofacial dyskinesias, oculomotor manifestations (nystagmus, dysmetric saccades, strabismus), psychiatric manifestations, and cognitive impairment as additional symptoms. Neuroimaging examinations reveal cerebellar atrophy and degeneration of the basal ganglia.

3.1.2.14. SCA28

The disease results from mutations in the *AFG3L2* gene encoding AFG3 Like Matrix AAA-a mitochondrial metalloprotease required for protein processing in mitochondria, calcium import, and neuronal development. This metalloprotease is selectively expressed in Purkinje cells. It has been suggested that mutations lead to a decrease in energy production and hence to cell death.

It is characterized by ataxia, ptosis, ophthalmoparesis, nystagmus, saccadic eye movements, pathologically lively T-reflexes and dysarthria. Brain MRI is suggestive of cerebellar atrophy.

3.1.2.15. SCA30

SCA30 is a relatively pure ataxia presenting slow progression, with onset in adulthood, associated with locus 4q34.3-q35.1, where the candidate gene *ODZ3* is found. This gene is known to encode the transmembrane protein teneurin 3, which is expressed in the brain.

3.1.2.16. SCA32

It has been described in Chinese patients. It is associated with locus 7q32-q33, with no specific gene identified. Clinical features include onset before 40 years of age, presenting with ataxia, cognitive deficits and azoospermia. MRI is suggestive of cerebellar atrophy.

3.1.2.17. SCA34

It is caused by mutations in the *ELOVL4* gene. ELOVL Fatty Acid Elongase 4, a membrane-bound protein of the endoplasmic reticulum, is involved in fatty acid biosynthesis by catalyzing the first step of elongation of long-chain fatty acids. The exact mechanism by which dysfunction of this protein leads to disruption of cerebellar function and skin lesions is still unknown.

It is also known as ataxia with erythrokeratoderma, where skin problems usually disappear by the age of 24, and in some patients may not occur at all. The ataxia itself is of late onset, with additional manifestations being nystagmus, retinitis pigmentosa and weakened deep tendon reflexes. MRI shows findings of atrophy of cerebrum, cerebellum and pons.

3.1.2.18. SCA35

The disease results from mutations in the *TGM6* gene, which encodes transglutaminase 6. Glutaminases are Ca^{2+} dependent enzymes that bind polyamines to proteins. SCA35 is a late-onset form (around the 5th decade of life) that slowly progresses over time and includes ataxia, nystagmus, delayed ocular saccades, central motor neuron involvement (pseudobulbar paresis, and lively T-reflexes). Brain MRI is suggestive of cerebellar atrophy.

3.1.2.19. SCA38

It is due to mutations in the *ELOVL5* gene, encoding ELOVL fatty acid elongase 5, which catalyzes the elongation of polyunsaturated fatty acids. It is expressed in the brain and endocrine glands. This form is pure and has a late onset and slow progression. Neuroimaging examinations show cerebellar atrophy.

3.1.2.20. SCA39

It is associated with duplication of 7.5 Mb in the long arm region of chromosome 11 (q21-22.3), however, no specific gene has been identified. The form has its onset in childhood. The ataxia is combined with spasticity in the lower limbs, dysarthria, strabismus, saccadic eye movements, mild mental retardation, and loss of independent gait in the 4th-5th decade of life. MRI is suggestive of cerebellar atrophy and leukoencephalopathy.

3.1.2.21. SCA40

It is associated with mutations in the *CCDC88C* gene, which encodes Coiled-Coil Domain Containing 88C (also known as KIAA1509). Mutations in this gene are supposed to lead to hyperphosphorylation of JNK (c-Jun N-terminal kinase) in cells and overexpression of *CCDC88C*. This disorder has a late onset and slow progression and is associated with oculomotor disorders, dysarthria and pathologically lively T-reflexes. Patients lose their independent gait within 17-18 years after disease onset. MRI shows findings of pontocerebellar atrophy.

3.1.2.22. SCA41

It is caused by mutations in the *TRPC3* gene, which encodes a receptor in the C3 cation channel. Dysfunction of this receptor results in impaired calcium homeostasis. In this form, a more pronounced locomotor ataxia is found associated with MRI evidence of cerebellar vermal atrophy.

3.1.2.23. SCA43

It is associated with mutations in the *MME* gene, which encodes membrane metalloendopeptidase (Neprilysin). This peptidase is expressed in various tissues and inactivates various proteins, such as Met-enkephalin and Leu-enkephalin, angiotensin-(1-9), amyloid-beta (A β) and atrial natriuretic factor (ANF), and brain natriuretic factor (BNP(1-32)). The exact mechanisms by which mutations in this gene lead to neurodegeneration are not fully understood. In SCA43, ataxia is combined with sensorimotor polyneuropathy, and brain MRI shows findings of cerebellar atrophy.

3.1.2.24. SCA45

This form is associated with mutations in the *FAT2* gene, encoding the integral membrane protein FAT atypical cadherin 2, which has the function of a cell adhesion protein. It is involved in brain development by modulating the function of parallel fibres. SCA45 is a late form in which ataxia is not associated with other clinical manifestations and atrophy is more pronounced for the cerebellar vermis.

3.1.2.25. SCA46

Mutations in the *PLD3* gene are responsible for the disease. PLD3 catalyzes the hydrolysis of cell membrane phospholipids. SCA46 is a late-onset form in which ataxia is combined with sensory axonal neuropathy. The onset is in adulthood.

3.1.2.26. SCA47

It is associated with mutations in the *PUM1* gene encoding Pumilio RNA Binding Family Member 1. This is an RNA-binding protein that plays a role in a number of processes regulating neuronal function. PUM1 binds to ATXN1 and maintains normal levels of ATXN1. Decreased binding of PUM1 to ATXN1 results in increased levels of ataxin with subsequent intracellular precipitation. The phenotypes of SCA type 1 and SCA type 47 largely overlap. SCA47 is a form with a variable age of onset from childhood to adulthood. Cognitive deficits, epilepsy, spasticity and visual disorders are present in some of the affected persons. Neuroimaging examinations reveal atrophy of the cerebellar vermis.

3.1.2.27. SCA48

It develops as a consequence of mutations in the *STUB1* gene localized on 16p13.3. *STUB1* encodes STIP1 homology and U-box containing protein 1. Among other functions, this protein is involved in the degradation of ATXN3. SCA48 manifests with onset in adulthood with ataxia, dysarthria, cognitive decline, depression and anxiety. Brain MRI shows findings of atrophy of the posterior part of the cerebellar vermis.

3.2. Autosomal recessive cerebellar ataxias

There is no uniform classification of AR cerebellar ataxias.

They are defined as diseases in which cerebellar motor syndrome is present, together with static locomotor ataxia, dysmetria and adiadochokinesia, nystagmus and dysarthria associated with cerebellar degeneration, established by neuroimaging examinations or as a pathological anatomical finding. When a mutation in a gene is identified, it must be described in at least two unrelated families. Malformative syndromes and diseases with a complex phenotype, in which ataxia is a late or secondary feature, are excluded.

Table 4 presents the most common AR cerebellar degenerations with their underlying genetic defects and main clinical symptoms.

Table 4. Clinical characteristics and genetic defects in AR HCA

Disease	Gene	OMIM	Onset	Additional clinical manifestations and features from neuroimaging examinations
Ataxia-telangiectasia (A-T)	<i>ATM</i>	208900	Childhood	Telangiectasia, oculomotor apraxia, photosensitivity, immunodeficiency, increased risk of neoplasms, elevated α -fetoprotein levels, cerebellar atrophy
Ataxia-telangiectasia-like diseases (ATLD)	<i>MRE11</i>	604391	Childhood	Oculomotor apraxia, MRI findings of cerebellar atrophy
ATLD2	<i>PCNA</i>	615919	Childhood	Telangiectasia, decreased hearing, photosensitivity, cognitive deficits, short stature, MRI findings of cerebellar atrophy
Ataxia-oculomotor apraxia 1 (AOA1)	<i>EAOH</i> <i>APTX</i>	208920	Childhood	Oculomotor apraxia, cognitive deficit, hypoalbuminemia, hypercholesterolemia, cerebellar atrophy
AOA2	<i>SETX</i>	606002	Adolescence	Polyneuropathy, pyramidal signs, oculomotor apraxia, head tremor, dystonia, elevated alpha-fetoprotein levels, cerebellar atrophy
AOA3	<i>PIK3R5</i>	615217	Adolescence	Oculomotor apraxia, sensorimotor polyneuropathy, MRI findings of cerebellar atrophy
AOA4	<i>PNKP</i>	616267	Childhood	Dystonia, oculomotor apraxia, polyneuropathy, cognitive deficit, MRI findings of cerebellar atrophy

Cerebrotendinous xanthomatosis (CTX)	<i>CYP27A1</i>	213700	Childhood	Dementia, pareses, tendon xanthomas, atherosclerosis, cataracts, elevated cholestanol levels, MRI findings of cerebellar atrophy, cerebellar and cerebral leukoencephalopathy
Ataxia with vitamin E deficiency (AVED)	<i>TTPA</i>	277460	Adolescence	Retinitis pigmentosa, head titubation, low serum vitamin E levels, MRI findings of spinal cord atrophy, absence of cerebellar atrophy
Friedreich's ataxia (FRDA)	<i>FXN</i>	229300	Childhood-adolescence	Pyramidal signs in the setting of positive Babinski reflex, scoliosis, hypertrophic cardiomyopathy, sensory axonal neuropathy, MRI findings of spinal cord atrophy, absence of cerebellar atrophy
AR spastic ataxia of Charlevoix-Saguenay (ARSACS)	<i>SACS</i>	270550	Neonatal period or childhood	Spastic paraparesis, <i>pes cavus</i> , MRI findings of cerebellar atrophy, linear hypointense T ₂ lesions in pons
Spinocerebellar ataxia with axonal neuropathy 1 (SCAN1)	<i>TDP1</i>	607250	Adolescence	Axonal sensorimotor polyneuropathy, distal muscle atrophy, hypercholesterolemia, MRI findings of cerebellar atrophy
Cayman ataxia	<i>ATCAY</i>	601238	Neonatal	Psychomotor retardation, hypotonia, strabismus, MRI findings of cerebellar hypoplasia
Sensory ataxia, neuropathy, dysarthria and ophthalmoplegia (SANDO) and mitochondrial recessive ataxia (MIRAS/SCAE)	<i>POLG1</i>	607459	Adulthood Childhood or adolescence	SANDO - sensory ataxia, ophthalmoparesis, myoclonus, ptosis, MRI findings of cerebellar atrophy, white matter lesions MIRAS - cerebellar and sensory ataxia, epilepsy, migraine, myoclonus, MRI confirmed lesions in cerebellar white matter and thalamus

Disequilibrium syndrome, cerebellar ataxia, mental retardation with or without quadrupedal locomotion 1 (DES, CAMRQ1)	<i>VLDLR</i>	224050	Neonatal	Nonprogressive cerebellar ataxia, mental retardation, hypotonia, strabismus, quadrupedal locomotion, MRI findings of hypoplasia of the inferior cerebellum, pachygyria
Cerebellar ataxia, mental retardation with or without quadrupedal locomotion 2 (CAMRQ2)	<i>WDR81</i>	610185	Neonatal	Quadrupedal locomotion, cognitive deficits, MRI findings of hypoplasia of the cerebellum and corpus callosum
CAMRQ3	<i>CA8</i>	613227	Neonatal	Mild mental retardation, quadrupedal locomotion, MRI findings of cerebellar atrophy and white matter lesions
CAMRQ4	<i>ATP8A2</i>	615268	Neonatal	Cognitive deficit, quadrupedal locomotion, MRI findings of cerebellar atrophy
Spinocerebellar ataxia with onset in infancy (IOSCA/MTDPS7)	<i>C10orf2</i>	271245	Neonatal	Athetosis, hypotonia, optic atrophy, ophthalmoplegia, incipient hearing loss, epilepsy, hypogonadism, hepatic involvement, MRI findings of moderate atrophy of the brainstem and cerebellum
Marinesco-Sjögren syndrome (MSS)	<i>SIL1</i>	248800	Childhood age	Cataracts, mental retardation, myopathy, short stature, MRI findings of cerebellar atrophy
Dilated cardiomyopathy with ataxia (DCMA/MGCA5)	<i>DNAJC19</i>	610198	Neonatal	Dilated cardiomyopathy, non-progressive cerebellar ataxia, mental retardation, testicular dysgenesis, anaemia, high levels of urinary 3-methylglutaconate acid, infantile onset
AR cerebellar ataxia 1 (ARCA1)	<i>SYNE1</i>	612016	Adulthood	Pure cerebellar ataxia, cognitive deficit, pyramidal signs, MRI findings of cerebellar atrophy

ARCA2	<i>ADCK3</i> (<i>CABC1</i>)	612780	Childhood	Exercise intolerance, epilepsy, myoclonus, cognitive deficits, MRI findings of cerebellar atrophy, glial foci
ARCA3	<i>ANO10</i>	613728	Adolescence or adulthood	Cognitive deficit, downbeat nystagmus, MRI findings of cerebellar atrophy
Seizures, sensorineural deafness, ataxia, mental retardation, and electrolyte imbalance (SeSAME)	<i>KCNJ10</i>	612780	Neonatal	Epilepsy, reduced hearing, mental retardation, tubulopathy, electrolyte imbalance, MRI without cerebellar atrophy
Combined cerebellar and peripheral ataxia with hearing loss and diabetes mellitus (ACPHD)	<i>DNAJC3</i>	616192	From childhood to adulthood	Diabetes mellitus, central motor neuron involvement, deafness, MRI findings of generalized supratentorial and infratentorial brain atrophy
Ataxia with hypogonadism	<i>RNF216</i>	212840	From childhood to adulthood	Hypogonadotropic hypogonadism, dementia, chorea, MRI findings of cerebral and cerebellar atrophy
Spastic Ataxia 4 (SPAX4)	<i>MTPAP</i>	613672	Childhood	Spastic paraparesis, optic atrophy, cognitive deficit
PHARC	<i>ABHD12</i>	612674	Adolescence	Sensorimotor polyneuropathy, cataracts, reduced hearing, MRI findings of variable cerebellar atrophy
Spinocerebellar ataxia – AR 11 (SCAR11)	<i>SYT14</i>	614229	Adulthood	Psychomotor retardation, MRI findings of cerebellar atrophy
SCAR13	<i>GRM1</i>	614831	Neonatal	Cognitive deficits, pyramidal signs, short stature, epileptic seizures, MRI findings of cerebellar atrophy
Salih ataxia/ SCAR15	<i>KIAA0226</i>	615705	Childhood	Epilepsy, mental retardation, MRI findings of absence of cerebellar atrophy

SCAR7	<i>TPP1</i>	609270	Childhood	Pyramidal signs, involvement of posterior (inferior) cerebellar peduncles, tremor, MRI findings of cerebellar and pontine atrophy
SCAR18	<i>GRID2</i>	616204	Neonatal	Psychomotor retardation, retinal dystrophy, MRI findings of cerebellar atrophy
SCAR16	<i>STUB1</i>	615768	Variable	Pyramidal signs, neuropathy, hypogonadism, MRI findings of cerebellar atrophy
SCAR12	<i>WWOX</i>	614322	Neonatal to childhood	Epilepsy with GTCS, mental retardation, spasticity, MRI findings of cerebral and cerebellar atrophy
SCAR20	<i>SNX14</i>	616354	Neonatal	Mental retardation, reduced hearing, macrocephaly, dysmorphism, MRI findings of cerebellar atrophy
SCAR17	<i>CWF19L1</i>	616127	Neonatal	Mental retardation, MRI findings of cerebellar hypoplasia
LIKNS/SCAR19	<i>SLC9A1</i>	616291	Childhood	Deafness, MRI findings of vermal atrophy
SCAR2	<i>PMPCA</i>	213200	Neonatal	Non-progressive cerebellar ataxia, cognitive deficit, short stature, MRI findings of cerebellar atrophy
SCAR21	<i>SCYL1</i>	616719	Childhood	Liver failure, neuropathy, mild cognitive deficit, MRI findings of cerebellar atrophy, thinning of the optic nerve (<i>n. opticus</i>)
SCAR22	<i>VWA3B</i>	616948	Adulthood	Cognitive deficits, pyramidal signs, MRI findings of cerebellar atrophy and thin <i>corpus callosum</i>
SCAR23	<i>TDP2</i>	616949	Childhood	Tonic seizures, cognitive deficit, dysmorphism
SCAR24	<i>UBA5</i>	617133	Childhood	Cataracts, neuropathy, MRI findings of cerebellar atrophy
Cerebellar ataxia with mental retardation	<i>THG1L</i>	-	Childhood	Psychomotor retardation, pyramidal signs, MRI findings of cerebellar vermis hypoplasia

Table 5. Other AR diseases, presenting with ataxia as a prominent symptom, included in the differential diagnoses of AR HCA.

Disease	Gene	OMIM	Additional clinical manifestations and features from neuroimaging examinations
Abetalipoproteinemia	<i>MTTP</i>	200100	Impaired intestinal fat absorption, hypercholesterolemia, hypotriglyceridemia, acanthocytosis, Friedreich's-like ataxia, neonatal onset, absence of cerebellar atrophy established via MRI
Niemann-Pick disease type B	<i>SMPD1</i>	607608	Hepatosplenomegaly, interstitial lung disease, dyslipidaemia, ataxia, neuropsychological development delay, thrombocytopenia
Niemann-Pick disease type C	<i>NPC1</i> <i>NPC2</i>	257220 607625	Vertical supranuclear ophthalmoplegia, ataxia, hepatomegaly, splenomegaly, variable age of onset, cerebellar atrophy and cerebral atrophy, and white matter lesions established via MRI
Refsum disease	<i>PAHX</i>	266500	Retinitis pigmentosa, polyneuropathy, ataxia, hyperproteinorachia, anosmia, decreased hearing, ichthyosis, onset in adolescence, elevated levels of serum phytic acid, no MRI findings of cerebellar atrophy
Late-onset form of GM2 gangliosidosis (Tay-Sachs and Sandhoff)	<i>HEXA</i> <i>HEXB</i>	272800 268800	Ataxia, dysarthria, cognitive deficits, extrapyramidal manifestations, adult onset, MRI findings of cerebellar atrophy
SPARCA1/ allelic to SCA5	<i>SPTBN2</i>	615386	Ataxia, cognitive deficits, oculomotor disorders, onset in infancy, cerebellar atrophy
SPAX5/ allelic to SCA28	<i>AFG3L2</i>	614487	Ataxia, spasticity, oculomotor apraxia, myoclonic epilepsy, neuropathy, dystonia, optic atrophy, onset in infancy, MRI findings of cerebellar atrophy
Boucher-Neuhäuser syndrome (BNS) / Gordon Holmes syndrome	<i>PNPLA6</i>	215470	Ataxia, hypogonadotropic hypogonadism, chorioretinal dystrophy, lively T-reflexes, onset in infancy, MRI findings of cerebellar atrophy and pontine atrophy

Gillespie syndrome /allelic to SCA15/SCA 29	<i>ITPR1</i>	206700	Nonprogressive cerebellar ataxia, iris hypoplasia, cognitive deficit, neonatal onset MRI findings of progressive cerebellar atrophy
SPAX2/SPG58	<i>KIF1C</i>	611302	Spastic paraparesis, cerebellar ataxia, onset in childhood or adolescence, MRI findings of lesions in the white matter of <i>capsula interna</i>
SPG7	<i>SPG7</i>	607259	Spasticity, pyramidal signs, ataxia, optic neuropathy, ptosis, onset in adolescence or adulthood, MRI findings of cerebellar atrophy
SPG5	<i>CYP7B1</i>	270800	Spasticity, cerebellar ataxia and sensory ataxia, onset in childhood or adolescence, MRI findings of cerebral white matter lesions
SPG11	<i>KIAA1840</i>	604360	Spasticity, ataxia, cognitive deficit, sensorimotor polyneuropathy, onset in childhood or adolescence, MRI findings of thin <i>corpus callosum</i> and lesions in the cervical myelon
SPG46	<i>GBA2</i>	614409	Cerebellar ataxia, spastic dysarthria, mild cognitive deficit, deafness, cataracts, onset in childhood, MRI findings of cerebellar atrophy and thin <i>corpus callosum</i>
Congenital disorder of glycosylation type 1a	<i>PMM2</i>	212065	Psychomotor retardation, axial hypotonia, abnormal eye movements peripheral neuropathy, congenital onset, MRI findings of cerebellar hypoplasia
LBSL	<i>DARS2</i>	611105	Cerebellar ataxia, tremor, spasticity, posterior column ataxia, axonal neuropathy, childhood to adult onset, MRI findings of lesions in white matter, brainstem and spinal cord
Mitochondrial complex IV deficiency	<i>COX20</i>	220110	Cerebellar ataxia, dystonia, sensory axonal neuropathy, onset in childhood or adolescence, MRI findings of cerebellar atrophy
Aceruloplasminemia	<i>CP</i>	604290	Diabetes, dementia, cerebellar ataxia, retinal degeneration, late onset, MRI findings of hypointense lesions in the thalamus, basal ganglia and <i>nucleus dentatus</i>

Neurodegeneration with brain iron accumulation type 2A and 2B	<i>PLA2G6</i>	256600	Cerebellar ataxia, psychomotor retardation, mental manifestations, axonal sensorimotor polyneuropathy, onset in infancy to adolescence, MRI findings of cerebellar atrophy and iron accumulation in <i>globus pallidus</i>
Poretti-Boltshauser syndrome	<i>LAMA1</i>	615960	Nonprogressive ataxia, psychomotor retardation, onset in infancy, MRI findings of cerebellar dysplasia with cysts.
Posterior column ataxia with retinitis pigmentosa	<i>FLVCR1</i>	609033	Degeneration of the posterior columns, retinitis pigmentosa, childhood onset, MRI findings of signal abnormalities in the cervical myelon
Neuronal ceroid lipofuscinoses	<i>CLN5</i> <i>CLN6</i>	256731 601780	Psychomotor retardation, epileptic seizures, visual disturbances, onset in childhood or adolescence, MRI findings of cerebral or cerebellar atrophy
Sialic acid storage disease	<i>SLC17A5</i>	604369 269920	Hypotonia, cerebellar ataxia, mental retardation, neonatal to adult onset, MRI findings of cerebellar atrophy and demyelination
Joubert syndrome	<i>AHI1</i> , <i>ARL13B</i> , <i>CC2D2A</i>		Ataxia, hypotonia, neonatal respiratory disturbances, mental retardation, nephronophthisis, congenital onset, MRI findings of agenesis of the cerebellar vermis
Hartnup's disease	<i>SLC6A19</i>	234500	Pellagra, cerebellar ataxia, psychosis, aminoaciduria, early onset
Childhood ataxia with central nervous system hypomyelination (Vanishing white matter disease)	<i>eIF2B</i>	603896	Cerebellar ataxia with spasticity, rapid progression after head trauma or febrility, onset from infancy to adulthood, MRI findings of leukoencephalopathy

L-2-Hydroxyglutaric aciduria	<i>L2HGDH</i>	236792	Psychomotor retardation, epilepsy, macrocephaly, cerebellar ataxia, onset in infancy, MRI findings of subcortical leukoencephalopathy and cerebellar atrophy
GOSR2-associated myoclonic epilepsy	<i>GOSR2</i>	614018	Ataxia, myoclonic epilepsy, elevated levels of creatine kinase, onset in infancy, MRI findings of cerebellar atrophy and cerebral atrophy
Tremor-ataxia with central hypomyelination	<i>POLR3A</i>	607694	Tremor, cerebellar ataxia, cognitive decline, central motor neuron involvement, onset in childhood, MRI findings of hypomyelination, cerebellar atrophy and thin <i>corpus callosum</i>
Behr syndrome	<i>OPA1</i>	210000	Optic atrophy, neuropathy, gastrointestinal symptoms, onset in infancy or childhood, MRI findings of cerebellar atrophy
Hypomyelination with atrophy of the basal ganglia and cerebellum (H-ABC)	<i>TUBB4A</i>		Tremor, cerebellar ataxia, central motor neuron involvement, onset in childhood, MRI findings of hypomyelination, atrophy of basal ganglia and cerebellum

3.2.1. Friedreich's ataxia

Friedreich's ataxia (FRDA) is the most common inherited ataxia, occurring in an average of 1 in 40 000 people in Europe. There is a wide variation in incidence from 1 in 20 000 in south-western Europe to 1 in 250 000 in northern and eastern Europe.

It is due to a homozygous or double heterozygous mutation in the *FXN* gene. Approximately 96% of patients are homozygous carriers of a pathological GAA expansion in intron 1 of the gene. The normal number of GAA repeats is up to 36, while in patients this number ranges from 56 to 1300, the disease severity being more pronounced in the cases of larger expansions. 1-3% of patients are double heterozygotes with a point mutation or deletion on one allele.

The *FXN* gene comprises 5 exons and the frataxin protein it encodes consists of 210 amino acids. The N-terminal end is responsible for mitochondrial function, while the highly conserved C-terminal end is the active end. Dynamic mutations disrupt transcription processes and reduce rRNA and frataxin protein levels respectively. Point mutations in the gene lead to a stop codon with a synthesis of a non-functional and rapidly degrading protein.

Frataxin is synthesized in the cytoplasm as a precursor and transported into mitochondria where it is transformed into an active form by mitochondrial peptidase. Impaired function of this peptidase can disrupt frataxin maturation and lead to clinical manifestations similar to those of Friedreich's ataxia.

Mitochondrial dysfunction is one of the major pathogenetic mechanisms in Friedreich's ataxia. Frataxin localizes in the matrix and the inner mitochondrial membrane. High levels of iron, as well as reduced enzymatic activity (subunits of complexes I, II, III of the respiratory chain) have been found in the mitochondria of the cardiomyocytes. Similar changes are present in neurons. Detailed functional studies found that frataxin, together with other mitochondrial proteins, regulate active iron transport across the mitochondrial membrane. High iron concentrations increase free radical levels, leading to mitochondrial damage and apoptosis. In studies of skeletal muscle of patients, ATP levels are reduced. Increased iron levels in mitochondria in patients did not lead to changes in serum iron levels and serum ferritin levels.

Pathoanatomical examinations in FRDA patients revealed that the spinal cord had reduced posterior and lateral column volume, degeneration and gliosis in the dorsal columns, more pronounced in the *fasciculus gracilis*, spinocerebellar tracts, posterior roots, and pyramidal tracts distally, after their re-crossing in the medulla

oblongata, with relatively preserved proximal structures. There are degenerative changes and reduced numbers of large neurons in the spinal ganglia, Clarke's column cells in the posterior horns of the spinal cord, *nucleus dentatus*, and nuclei of VIII, X, and XII cranial nerves (CN). Degeneration of thickly myelinated nerve fibres was found with relatively preserved unmyelinated fibres. Cardiac involvement includes hypertrophic cardiomyopathy with iron deposits in myocytes and myocardial fibrosis.

The main clinical manifestations of Friedreich's ataxia result from involvement of the central nervous system, peripheral nervous system, heart, and endocrine pancreas.

The disease is classified as classic form with atypical forms with late onset - after 25 years of age and very late onset after 40 years of age. In atypical forms, systemic manifestations such as cardiomyopathy, diabetes and skeletal deformities are less common.

Friedreich's ataxia is a slowly progressive disorder with onset in the classic variant in childhood and adolescence (median: 15.5 years), presenting with static and locomotor ataxia, with a complex genesis due to sensory neuropathy, degeneration of the dorsal spinal cord columns, cerebellar and vestibular dysfunction. Loss of independent gait is observed on average around 11-15 years after the onset of the disease, most commonly in the third decade of life.

Other manifestations include dysarthria, areflexia (preserved tendon reflexes do not exclude Friedreich's ataxia), distal muscle weakness, hypotrophies and deformities, more pronounced in the lower limbs, disturbed deep sensation.

In about 20% of the patients, a decrease in vision due to optic atrophy is found. Oculomotor disturbances such as impaired fixation, square-wave jerks, and gaze-evoked nystagmus are common.

A progressive decrease in hearing is found. Auditory processing at the central level is disturbed, which is found within the disturbed CAEPs.

Autonomic disorders are more pronounced in the lower extremities.

Urge urination is seen in 23-41% of affected patients and is probably due to pyramidal damage.

Dysphagia is found in the more advanced stages of the disease, leading to aspiration pneumonia.

There are mild cognitive impairments affecting various domains, such as executive functions, attention, working memory, and visuospatial perception.

Of the systemic manifestations, hypertrophic cardiomyopathy is established before the age of 40. ECG in Friedreich's ataxia patients shows evidence of repolarization abnormalities, such as inverted T-wave, ST-segment depression or elevation. Typical echocardiographic findings include left ventricular hypertrophy and increased septal diameter and increased posterior wall diameter. The EF is reduced in about 20% of patients and continues to decrease over the course of the disease.

Diabetes mellitus is present in 8-49% of patients. Earlier onset and longer progression is associated with an increased risk of diabetes mellitus, which may begin acutely with ketoacidosis.

Scoliosis and foot deformities (pes cavus, hammertoe, pes planus) are very typical manifestations.

Somatic neurological status, neurophysiological examinations and genetic tests are of primary importance for making the diagnosis.

The diagnostic criteria for Friedreich's ataxia (according to A. Harding) are divided into the following groups:

1. Main criteria observed in over 95% of cases
 - Autosomal recessive inheritance
 - Onset before the age of 25
 - Progressive ataxia of limbs and gait
 - Absent patellar reflex and Achilles reflex
 - Extensor plantar response (Babinski reflex)
 - Conduction velocity along the motor fibres of *n. medianus* > below 40 m/s
 - Low or absent SNAP
2. Additional criteria observed in > 65% of cases
 - Dysarthria*
 - Pyramidal signs in the legs*
 - Missing hand reflexes*
 - Distal loss of joint and muscle sensation in the legs*
 - Scoliosis
 - Abnormal ECG
3. Other criteria observed in < 50% of cases
 - Nystagmus
 - Optic atrophy
 - Deafness

- Distal weakness and amyotrophy
- Pes cavus
- Diabetes mellitus

* After 5-10 years of disease progression these are found in all patients

A characteristic feature of FRDA patients is axonal sensory neuropathy, in which L. Santoro et al. found an inverse correlation between a higher number of GAA repeats and:

- Lower SNAP amplitude for *n. suralis* and *n. medianus*
- Smaller number of large fibres $>7\ \mu\text{m}$ than biopsy *n. suralis*

The conduction velocity along the motor fibres of the peripheral nerves is slightly slowed or is within normal limits. No pronounced dynamics of ENG parameters was observed in the course of the disease. With regard to the evoked potentials, the following were found:

- VEPs - progressive increase of latencies and decrease of amplitudes in the course of the disease
- CAEPs - disordered organization with low amplitude of potential V and prolonged interpeak latencies
- SSEPs - with extended central conduction time (N13-N20 interpeak latencies)

At transcranial magnetic stimulation, the central motor conduction time from small hand muscles is prolonged and MEPs amplitude is reduced, and these changes progress over the course of the disease.

The main diseases that are into the differential diagnosis of AF are:

- Ataxia with vitamin E deficiency
- Ataxia with coenzyme Q 10 deficiency
- Spastic ataxia of Charlevoix-Saguenay (ARSACS)
- Ataxia oculomotor ataxia type 1 and type 2
- Ataxia telangiectasia
- Mitochondrial ataxias due to mutations in the POLG gene
- A β -lipoproteinemia
- Refsum disease
- Late-onset Tay-Sachs disease
- Cerebrotendinous xanthomatosis
- Hereditary sensory and motor neuropathies

3.2.2. AR ataxias caused by impaired DNA repair: AOA1, AO2, AT and ataxia-telangiectasia-like syndrome.

3.2.2.1. Ataxia-telangiectasia (AT)

Ataxia-telangiectasia (AT) or Louis-Bar syndrome is a multisystem neurodegenerative disorder that combines ataxia, oculocutaneous telangiectasia, immunodeficiency with frequent upper respiratory tract and lung infections, radiosensitivity, premature aging, and increased risk of malignancies.

The disease is caused by mutations in the *ATM* gene on 11q22.3 (MIM 208900), encoding a serine-threonine kinase playing a crucial role in DNA repair processes. Cell cultures from AT patients showed sensitivity to ionizing radiation, chromosomal instability, shortened telomeres and defective DNA repair.

The incidence is estimated at 1-9/100 000, with morbidity ranging between 1/300 000 and 1/40 000.

Based on the clinical course, AT is classified into two main forms - classic and variant (Table 6).

The classic phenotype is the consequence of nonsense mutations in the *ATM* gene that completely lack a functional protein. It is characterized by static and locomotor ataxia with onset between 1 and 4 years of age, after normal early motor development. Children walk on time but gradually develop progressive ataxia, dysarthria and oculomotor apraxia. Because the clinical manifestations of ataxia do not progress significantly in the first 4-5 years, these patients are not infrequently diagnosed with the ataxic form of cerebral palsy. Subsequently, the impaired coordination intensifies over time to the extent that by the beginning of the second decade of their lives, patients with the classic phenotype lose independent gait. Oculocutaneous telangiectasias appear several years after the onset of ataxia, but their absence is not an exclusion criterion for the disease. Occasionally telangiectasia is seen on skin areas exposed to the sun - face and ears. Patients with AT may develop at any age involuntary movements - chorea, athetosis, dystonia, myoclonia, tremor. In rarer cases, hypokinesia, bradykinesia and hypomimia may be observed.

Hyporeflexia to areflexia, progressing from distal to proximal, is found secondary to axonal-type peripheral-stem injury of peripheral nerves.

Ocular disturbances include: oculomotor apraxia, horizontal and rotator nystagmus, hypometric saccades, saccadic intrusions, strabismus.

Cognitive deficits are identified in childhood and worsen over time, with non-verbal memory, arithmetic and executive functions being primarily affected.

About two-thirds of patients have Immunodeficiency with low levels of immunoglobulins (IgG, IgA, IgM and IgG subclasses), inability to form antibodies after live vaccine administration and infections, and lymphopenia with more severe T lymphocyte involvement. Sinopulmonary infections are common from infancy, and some patients also develop autoimmune or chronic inflammatory diseases as a consequence of immunodeficiency, not because of the lack of ATM protein.

The increased risk of neoplasms in patients younger than 20 years includes mainly leukemias and lymphomas, while older patients are also diagnosed with solid tumours (mammary gland, liver, stomach, esophagus).

Other manifestations include growth retardation, gonadal atrophy, delayed sexual development and insulin-resistant diabetes.

Fatal outcome occurs most often by the age of 30 as a result of respiratory failure or oncological diseases.

The main neuropathological features of the classic form of AT are diffuse degeneration or atrophy of the cerebellar vermis and cerebellar hemispheres, with involvement of Purkinje cells and, to a lesser extent, granulosal cells. MRI of the cerebrum in infancy shows no pathological changes, however diffuse cerebellar atrophy develops with disease progression, and no correlation has been established between imaging findings and severity of ataxia. In addition, lesions in the cerebral white matter, including deposits of hemosiderin and telangiectatic deep vessels, were found in older patients.

ENG shows findings of axonal sensorimotor polyneuropathy.

The AT variant is characterized by later onset, slower progression and/or incomplete phenotype. Mutations causing this form are missense or splice site mutations, in which a certain amount of ATM protein with residual function is synthesized. Involuntary extrapyramidal hyperkinesias are more pronounced than ataxia in the AT variant, with some patients showing no ataxia at all. Choreoathetosis or a combination of dystonia, chorea, and myoclonus are most commonly found in these patients. They mainly affect the face, neck and upper limbs. Static or postural tremor is found in a large proportion of patients. Affected patients can be divided into three main groups depending on the prominent phenotype: 1. patients with cerebellar ataxia and/or polyneuropathy, without or with minimal extrapyramidal manifestations;

2. patients with ataxia, polyneuropathy and extrapyramidal manifestations; 3. patients with extrapyramidal manifestations as the prominent symptom. Systemic manifestations are very mild but the risk of neoplasms is significantly increased. Oculomotor apraxia is not typical in these patients.

Oculocutaneous telangiectasias are found in about 50% of patients with the AT variant. Endocrine and pulmonary manifestations are extremely rare in this form. Reduced IgG2 and IgG4 levels are found in a minority of patients, and there may rarely be a history of more common upper respiratory tract infections in this group.

About 30% of affected patients have NCS changes, consistent with sensorimotor polyneuropathy, less frequently with findings of peripheral motor neuron damage.

Neuroimaging examinations may be normal, but cerebellar atrophy, lesions in the cerebral white matter, microhaemorrhages are also found in some cases.

Relatives of patients carrying one mutation are at increased risk of breast cancer, gastrointestinal tract cancer, and coronary artery disease, necessitating systematic follow-up.

Elevated serum alpha-fetoprotein levels are found in both forms of AT.

In Bulgaria, the AT variant has been described among Bulgarian- Muslims.

Diagnosis is based on clinical phenotype, ENG examinations, brain MRI, immunological and serum alpha-fetoprotein testing.

The differential diagnosis of the classic form of AT includes cerebral palsy, Friedreich's ataxia, AOA1, AOA2, and ataxia with vitamin E deficiency.

In the AT variant, the main differential diagnosis should be made with essential tremor and dystonias.

In patients with AT, regardless of the variant, systematic follow-up for neoplasms is essential.

Table 6: Comparative presentation of the classic form and the variant of ataxia - telangiectasia

Classic form of AT		Variant of AT
1-5 years of age	Onset	0-34 years of age
Static and locomotor ataxia	Initial symptoms	Varied - choreoathetotic hyperkinesias, resting tremor
+	Ataxia	+/-
+	Cerebellar dysarthria	+/-
+	Oculomotor apraxia	+/-
+	Nystagmus	+/-
+/-	Chorea and dystonia	+
+/- (25%)	Myoclonus	+/-
+	Tremor	+
8-10 years of age	Loss of independent gait	Wide variation
+ about 6 years of age	Ocular and cutaneous telangiectasias	Rarely
Growth retardation	Endocrine disorders	Rarely delayed sexual development
Absence of secondary sexual characteristics		

Diabetes mellitus		
T-cell leukemias, B-cell lymphomas, mammary, ovarian, gastric tumours, melanomas, etc.	Malignant neoplasms	T-cell leukemias, B-cell lymphomas, mammary, ovarian, gastric tumours, melanomas, etc.
Deficiency of IgA, IgG2 and IgG4	Immunodeficiency	Reduced levels of IgG2 and IgG4
+	Restrictive type respiratory failure	-
+	Elevated alpha-fetoprotein levels	+
Axonal sensorimotor polyneuropathy	EMG	Axonal sensorimotor polyneuropathy Anterior horn damage
Cerebellar atrophy	Brain MRI	Normal to cerebellar atrophy with more pronounced involvement of the vermis

Table 7. Syndromes of ataxia associated with involuntary extrapyramidal movements

	Involuntary movements						
Disease	Gene	Dystonia	Chorea	Myoclonus	Postural tremor	Other clinical manifestations	Laboratory findings
Ataxia telangiectasia	<i>ATM</i>	++	++	++	++	Immunodeficiency, increased risk of malignancy, oculomotor apraxia, telangiectasia	Increased serum alpha-fetoprotein (AFP) and CEA, IgG deficiency (subclasses 2 and 4)
Ataxia oculomotor apraxia 1 (AOA1)	<i>APTX</i>	++	++			Oculomotor apraxia, areflexia, sensorimotor polyneuropathy	Low serum albumin, elevated serum LDL and CK levels
Ataxia oculomotor apraxia 2 (AOA2)	<i>SETX</i>	+	+		+	Oculomotor apraxia, areflexia, sensorimotor polyneuropathy	Increased serum AFP levels

Friedreich's ataxia	<i>FXN</i>	+	+	+	+	Areflexia, pathological reflexes, scoliosis, pes cavus, reduced hearing, cardiomyopathy, diabetes mellitus, disturbed proprioception and vibratory sense, axonal sensory polyneuropathy	
Ataxia with vitamin E deficiency	<i>TTPA</i>	+			+	Areflexia, proprioception and vibratory sense; mild axonal sensory polyneuropathy	Low serum vitamin E levels

3.2.2.2. Ataxia oculomotor apraxia (AOA)

Includes a group of disorders with an AR type of inheritance whose main clinical features include ataxia, oculomotor apraxia and choreoathetosis. Two clinically overlapping forms, AOA1 and AOA2, are described. In recent years, form 3 and form 4 have also been described as ultra-rare forms (Table 4). Epidemiologically, in Europe, AOA2 is the second most common AR hereditary cerebellar ataxia after Friedreich's ataxia.

Despite the phenotypic similarity, these forms are due to mutations in different genes. AOA1 is caused by mutations (missense, nonsense, splice mutations, deletions and insertions) in the *APTX* gene localized on chromosome 9p13.3. The most common mutation observed in European populations is p.Trp279*. In the presence of at least one missense mutation, disease is of late onset and the phenotype is milder. *The APTX* gene encodes the protein aprataxin. Aprataxin is a nuclear protein with three distinct domains. It is involved in the processes of DNA repair and the protection of cells from the accumulation of toxic radicals that damage DNA and RNA.

AOA2 is caused by missense, nonsense, frameshift mutations and duplications in the *SETX* gene localized on chromosome 9q34. Dominant mutations in the *SETX* gene are associated with juvenile forms of ALS (ALS4) and tremor-ataxia syndrome. *The SETX* gene encodes a DNA/RNA helicase that is involved in DNA repair and RNA processing.

AOA1 has an onset between the ages 2 and 18 and presents with cerebellar ataxia, oculomotor apraxia, sensorimotor polyneuropathy with amyotrophy sometimes associated with dystonia, mental retardation, hypoalbuminemia, and hypercholesterolemia. The original descriptions of the disease include data of normal immunoglobulin and alpha-fetoprotein levels, however, with findings of abnormalities on a later stage. There is no evidence of chromosomal instability or increased risk of tumors.

Patients with AOA2 have a clinical onset of between the ages 10 and 22 years with ataxia, cerebellar atrophy, sensorimotor polyneuropathy, oculomotor apraxia, and elevated levels of immunoglobulins and alpha-fetoprotein. Oculomotor apraxia occurs in about 56% of patients. Other possible manifestations are pyramidal signs and movement disorders such as chorea and dystonia.

3.2.2.3. Cerebrotendinous xanthomatosis (CTX)

Cerebrotendinous xanthomatosis is an AR disease that also refers to inborn errors of lipid metabolism due to mutations in the *CYP27A1 gene* localized on 2q33-qter. This gene encodes the enzyme sterol 27-hydroxylase, the deficiency of which leads to reduced bile acid synthesis and subsequent accumulation of cholesterol and cholestanol in a number of tissues

The incidence among European populations is 2/100 000, with a median age of onset being 19 years, but the median age of accurate diagnosis is 10 years. Clinically, the disease presents with multiple organ involvement.

In childhood and adolescence, diarrhoea, tendon xanthomas, cataracts, early osteoporosis, atherosclerosis and respiratory failure occur. It is considered that early cataracts and xanthomas should assist in rapid diagnosis. Patients have reduced bone density despite normal vitamin D and calcium levels, as the pathogenesis of bone involvement is not fully understood.

In adulthood, progressive neurological symptomatology, such as ataxia, quadripylamidal syndrome, dystonia, neuropathy, is present. Psychiatric manifestations, such as behavioural disturbances, aggressive behaviour, hallucinations, suicidal attempts, are also described. Neuroimaging examinations show findings of cerebellar atrophy, lesions in the region of *nucl. dentatus* and confluent lesions in the cerebral white matter. Laboratory tests display high levels of bile acids and cholestanol. The patients also have low HDL, which correlates with their early-onset and severe atherosclerosis.

While clinical onset is around age 19, diagnosis is made around age 35, which is associated with a 16-year delay.

Early diagnosis is important because of treatment options with chenodeoxycholic acid (CDCA), which is known to normalize cholestanol levels and stabilize gastrointestinal and neurological manifestations. Other possible therapies to complement the effect of CDCA are vitamin E, liver transplantation, symptomatic treatment of epilepsy and depressive manifestations, botulinum toxin in dystonia. Surgical treatment of xanthomas may exacerbate ataxia and motor deficit and is not recommended.

3.2.2.4. Ataxia with vitamin E deficiency

Ataxia with vitamin E deficiency (AVED) clinically manifests in childhood or adolescence (most commonly between 5 and 15 years of age) with progressive ataxia, clumsiness, absence of deep tendon reflexes, and disturbed proprioception. Other manifestations include dysdiadochokinesia, dysarthria, head titubation, decreased visual acuity (due to retinitis pigmentosa and macular atrophy), and pyramidal signs. Psychotic episodes, intellectual decline and dystonia are described in some patients.

Laboratory tests show a normal lipid profile, with very low serum vitamin E concentrations. NCS are consistent with neuropathy, either pure sensory neuropathy (34%) or pure motor neuropathy (24%), or combination neuropathy (42%). On neuroimaging, cerebellar atrophy and periventricular hyperintense lesions were present in 50% of cases.

The main neuropathological changes that are found are:

- In the spinal cord - demyelination and dying back of the posterior columns, degeneration of neurons
- Neuronal lipofuscin accumulations in the cerebral cortex, thalamus, *corpus geniculatum laterale*, anterior and posterior horns of the spinal cord and spinal ganglia
- Loss of Purkinje cells

Patients are found to have homozygous or double heterozygous mutations in the *TTPA* gene, which encodes an alpha-tocopherol transfer protein required for the incorporation of alpha-tocopherol into lipoproteins secreted by the liver. Vitamin E is a fat-soluble antioxidant, and the exact mechanism by which vitamin E deficiency in the central nervous system leads to neurodegeneration is not yet known.

3.2.2.5 Disequilibrium syndrome - cerebellar ataxia, mental retardation with or without quadrupedal locomotion 1 (DES, CAMRQ1)

Genetically, it is a heterogeneous disorder that combines autosomal recessive cerebellar ataxia with moderate to severe mental retardation. Patients are lagging behind in their walking. The quadrupedal locomotion (four-legged gait) is considered a characteristic feature. Neuroimaging examinations show findings of cerebellar hypoplasia.

The disease is classified into three forms depending on the gene mutations found: CAMRQ1, CAMRQ2, CAMRQ3 and is associated with mutations in three

different genes: *VLDLR*, *WDR81* and *CA8*. It is typical for populations with high inbreeding - American Hutterites, families from Turkey, Iran, Saudi Arabia.

The VLDLR gene encodes a protein that is a member of the LRP (LDD-related protein) family, which includes apolipoprotein E receptor 2 (ApoER2), LDL receptor (LDLR), LRP and Megalin. These receptors mediate the endocytosis of extracellular ligands. Additionally, they are involved in a number of physiological processes, such as regulation of lipid metabolism, prevention of atherosclerosis, development of the nervous system, signaling and transport of nutrients and vitamins. In fact, *VLDLR* is involved in the Reelin signaling pathway that controls neuroblast migration in the cerebral cortex and cerebellum. *The WDR81* gene encodes a protein that interacts with WDR91 in an endosomal protein complex that inhibits PtdIns3 kinase and thereby regulates the transformation of early endosomes to late endosomes. The *CA8* gene encodes the carbonic anhydrase VIII that is a member of the zinc metalloproteinase family.

Disequilibrium syndrome due to mutations in the *VLDLR* gene has been described among Roma.

3.2.2.6. Marinesco-Sjögren syndrome (MSS)

It is characterized by ataxia with early onset, cerebellar atrophy, cataracts, mental retardation and myopathy. Hypergonadotropic hypogonadism, skeletal abnormalities and short stature are found as additional manifestations. Cataracts may appear later compared to motor and intellectual impairment. Myopathy is progressive, appearing in childhood. CPK levels are normal or slightly elevated.

It is caused by mutations of the *SIL1* gene, which encodes a glycoprotein of the endoplasmic reticulum that is involved as a co-chaperone in protein translocation, folding and degradation, as well as in stress responses.

The main differential diagnosis is congenital cataracts, facial dysmorphism, neuropathy syndrome (CCFDN).

3.2.2.7. AR cerebellar ataxia 1 (ARCA1)

It is also known as autosomal spinocerebellar ataxia 8 and synaptic nuclear envelope protein 1 (SYNE1) ataxia. It was first described in Quebec, Canada as a pure form of ataxia, and subsequently in France, Brazil and Japan. Subsequently, the clinical spectrum has been broadened by describing an association of the discoordination

syndrome with involvement of central and peripheral motor neurons. It is also included in the group of spastic ataxias. According to a multicenter study of *SYNE1* mutations, the age of onset is between 6 to 42 years (median: 14 years). In 50% of patients, onset included clinical manifestations unrelated to ataxia, such as facial muscle fasciculations, dysarthria, spastically increased muscle tone, and cognitive deficit. It is now accepted that mutations in the *SYNE1* gene are associated with ataxia plus phenotype. Neuroimaging examination reveal cerebellar atrophy.

3.2.2.8. Autosomal recessive spastic ataxia of Charlevoix-Saguenay (ARSACS)

It is a rare neurodegenerative disorder first described in Canadian patients from the Saguenay-Lac-Saint-Jean region in Quebec. Subsequently, cases have been reported worldwide, including Bulgaria.

In 2000, the *SACS* gene causing the disease was also identified. The gene encodes a protein called saxin, which is expressed in neurons, including Purkinje cells, pyramidal cells, pontine nuclei, and reticular formation cells. Most mutations are localized in exon 10, which is also the largest one. In the homozygous or double heterozygous state, they result in nonfunctional saxin synthesis or reduced protein synthesis. There is also marked phenotypic variability.

In the original descriptions, the clinical presentation of the patients was homogeneous, including gait disturbances from infancy, cerebellar ataxia, spastically increased muscle tone, neuropathy, distal hypotrophies, joint deformities, and hypermyelination of retinal nerve fibres on fundoscopy. Eye movements are also impaired. Although the onset is in childhood, in most cases intelligence is preserved. Ataxia and pes cavus are already pronounced on reaching the age of 20 years. The disease is slowly progressive, but during the second or third decade of life an acceleration of progression may be observed and patients may lose their independent gait by their fifth decade. Bladder and bowel control disorders also occur around the fifth decade of life. Atypical symptoms, such as mental retardation, progressive cognitive impairment, epilepsy, and sensorineural hearing loss, have also been described.

The neuroimaging studies reveal atrophy of the superior cerebellar vermis, cerebellar hemispheres, cervical spinal cord, and cerebral cortex. Finding of parallel, paramedian, hypointense T₂ lesions in the region of the pons and hyperintense lesions in the thalamic region are considered pathognomonic. DTI in these patients reveal demyelination and axonal degeneration, predominantly in the region of the pyramidal

tracts, together with indurated transverse pontine fibres and pyramidal pathway disruption at the level of the pons. These changes are probably caused by impaired mitochondrial functions due to loss of saxin.

NCS show findings of mixed axonal-demyelinating polyneuropathy.

Retinal nerve fibre layer thickening is a characteristic feature of ARSACS patients. Optical coherence tomography (OCT) is considered the main diagnostic method for this disease.

In addition, patients may have various biochemical disorders, such as impaired pyruvate oxidation, hyperbilirubinemia, reduced HDL levels.

Given the early onset and pyramidal symptomatology, cerebral palsy and early complicated forms of hereditary spastic paraplegia (HSP) should be included in the differential diagnostic considerations.

3.2.2.9. Autosomal recessive cerebellar ataxia type 3 (ARCA3) due to a mutation in the *ANO10* gene

Mutations in *the ANO10* gene encoding anoctamine 10 lead to the development of ARCA3. Anoctamin 10 (ANO10), also known as TMEM16 K, is a member of the family of anoctamins, which are cell- and tissue-specific calcium-dependent chloride channels. It has been implicated that it takes part in the regulation of cell excitability (Figure 3). Impaired calcium signaling in Purkinje cells is one of the major mechanisms leading to cerebellar ataxia.

The c.1150_1151delTT mutation is considered to cause the founder effect in Roma patients and has been described in Bulgaria and Serbia.

The main clinical manifestations of the disease are ataxia with marked cerebellar atrophy, gaze-evoked downbeat nystagmus and dysarthria with onset between 6 and 45 years of age. Pyramidal signs with findings of pathologically lively deep tendon reflexes are also present. The disease has a relatively slow progression, with patients retaining independent gait for more than 10 years after onset.

In rarer cases, mental retardation, cognitive impairment progression, epilepsy, cataracts and retinal degeneration are found.

NCS and EMG show findings of peripheral motor neuron damage in some of the patients.

Brain MRI shows findings of marked cerebellar atrophy and hyperintense lesions in the cerebellum on T₂ MRI scan.

The homozygous mutation c.1150_1151delTT determines an earlier onset compared to the other defects described in *ANO10*, *probably* determined by modifier genes.

Three families with mutations in *ANO10* were also found to have low levels of CoQ10 in muscle. This necessitates further elucidation of the relationship of *ANO10* and CoQ10 to calcium signaling and of the possibility CoQ10 administration to have a therapeutic effect in these patients.

3.2.2.10. SCAR13

Autosomal recessive spinocerebellar ataxia 13 (SCAR13) is an ultra-rare disorder caused by mutations in *the GRM1* gene, which encodes glutamate metabotropic receptor 1. This receptor is highly expressed in Purkinje cells, playing a major role in cerebellar development, cognition and synaptic plasticity. Mutations in this gene leading to ataxia were first described in a cohort of Bulgarian Roma patients.

Patients described to date have global developmental delay, moderate to severe early static and locomotor ataxia, dysarthria, mild dysdiadochokinesia, dysmetria and tremor, intellectual deficit, and mild pyramidal signs. Brain imaging shows progressive generalized cerebellar atrophy, inferior vermian hypoplasia, and in some cases, constitutionally small brain size.

3.2.2.11. Niemann-Pick disease type B (NPB)

Mutations in the *SMPD1* gene result in a deficiency of the acid sphingomyelinase enzyme, responsible for the breakdown of sphingomyelin to ceramide and phosphocholine and involved in the ceramide signaling pathway.

The phenotype of this enzyme deficiency represents a continuum including the Niemann-Pick disease forms type A, type A/B and type B. Patients with early-onset neurovisceral involvement and a life expectancy of 2-3 years are classified as type A, and those with late-onset, chronic visceral involvement with no or mild neurological involvement, are type B. In Niemann-Pick disease type A (NPA), the most common initial symptom is hepatosplenomegaly, established by the age of 3 months, with hypersplenism developing over time. Children develop by the age of 1 year, after which there is progressive cognitive decline. Swallowing disorders are established around 2 years of life, with alternating diarrhoea and constipation. Cherry-red spot or macular halo type changes are pathognomonic. These changes result from the accumulation

of lipids in the retinal ganglion cells that form a white ring around the red fovea. Children have frequent pulmonary infections due to sphingomyelin accumulation in lung macrophages and die before 3 years of age. NPB has a later clinical onset than NPA and manifests with progressive hepatosplenomegaly, impaired liver and lung function, osteopenia and an atherogenic lipid profile. CNS involvement is absent or mild. In the intermediate form NP A/B, the clinical presentation is highly variable, with neurological and psychiatric manifestations. These patients survive to adulthood.

In Bulgaria, Mihaylova V. et al. in 2007 described a large cohort of Roma patients with type B and type A/B NP due to homozygous W391G mutation in *SMPD1* in the setting of residual acid sphingomyelinase activity present. The clinical heterogeneity in terms of neurological involvement is interesting, ranging from subclinical retinal involvement to severe ataxia, cognitive deficits, and psychiatric manifestations.

3.2.2.12. Niemann-Pick disease type C (NPC)

It is an AR lysosomal disorder with an incidence of about 1/89,000 live births, caused by mutations in the *NPC1* gene (95% of cases, incidence 1/92,104) or the *NPC2* gene (5% of cases, incidence 1/2,858,998), with subsequent disruption of intracellular lipid transport. It is characterized by extreme clinical variability - from fatal neonatal forms due to severe hepatic involvement to late onset forms in adulthood with neurological or psychiatric symptoms as the prominent manifestations.

NPC1 encodes an endosomal transmembrane glycoprotein, whereas *NPC2* determines the synthesis of a small lysosomal protein with high affinity for cholesterol. Dysfunction of either of these proteins results in accumulation of GM2 and GM3 in cellular endosomes/lysosomes in the central nervous system and of unesterified cholesterol, sphingomyelin, glycosphingolipids and sphingosine in spleen and liver.

Certain structures of the central nervous system are damaged earlier and more severely in patients with NPC, which correlates with the prominent clinical manifestations. The decrease in Purkinje cell number is an early manifestation of the disease associated with the locomotor ataxia, dysarthria, and dysphagia that are typical in patients. Neurofibrillary degeneration, ectopic dendritogenesis and the formation of meganeurites in the cerebral cortex are responsible for the manifestation of epileptic seizures and cognitive deficit. Marked neuronal loss is found in the rostral interstitial nucleus of the *fasciculus longitudinalis medialis* controlling vertical eye

movements, whereas the paramedian pontine reticular formation associated with horizontal eye movements is relatively more preserved.

The clinical manifestations of the disease are characterized by extreme heterogeneity in terms of age of onset (from the perinatal period to the seventh decade of life) and life expectancy (from a few days after birth to over 70 years of age).

The clinical presentation leading to the diagnosis of the disease is based on the combination of visceral (hepatomegaly and/or splenomegaly), neurological and psychiatric manifestations.

Neurological manifestations include vertical and horizontal gaze palsy, apraxia of gaze, ataxia, dysarthria, dysphagia, dystonia, gelastic cataplexy, epileptic seizures, progressive dementia, and sensorineural hearing loss. Initially, there is a slowing of the vertical ocular saccades followed by the horizontal ones, with complete vertical gaze palsy most commonly present at diagnosis.

Mental symptoms and cognitive impairment were found in 45% and 61%, respectively, of patients with late-onset NPC without a specific profile. The most frequently observed manifestations were cognitive impairment with memory and executive function decline, psychomotor retardation, atypical schizophrenia-like manifestations and mood changes. Psychiatric manifestations include psychoses, depression, bipolar affective disorder or obsessive-compulsive disorder refractory to therapy.

Hepatomegaly and splenomegaly are common, but their absence especially in late-onset forms does not exclude the diagnosis of NPC. Pulmonary infiltrates occur in the childhood forms. Depending on the age of onset, NPC disease is classified into the following forms:

- Prenatal/perinatal form with onset before 3 months of age, presenting with *hydrops foetalis*, foetal ascites, prolonged icterus, hepatic and respiratory failure.
- Early infantile form with onset between 3 months and 2 years, characterized by hepatomegaly/splenomegaly, neuropsychological development delay, muscular hypotonia, hearing loss, vertical gaze palsy.
- Late infantile form with onset between 2 and 6 years of age, presenting with gait changes, clumsiness, frequent falls, speech delay, cataplexy and epilepsy, hearing loss and isolated organomegaly.

- Juvenile form with onset between 6 and 15 years of age, in which ataxia, epileptic seizures and cataplexy, cognitive impairment, sleep disturbances, expressive language disorders, hyperkinetic disorder, schizophrenia-like psychoses are present.
- Adult form - after the age of 15, characterized by ataxia, dystonia, vertical gaze palsy and oculomotor apraxia, dementia and psychiatric disorders, hearing loss and epileptic seizures occurring less frequently than with the early-onset forms.

Diagnosis of Niemann-Pick disease type C is based on clinical findings of neurovisceral involvement, neuroimaging findings, which may be normal or may identify hyperintense lesions in cerebral white matter on MRI T₂ scan, involvement of hippocampus, thalamus, striatum, corpus callosum in the infantile forms and progressive atrophy of the superior and anterior parts of the cerebellar vermis, thinning of the corpus callosum and mild general cerebral atrophy in adults, neuro-ophthalmological examination, electroencephalography, audiometry, electromyography, and abdominal ultrasonography.

An NPC Suspicion Index (<http://www npc-si.com/calculator>) tool has been developed to facilitate and expedite diagnosis of the disease. Based on this index, presented in Table 8, patients are divided into three broad groups:

- With a score < 40 points - patients at low risk for NPC (other causes of clinical symptoms should be sought first)
- With a score of 40-69 points - possible diagnosis requiring further follow-up and discussion of the patient
- With a score > 70 points – referral to a NPC centre for further biochemical, histological and genetic diagnostics is mandatory.

Routine laboratory tests such as standard biochemistry, lipid profile, urinalysis and cerebrospinal fluid are usually normal except in patients with hypersplenism and icterus. A screening indicator is the serum chitotriosidase test, the levels of which is also elevated in other lysosomal diseases (Gaucher's disease) and its increase is more significant in paediatric forms.

The diagnosis of Niemann-Pick disease type C is delayed by an average of 4.1 years from the onset of neurological manifestations, which significantly limits therapeutic options.

Table 8: Patients at increased risk of NPC

Clinical contingent at increased risk for NPC	Symptoms to look for
Ataxia	With an early onset (40 years ago)
	"Ataxia plus" impaired vertical eye saccades, dystonia, cognitive disorders, atypical mental disorders Possible - pyramidal signs and mental retardation
	Without neuropathy
	With unclear aetiology
Psychomotor retardation	Visceral manifestations (hepatosplenomegaly)
	Ataxia, dystonia, impaired vertical eye saccades
Dystonia	Generalized dystonia
	Age under 40
	"Dystonia plus" impaired vertical eye saccades, cognitive disorders, atypical mental disorders
Frontotemporal dementia	With onset earlier than 40 years of age
Early-onset atypical schizophrenia/psychosis	Therapy resistance
	Neurological symptoms - ataxia, dystonia, impaired vertical eye saccades
Visceral manifestations in the paediatric population	Isolated infantile splenomegaly or cholestasis or hepatomegaly or foetal

	neonatal ascites with neurological manifestations
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In risk groups, biomarker testing and subsequent genetic testing is important.

Biomarkers are the first step in screening at-risk populations (Table 9), and different biomarkers vary in their specificity and sensitivity.

Oxysterols are the most widely used biomarkers. Cholestane-3b,5a,6b-triol (C-triol) and 7-ketocholesterol (7-KC) are elevated in the plasma of patients with NPC. C-triol is more sensitive compared to 7-KC. These two biomarkers are also elevated in patients with NPA and NPB. Prolonged storage of samples may lead to false negative results due to cholesterol auto-oxidation, which requires control of sample collection and transport conditions.

Lysosphingomyelin-509 (Lyso-SM-509) and other lysosphingolipids

Lyso-SM-509 is elevated in the plasma of NPC and NP-A/B patients, and this biomarker is significantly increased in NP-A/B patients.

Bile acids

3b,5a,6b-trihydroxy-cholanoyl-glycine is examined in dried drop of blood, plasma and urine. It is elevated in NPC, NP-A/B, allowing differentiation of affected persons from carriers.

In patients with positive biomarkers, the diagnosis is proven by genetic testing and Philippin staining.

Although Philippin staining used to be considered the gold standard in the diagnosis of NPC, today it is mainly applied in the demonstration of the pathogenicity of novel gene defects in the *NPC1* gene and the *NPC2* gene, and in patients with one established mutation and a typical clinical presentation (Vanier MT et al. 2016).

In patients with clinical suspicion and a biomarker profile consistent with NPC, genetic testing is mandatory. Routine sequencing of the *NPC1* gene and the *NPC2* gene allows detection of 90% of mutations in both alleles.

The *NPC1* gene and the *NPC2* gene were included in the panels for early-onset ataxias, epilepsy, dystonia, infantile cholestasis, inborn errors of metabolism, organic psychoses, early-onset dementias, hepatomegaly, and psychomotor retardation.

Clinical variability and wide differential diagnosis of the disease are the main reasons for late diagnosis in NPC. Infantile forms should be differentiated from biliary

atresia, congenital infections, alpha-1 antitrypsin deficiency, tyrosinemia, and hematologic diseases (leukaemia, lymphoma, histiocytosis), other storage diseases (Gaucher disease, Niemann-Pick type A and B), chromosomal aberrations, congenital heart malformations, infectious diseases, Haemoglobinopathies in cases with *hydrops foetalis*. In the juvenile form, tumours in the midbrain and pineal gland, hydrocephalus, GM2 gangliosidosis, mitochondrial cytopathies, aminoaciduria, and organic acidopathies should be considered, as well as neuronal ceroid lipofuscinoses, ADHD, idiopathic torsion dystonia, dopa-sensitive dystonia, Wilson's disease, pseudodementia in depression, subacute sclerosing panencephalitis, HIV-associated encephalopathy. In late-onset forms, the disease should be differentiated from Alzheimer's disease, frontotemporal dementia, progressive supranuclear palsy, neurolues, HIV encephalopathy, primary psychiatric diseases.

3.2.2.13. Tremor-ataxia with central hypomyelination

POLR3-related leukodystrophies include various nosological entities, such as: hypomyelination, hypodontia, hypogonadotropic hypogonadism (4H syndrome); ataxia, delayed tooth eruption and hypomyelination (ADDH); tremor, ataxia and central hypomyelination (TACH); leukodystrophy and oligodontia (LO); and hypomyelination with cerebellar atrophy and hypoplasia of the corpus callosum (HCAHC).

POLR3A, *POLR3B*, *POLR1C*, *POLR3K* genes are (by interaction with *POLR3B*) responsible for RNA polymerase III (Pol III) synthesis. Mutations in these genes lead to the synthesis of abnormal transfer RNA, thereby impairing cell growth, differentiation and apoptosis.

This group of diseases are inherited in an AR manner, with their onset being in the neonatal period through childhood, varying in severity and affecting cerebral and extracerebral structures. The main clinical manifestations include ataxia, tremor, spastically increased muscle tone, cognitive impairment, dental abnormalities (delayed tooth growth, agenesis, abnormal shape and alignment), short stature, dysphagia, hypogonadotropic hypogonadism, progressive ocular abnormalities (myopia, optic atrophy). Myopia and short stature are present in about 50% of patients. Brain MRI reveals a combination of hypomyelination with T₂ hypointense lesions in the ventral thalamus, optic radiation, *globus pallidus*, *nucleus dentatus*, cerebellar atrophy and thin corpus callosum.

3.2.2.14. Boucher-Neuhäuser syndrome (BNS)

Mutations in the patatin-like phospholipase domain-containing protein 6 (PNPLA6) gene are the most common cause of two syndromes combining ataxia and hypogonadotropic hypogonadism: Boucher-Neuhäuser (BNS) and Gordon Holmes (GHS). Mutations in PNPLA6 can also lead to Laurence-Moon syndrome and Oliver-McFarlane syndrome, as well as in pure forms of ataxia.

PNPLA6 belongs to the family of patatin-like phospholipase-containing proteins. The phospholipid-esterase domain (EST) is altered upon organophosphate intoxication. The mutations described so far lead to disruptions in the enzymatic activity of the above-mentioned domain. In recent years, PNPLA6 has been added to the rapidly growing number of genes involved in lipid metabolism and leading to neurodegenerative diseases.

The main clinical features of BNS include early-onset ataxia, hypogonadotropic hypogonadism, visual disturbances due to retino-choroidal dystrophy, peripheral sensorimotor polyneuropathy and hypersegmented neutrophil granulocytes, whereas in GHS ataxia and hypogonadotropic hypogonadism are associated with marked pyramidal symptomatology in the absence of visual involvement. Less commonly, ataxia may also manifest later, in the third or fourth decade of life. Neuro-ophthalmologic manifestations can be variable, with changes in the fundus ranging from discrete with relatively preserved visual acuity to severe chorioretinal atrophy with vision impairment. The electroretinograms are abnormal with photopic and scotopic responses.

3.3. X-linked cerebellar ataxias

To this group we refer the fragile X-associated tremor/ataxia syndrome. The disease is caused by a pathological (over 200) trinucleotide CGG repeat expansion in the 5' UTR of the *FMR1* gene. The normal number of repeats is 5-44.

Affected male patients present with neuropsychological development delay and behavioural disorders. Between 50% and 70% of patients have autism spectrum disorders. Other clinical manifestations seen in childhood are muscular hypotonia, gastroesophageal reflux, strabismus, epileptic seizures, sleep disorders, scoliosis, joint hypermobility, pes planus, and recurrent otitis media. Patients have hypogonadotropic hypogonadism.

In adult patients, mitral valve prolapse, aortic root dilatation develop. Ataxia develops in adulthood, followed by psychiatric manifestations. Parkinson's syndrome, axonal sensorimotor polyneuropathy may also be present. Brain MRI reveals lesions in the white matter of the middle cerebellar peduncle, diffuse confluent lesions in the subcortical white matter of the cerebellum, including the splenium of the corpus callosum, and atrophy of the cerebellum and cerebrum.

3.4. Mitochondrial cerebellar ataxias

Mitochondrial cytopathies are a heterogeneous group of multisystem diseases caused by mutations in nuclear or mitochondrial DNA leading to impaired oxidative phosphorylation and energy production in cells. Pancerebellar syndrome is an element of the complex phenotype of a number of mitochondrial diseases. On the other hand, mitochondrial dysfunction is also an element of the pathogenesis of a number of forms with AD and AR type of inheritance.

A typical example in this respect are the mutations in *MT-ATP6*, the gene encoding ATP synthase, known as Complex V, in the mitochondrial respiratory chain. Hydrolysis of ATP is impaired and this leads to a reduction of energy in the cells. Clinical manifestations include late-onset ataxia, nystagmus, tremor and cognitive impairments. Mutations in this gene are also associated with a number of other diseases: Leigh syndrome, NARP (neuropathy, ataxia and retinitis pigmentosa), Charcot-Marie-Tooth disease.

4. Diagnosis of cerebellar ataxias

Diagnosis is based on a detailed history of the chief complaints, age of onset, rate of progression, and family history in order to differentiate genetic ataxias from acquired ataxias (Figure 3). Neurological examination with identification of a paleo-, neo- or pan-cerebellar syndrome of varying degrees of expression, which may be isolated or combined with other manifestations on the part of the central, peripheral nervous system or other organs and systems; MRI - with findings of cerebellar atrophy and/or brainstem atrophy; molecular genetic testing to identify the gene defect of the disease.

The main clinical and paraclinical examinations include:

- Family history, including genealogical analysis
- Neurological status, including scales to assess the severity of ataxia
- Somatic status
- Neuro-ophthalmological examination
- Otoneurological examination
- Neurophysiological testing (NCS, electromyography, evoked potentials study, electroencephalography)
- Standard blood laboratory tests
- Neuropsychological testing
- Magnetic resonance imaging of the brain and spinal cord

Various scales are used to assess the severity of ataxia and its progression (Scale for the Assessment and Rating of Ataxia (SARA), International Cooperative Ataxia Rating Scale (ICARS), Friedreich's Ataxia Rating Scale (FARS)).

Figure 3. Common diagnostic algorithm in cerebellar ataxias

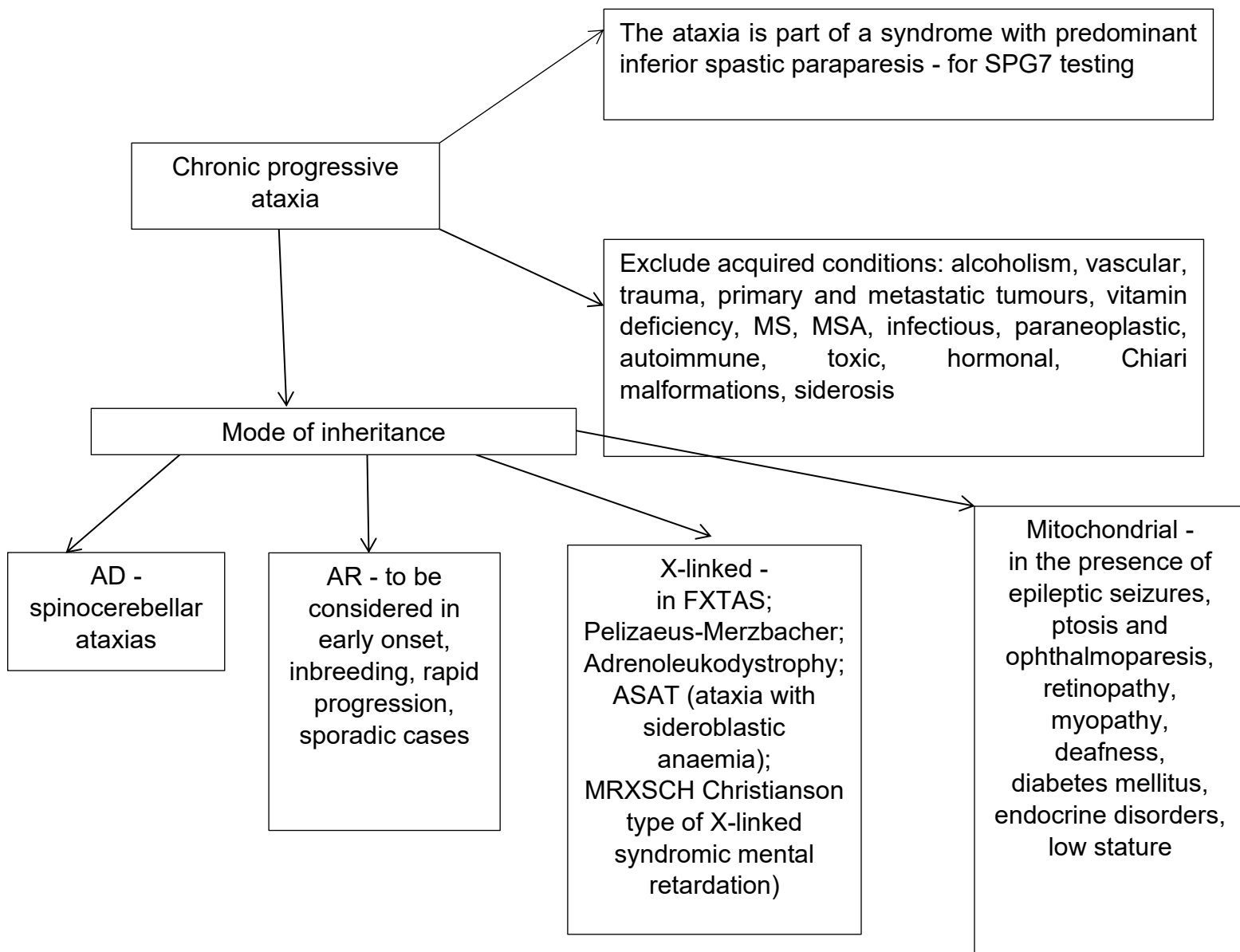


Table 9. Necessary examinations for the diagnosis of patients with ataxia

Standard laboratory tests	CBC	Glucose	Radiography of the lung
	C-reactive protein	ASAT, ALAT	
	ESR	γ-GT	
	Urea	Thyroid enzymes	
	Creatinine	Vitamin B ₁₂	
	Creatine phosphokinase	Folic acid	
	Electrolytes		
Specialized examinations	Alpha-fetoprotein	Cerebrospinal fluid (CSF) examination	Anti-Hu/ Anti-Yo and other paraneoplastic antibodies
	Blood smear	14-3-3 protein in SCF for prion infections	
	Ceruloplasmin/serum copper	EEG	
	Celiac disease screening for	EMG	Anti-GAD
	Lactate	Consultation with an ophthalmologist/OCT	Anti-VGCC
	Vitamin E	MRI of the brain and cervical spine	CT (chest, abdominal cavity, pelvis)
	Lipoproteins		
	Genetic testing , FRDA, SCA 1, 2, 3, 6, 7 (12, 17) and FXTAS		
	Cholestanol	Muscle biopsy	NGS
	Plasma oxysterols	Phytanic acid	Whole Body PET
	Bile acids		
	Coenzyme Q10		

Very long-chain fatty acids

Very often, standard MRI of the brain has to be combined with volumetric evaluations of the cerebellum and spectroscopy to assess afferent and efferent pathways. If acquired causes of ataxia are ruled out, genetic testing should be performed.

Recommendations for the sequence of genetic tests to be performed when hereditary cerebellar degeneration is suspected are as follows:

1. Testing for a specific gene in cases where the phenotype or paraclinical tests point to the respective disease or in populations with a high incidence of the disease.
2. In case of a negative result of the testing referred to in item 1 - NGS
 - (a) Multigene panels
 - (b) Whole exome sequencing (WES)
 - (c) Whole Genome Sequencing (WGS)

Actions of the general practitioner: Disease history to identify the onset, presence of inflammatory disease, acute, subacute or slowly progressive balance and gait disturbance, presence of familiarity; somatic status, complete blood count, differential blood count, vitamin B₁₂, alpha-fetoprotein, serum copper and urine copper, ceruloplasmin, referral to neurologist; follow up of patient's somatic status - cardiac problems, diabetes mellitus, history of tumour process.

Actions of the specialist neurologist in pre-hospital care: neurological status for the presence of paleo-, neo- or pan-cerebellar syndrome – either isolated or in combination with quadripylamidal syndrome and polyneuropathy syndrome, cognitive deficit, analysis of laboratory tests for pathological levels of vitamin B₁₂, alpha-fetoprotein, serum copper and urine copper, ceruloplasmin. Referral to a neurological diseases clinic for clarification of the type of disease, specialized tests for genetic verification; follow-up of the course of the disease

Actions of the neurologist in the hospital care: clarification of the type of cerebellar involvement and in case of exclusion of possible acquired causes - determination of the type of inheritance, referral of the patient for genetic testing and genetic consultation.

5. Differential diagnosis of hereditary cerebellar degenerations

Hereditary cerebellar ataxias should be differentiated from acquired diseases - cerebrovascular diseases, inflammatory and infectious cerebellitis, autoimmune and paraneoplastic cerebellitis, demyelinating diseases, toxic and non-infectious cerebellar degenerations, and other hereditary and metabolic diseases with cerebellar involvement. Acquired causes such as: alcoholism, vascular causes, trauma, primary and metastatic tumours, vitamin deficiencies, MS, MSA, infectious, paraneoplastic, autoimmune, toxic and hormonal causes, Chiari malformations, siderosis, other genetic diseases such as Wilson's disease, progressive myoclonic epilepsies should always be in consideration.

1. Immune-mediated cerebellar ataxias include: gluten-related ataxia, GAD65-associated cerebellar ataxia, primary autoimmune cerebellar ataxia, cerebellar form of Hashimoto's encephalopathy, paraneoplastic cerebellar degeneration, opsoclonus-myoclonus syndrome, postinfectious cerebellitis, and Miller-Fisher syndrome.

Table 10. Autoantibodies associated with immune-mediated cerebellar ataxias

Antibodies	Associated cerebellar ataxias
Antigliadin (IgG/IgA) Anti-TG 2/6	Gluten-associated ataxia
Anti-GAD65	Anti-GAD65- associated ataxia
Anti-TPO	Hashimoto-associated encephalopathy
Anti-Yo	Paraneoplastic cerebellar degeneration (carcinomas breast, uterine, ovarian cancer)
Anti-Hu	Paraneoplastic cerebellar degeneration (small cell lung cancer)
Anti-CV2/CRMP5	Paraneoplastic cerebellar degeneration (small cell lung carcinoma and thymoma)

Anti-Ri	Paraneoplastic cerebellar degeneration (small cell lung cancer and breast cancer), Opsoclonus-myoclonus syndrome
Anti-Ma2	Paraneoplastic cerebellar degeneration (small cell lung cancer and testicular carcinoma)
Anti-Tr	Paraneoplastic cerebellar degeneration (Hodgkin lymphoma)
Anti-VGCC (P/Q type)	Paraneoplastic cerebellar degeneration (small cell lung cancer), primary autoimmune cerebellar ataxia
Anti-MAP1B	Paraneoplastic cerebellar degeneration (small cell lung cancer)
Anti-CARP VIII	Paraneoplastic cerebellar degeneration (ovarian cancer and melanoma)
Anti-ITPR1	Paraneoplastic cerebellar degeneration (breast cancer)
AntimGluR1, Anti-PKC g	Paraneoplastic cerebellar degeneration (prostate cancer and bladder cancer)
Anti-Homer-3	Neoplasms, postinfectious cerebellitis
Anti-GluRd2	Postinfectious cerebellitis

6. Treatment of hereditary cerebellar ataxias

To the group of ataxias with possible etiopathogenetic treatment belong:

- Gluten-related ataxia. For this purpose, it is necessary to test anti-gliadin antibodies and anti-TG6 antibodies and, if positive, to start a gluten-free diet with subsequent monitoring of antibody titers every 6 months.

- Ataxia-telangiectasia. Treatment is carried out with symptomatic agents for the treatment of extrapyramidal disorders (amantadine and 4-aminopyridine), which have a variable effect. Early physiotherapy is important for the prevention of joint contractures. In patients with immunodeficiency, administration of intravenous immunoglobulins is recommended.
- Friedreich's ataxia. Omaveloxolone is the only medical substance approved for treatment in patients over 16 years of age. Frataxin deficiency in FA leads to impaired antioxidant defences, due to a vicious cycle of mitochondrial dysfunction, reduced nuclear factor erythroid 2-related factor 2 (Nrf2) signaling, and decreased ATP production.

Omaveloxolone acts as an activator of Nrf2, the recommended dose being 150 mg (3 tabs x 50 mg) administered once daily in the morning 1 hour before meals or 2 hours after meals.

In pivotal registration clinical trials, the medical substance has demonstrated statistically significant efficacy on the Modified Friedreich's Ataxia Rating Scale (mFARS) metrics, (Appendix 1). The mFARS is used to assess the severity of neurological (nerve or nervous system related) symptoms of Friedreich's ataxia. If the mFARS score decreases, it means that there is a decrease in physical impairment.

The dose should be reduced if the patient is taking other CYP3A inhibitor medications.

The most common unwanted side effects with the administration of Omaveloxolone are: elevation of liver enzymes, headache, appetite loss, weight loss, vomiting, diarrhoea, fatigue, mouth and throat pain, back pain, muscle cramps, and flu-like symptoms.

Inclusion criteria:

Patients with genetically verified disease

Age 16+

Exclusion criteria

Hypersensitivity to some of the ingredients of Omaveloxolone

The mFARS scale should be used to evaluate the effectiveness of therapy before initiation of therapy and every 6 months.

ALT, AST, and bilirubin should be monitored prior to initiation of therapy, monthly during the first 3 months of treatment, and periodically thereafter depending

on the clinical indications. If ALT or AST rises to $> 5 \times \text{ULN}$, Omaveloxolone should be discontinued immediately and liver function tests should be repeated as soon as possible. If laboratory abnormalities stabilize or resolve, treatment with Omaveloxolone may be restarted. If ALT or AST rises to $> 3 \times \text{ULN}$ and bilirubin rises to $> 2 \times \text{ULN}$, omaveloxolone should be discontinued immediately and liver function tests should be repeated. Follow-up tests should be continued as appropriate.

Treatment with Omaveloxolone will be conducted and monitored in:

- The Clinic of Nervous Diseases of University Hospital “Alexandrovska”
The multi-profile hospital for active treatment in neurology and psychiatry
“St. Naum”

Because of the multisystem involvement, Friedreich’s ataxia therapy requires a multidisciplinary approach. Key aspects of follow-up of Friedreich’s ataxia patients include:

- For spastically increased tone are recommended: administration of botulinum toxin, pharmacotherapy (baclofen, tizanidine, gabapentin, benzodiazepines, etc.) and systemic rehabilitation
- Systematic gait rehabilitation to improve limb strength and mobility, use of orthotics
- ECG and echocardiogram should be performed once a year
- Pulmonary function tests and polysomnography should be performed once a year
- Scoliosis assessment should be performed on a regular basis. Individuals with Friedreich's ataxia, in combination with scoliosis and a Cobb angle between 20° and 40° and/or aged between 10 and 16 years should be monitored for progression. The use of corsets may not reduce or halt the progression of scoliosis; however, it may be useful in delaying surgical correction in children with Friedreich's ataxia. Patients with scoliosis $> 40^\circ$ are considered eligible for surgical correction.
- Orthopaedic surgery for the Friedreich's foot is conditionally recommended to facilitate mobility in combination with the use of orthotics.
- Annual screening for diabetes mellitus with HbA1c and fasting plasma glucose testing is recommended in children and adults with Friedreich's ataxia. Self-administration of insulin is recommended instead of insulin and

other glucose-lowering therapy as the primary treatment for most children with this disease.

- Vitamin D levels and bone density should be monitored and therapy should be administered if necessary.
- Ataxia with vitamin E deficiency and abetalipoproteinemia. These patients should be treated with high doses of vitamin E - 800-1500 mg (40 mg/kg), as ataxia and cognitive deficits are reversible in the setting of such therapy.
- Ataxia with vitamin B₁₂ deficiency, requiring vitamin B₁₂ substitution
- Ataxia with coenzyme Q10 deficiency. Administration of coenzyme Q10 is recommended.
- Cerebrotendinous xanthomatosis. Treatment with choledeoxycholic acid is recommended.
- Niemann-Pick disease type B, in which there is an approved therapy with Xenpozyme, a treatment specific for deficiency of the acid sphingomyelinase enzyme. It is an enzyme-replacement therapy developed to replace the deficient enzyme and thereby reduce the accumulation of lipids in the cells of various tissues. The greatest clinical benefit is expected in patients with chronic visceral forms of ASMD (NPB). Xenpozyme is in the form of powder for solution for infusion which is administered intravenously every two weeks.

The dose is gradually increased in order to reduce hypersensitivity and infusion-related reactions or elevated transaminase levels:

Dose 1 (day 1/week 0): 0.1 mg/kg i.v.

Dose 2 (week 2): 0.3 mg/kg i.v.

Dose 3 (week 4): 0.3 mg/kg i.v.

Dose 4 (week 6): 0.6 mg/kg i.v.

Dose 5 (week 8): 0.6 mg/kg i.v.

Dose 6 (week 10): 1 mg/kg i.v.

Dose 7 (week 12): 2 mg/kg i.v.

Dose 8 (week 14): 3 mg/kg i.v. (recommended maintenance dose)

The dose escalation phase includes the first dose of 3 mg/kg.

The most commonly reported adverse reactions in adults (incidence $\geq 10\%$) include headache, cough, diarrhoea, hypotension, and eye redness. The most

commonly reported adverse reactions in children (incidence $\geq 20\%$) include fever, cough, diarrhoea, runny nose, abdominal pain, vomiting, headache, nausea, rash, joint pain, itchy skin, fatigue, and sore throat.

Niemann-Pick disease type C for which Miglustat therapy is approved. The multisystem involvement in Niemann-Pick C disease necessitates a multidisciplinary approach to the treatment and follow-up of patients.

Miglustat is a small iminosugar molecule that crosses the blood-brain barrier and reversibly inhibits the glucocereamide synthetase enzyme, catalyzing the first stage of glycosphingolipid synthesis, thereby reducing their accumulation in tissues. This medication has a proven effect in terms of mild improvement, stabilisation or slowing of disease progression (the rate of horizontal eye saccades, dysphagia, motor deficits, and cognitive impairment, with better effects in the treatment of late childhood, juvenile and adult forms. This therapy is combined with symptomatic pharmacotherapy and non-drug therapy:

- Tricyclic antidepressants or CNS stimulants to control cataplexy
- Anticonvulsants (Valproate, Lamotrigine and Levetiracetam). Carbamazepine, Oxcarbazepine, Vigabatrin are not recommended due to the risk of inducing myoclonias; Phenytoin should not be administered due to the risk of worsening cerebellar symptomatology
- Dystonia and tremor - anticholinergic medications, botulinum toxin
- Melatonin to treat insomnia
- Gastrostomy for dysphagia
- Rehabilitation for the prevention of contractures

In the other forms of hereditary cerebellar ataxias, treatment is symptomatic with neuroprotective medications, speech therapy, prophylaxis of aspiration for bulbar weakness, symptomatic treatment of psychiatric manifestations, and physiotherapy.

Timely diagnosis allows genetic counselling and prevention of new cases in affected families.

7. Appendices

Appendix 1. Friedreich's Ataxia Rating Scale (FARS) and Modified FARS (mFARS)

FARS is a neurological rating scale developed to evaluate neurological involvement in Friedreich's ataxia. It is designed to reflect the specific structures affected in Friedreich's ataxia.

FARS includes scores in five subsections (Section A through Section E) measuring:

- Bulbar function,
- Upper limb coordination,
- Lower limb coordination,
- Peripheral nervous system,
- Upright stability.

The modified version (mFARS) has better psychometric characteristics and shortens the bulbar subsection to 2 items (instead of 4) and excludes the 5 items from the peripheral nervous system subsection

Preparation of participants:

- It is desirable that the evaluations be administered at one and the same time of day and in one and the same order as the other tests.
- Participants must be instructed:
 - to get a good night's sleep the night before,
 - to have a snack,
 - to arrive hydrated,
 - to wear comfortable clothing that allows the examination to be carried out easily.
- Patients must not perform heavy exercise or prolonged walking on the day of the test. If necessary, they should be offered a wheelchair or transport chair in the hospital.

Evaluation

Evaluation is based on a **sum score** of all five subsections:

- Maximum points for **mFARS: 93**
- Maximum points for **FARS: 125**

The scores for each individual task are given according to certain criteria, with **higher scores indicating greater severity of the impairment** (i.e., worse function).

Subscales and corresponding maximum points:

Subscale	mFARS points	FARS points
A. Bulbar function	5	11
B. Upper limb coordination	36	36
C. Lower limb coordination	16	16
E. Upright stability	36	36
D. Peripheral nervous system	-	26

| **Total** | **93** | **125** |

Equipment

Necessary equipment for performing the test:

- Stopwatch
- Coloured tape for marking the floor
- Patient transport chair (e.g. **Stryker Prime Transport Chair**) or equivalent stable chair, including adapted patient systems
- Adjustable hospital couch or equivalent examination table/low footrest
- If the full FARS is conducted (including subsection D):
 - **128 Hz** tuning fork
 - Reflex (neurological) hammer for testing deep tendon reflexes

A. Bulbar function (Elements A3 - A4)**Position of the participant:**

Participant must be in a **sitting position** with:

- hip flexed at 90 degrees and knee flexed at 90 degrees
- feet firmly placed on the floor

Note: Items A1 and A2 from the original FARS test are not included in mFARS.

A3. Cough**Instructions:**

Ask the participant to **cough as loudly as possible three times**.

Accept **the loudest attempt** for assessment.

Evaluation details:

- Listen to the power of the cough.

- You can use **increments of 0.5 points** if you think the assessment falls between two levels of severity.

Rating scale:

Score	Description
0.0	Normal cough
0.5	Slightly weakened
1.0	Moderately weakened
1.5	Significantly weakened
2.0	Almost or completely missing

A4. Speech

Instructions:

Ask the participant to read or repeat the following two sentences:

- A. "The president lives in the White House."
- B. "The traffic is heavy today."

Assessment details:

- Assess speech intelligibility.
- You can use **increments of 0.5 points** for precision.

Rating scale:

Score	Description
0.0	Normal speech
0.5	Mild disorders (all or almost all words are intelligible)
1.0	
1.5	Moderate disorders (most words are unintelligible)
2.0	
2.5	
3.0	Severe disorders (no or almost no useful speech)

B. Upper limb coordination (Elements B1 - B5)

Position of the participant:

The participant is in an **upright sitting position** with:

- hip flexed at 90 degrees and knee flexed at 90 degrees
- feet firmly placed on the floor

If the participant **cannot sit independently**, he/she can remain in his/her adapted chair/seating system.

B1. Finger-to-finger test

Instructions:

- Help the participant to raise the arms so that the elbows reach a horizontal level (elbow flexion 75-90°).
- Hands should be ~25 cm away from the sternum (breastbone).
- While supporting the position of the hands, have them touch the tips of their index fingers and then to slightly separate them (~2.5 cm).
- Remove the support and observe for **10 seconds**.
- A slight relaxation of the elbows is permissible.

Evaluation details:

- **The amplitude** of the finger **oscillations** is evaluated.
- If the elbows touch the body or the support - automatically 3.0 points.
- Performed and evaluated **separately for right and left hand**.

Rating scale:

Score	Description
0.0	Normal (0-0.5 cm oscillation)
0.5-1.5	Mild oscillation (0.5-2.0 cm)
2.0-2.5	Moderate oscillation (2.0-6.0 cm)
3.0	Severe oscillation (>6.0 cm) or inability to perform without support

B2. Finger-to-nose test

Instructions:

- The examiner holds his/her index finger at 90% of the participant's maximum reach range.

- The participant performs **3 nose-to-finger-to-nose cycles**.
- Evaluate the movement **from a front view**.

Evaluation details:

- **Tremor on movement** and especially at the end of movement is evaluated.
- It is performed **separately for right hand and left hand**.

Rating scale:

Score	Description
0.0	Without tremor
1.0	Mild tremor (<2 cm amplitude)
2.0	Moderate tremor (2-6 cm)
3.0	Severe tremor (>6 cm)
4.0	Inability to perform

B3. Dysmetria test

Instructions:

- Explain to the participant to touch the tip of the examiner's finger while the examiner moves it along **an imaginary square** (~25 cm sides).
- The participant is required to follow the fast moving target with his hand, starting from his chin.

Evaluation details:

- **The accuracy of the touch** is evaluated (no penalty for tremor).
- It is performed **separately for right hand and left hand**.

Rating scale:

Score	Description
0.0	No misses
1.0	Mild misses (1-2 times)
2.0	Moderate misses (3-5 times)
3.0	Severe misses (6-8 times)

4.0	Inability to perform
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B4. Rapid alternating hand movements

Instructions:

- Position: elbow bent, forearm ~15 cm above thigh, palm up.
- Demonstrate a **pronation/supination** movement (such as rotating a handle).
- Perform **10 cycles as quickly as possible**.
- Use a **stopwatch** to measure time.

Evaluation details:

- **Speed, rhythm, position and accuracy** are evaluated.
- If the execution time is >7 seconds - 0.5 points are added.

Rating scale:

Score	Description
0.0	Normal performance
0.5-1.5	Mildly delayed or uneven performance
2.0-2.5	Moderately delayed or compensates with supporting the elbow
3.0	Inability to perform

B5. Rapid finger tapping

Instructions:

- Position: shoulders raised horizontally, elbows bent at 75-90°.
- The participant should **tap the tip of the thumb with the index finger** (above the crease of the DIP joint) with amplitude **of at least 1 cm**.
- Perform **15 taps** as quickly as possible.
- Measure the time with a stopwatch.

Evaluation details:

- The number of missed shots counts as errors.
- If the completion time is >6 seconds - add 1 point.

Rating scale:

Score	Description
0.0	No misses
1.0	Mild error (1-3 misses)
2.0	Moderate error (4-9 misses)
3.0	Severe error (10-15 misses)
4.0	Inability to perform or inability to maintain a starting position

Note: If the participant has long fingernails, they should be instructed to use the **tip of the index finger**, not the fingernail.

C. Lower limb coordination (Elements C1 and C2)**Position of the participant:**

The participant must be in a **supine position** on a couch (flat surface) with:

- head raised (in order to be able to see the legs),
- legs stretched forward,
- knees and toes pointing up.

If the participant has difficulty transferring, the test can be performed in **their adapted seat**, using a **low stool** to support the legs in a stretched position in front.

C1. Heel-along-shin slide**Instructions:**

- Demonstrate the movement:
Lift the participant's leg, place his heel just below the knee of the opposite leg, **slide** the heel along the front of the shin up to the ankle, **lift the heel**, return it to the couch, and again place the heel on the shin below the knee cap.
- Perform **3 cycles** of the movement.
- Pace: about **1 second per movement** (hip flexion/extension).
- It is performed **separately for each leg**.

Evaluation details:

- Evaluate **shank contact** and **smoothness of movement**.

Rating scale:

Score	Description
0.0	Normal (heel is in contact with the shin all the time)
1.0	Mild deviation (movement is slow/jittery but contact is maintained)
2.0	Moderate deviation (heel deviates ≤ 3 times in 3 cycles)
3.0	Severe deviation (heel deviates ≥ 4 times in 3 cycles)
4.0	Inability to perform or inability to assume the starting position (due to contractures or other disorders)

C2. Heel-to-Shin Tap**Instructions:**

- The participant chooses a convenient **point midway down the shin** of the opposite leg as the **target**.
- Under visual control, the participant must:
 - **tap his/her heel on that point 8 times**,
 - from a height of about **15-25 cm**.
- It is performed **separately for each leg**.
- The examiner counts and says "start" and "stop".

Evaluation details:

- Score the **number of times the heel misses the selected point**.

Rating scale:

Score	Description
0.0	Normal (heel stays on target)
1.0	Mild deviation (1-2 misses)
2.0	Moderate deviation (3-5 misses)
3.0	Serious deviation (>5 misses)
4.0	Inability to perform or inability to assume the starting position (due to contractures, etc.)

E. Upright stability (Elements E1 - E7)

- ◆ The participant **must be barefoot** during the tests. If he/she refuses, he/she may wear shoes, but this must **be noted** (note whether the participant is barefoot, the type of floor, wearing splints, etc.).
- ◆ All tests must be conducted on a **firm stable surface** (not carpet).
- ◆ **The examiner should always be next to the participant** for safety. If there is a risk of falling, **the test is not conducted** and the **maximum score** is awarded.
- ◆ For some tasks (e.g., standing with legs spread), **if the first test cannot be completed**, the remaining tests are skipped and scored with the maximum score.
- ◆ For each of the tests, **3 attempts** are performed and the **average** is calculated (it is recommended to do this automatically from the database).

E1. Sitting

Position:

The participant sits on the edge of a couch or backless chair.

- Knees and hips - 90°
- Arms - crossed on the chest (palms on elbows)
- If it cannot sit up independently - a **score of 4** is automatically given

Instructions:

The examiner stands in front of the participant, the assistant - behind him.

Observe **for 30 seconds**.

Rating scale:

Score	Description
0.0	Normal posture
1.0	Mild oscillations of head/torso
2.0	Moderate oscillations; requires supervision but no physical assistance
3.0	Severe oscillations; need contact or minimal help from 1-2 people
4.0	Needs significant assistance or is unable to assume the position

E2a. Stance - feet apart (eyes open)**Position:**

- Feet - ~20 cm distance
- Toes - forward
- Hands - next to the body or at the participant's choice
- Gaze - fixed at a selected point

Instructions:

Measure up to **60 seconds**, up to 3 attempts. If the participant **maintains the position 60 seconds in the first 2 attempts**, a third attempt is not required.

Rating scale:

Score	Description
0.0	≥ 60 seconds
1.0	45-59 seconds
2.0	30-44 seconds
3.0	15-29 seconds
4.0	< 15 seconds, or need of assistance/support, or inability to stay in the position

E2b. Stance - feet apart (eyes closed)

Same position as for E2a.

Instructions:

When the participant is ready, say "start" – he/she should close his/her eyes.

Stop if he opens his/her eyes. Up to 3 attempts.

Rating scale: (*same as E2a*)

E3a. Stance - Feet Together (eyes open)**Position:**

- Feet - touching in front (toes) and heels.

If there is a deformation - contact at one end only is allowed.

Instructions:

Stop-clock measurement is used. Up to 3 attempts are allowed. Assistant - on both sides.

Rating scale: *(same as E2a)*

E3b. Stance - Feet Together (eyes closed)

Same position as E3a.

Instruction - identical to E2b.

E4. Tandem stance (one leg in front of the other)

Position:

- The dominant leg is behind, the other is in front.
- The toes of the back foot touch the heel of the front foot.

The dominant leg is the one with which the participant balances best. It is identified and used in future assessments.

Instructions:

Up to 3 attempts, measuring with a stopwatch.

Rating scale: *(same as E2a)*

E5. Stance - Dominant Foot

Position:

- Straight knee of the dominant leg
- Opposite leg - bent at the hip, heel a few inches above the floor

Instructions:

Measure up to 3 attempts.

Rating scale: *(same as E2a)*

E6. Tandem walk (in a straight line)

Position:

- The participant makes **at least 8 steps, each time with the heel of the front foot touching the toes of the back foot**
- Surface - hard, no furniture nearby (<1 m), no carpet

Instructions:

Demonstrate the exercise. The participant starts from a tandem standing position.

One attempt.

Rating scale:

Score	Description
0.0	8 or more consecutive steps
1.0	More than 4 but less than 8

2.0	Up to 4 steps before loss of balance
3.0	Inability to experience

E7. Gait (normal gait)

Position:

- Distance: 8 meters or 25 feet
- Performed with or without aids

Instructions:

The participant walks at his usual speed. Evaluate based on the severity of **ataxia** and need for assistance.

Rating scale:

Score	Description
0.0	Normal gait
1.0	Mild ataxia, deviations, difficulty turning; does not need support
2.0	Marked ataxia; need for periodic support
3.0	Moderate ataxia; uses a cane or examiner's hand
4.0	Severe ataxia; needs a walker or 2-handed support
5.0	Inability to walk (wheelchair-bound state)