Chapter 25
Rare Neurodegenerative Diseases: Clinical and Genetic Update

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Abstract More than 600 human disorders afflict the nervous system. Of these, neurodegenerative diseases are usually characterised by onset in late adulthood, progressive clinical course, and neuronal loss with regional specificity in the central nervous system. They include Alzheimer's disease and other less frequent dementias, brain cancer, degenerative nerve diseases, encephalitis, epilepsy, genetic brain disorders, head and brain malformations, hydrocephalus, stroke, Parkinson's disease, multiple sclerosis, amyotrophic lateral sclerosis (ALS or Lou Gehrig's Disease), Huntington's disease, and Prion diseases, among others. Neurodegeneration usually affects, but is not limited to, the cerebral cortex, intracranial white matter, basal ganglia, thalamus, hypothalamus, brain stem, and cerebellum. Although the majority of neurodegenerative diseases are sporadic, Mendelian inheritance is well documented. Intriguingly, the clinical presentations and neuropathological findings

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in inherited neurodegenerative forms are often indistinguishable from those of sporadic cases, suggesting that converging genomic signatures and pathophysiologic mechanisms underlie both hereditary and sporadic neurodegenerative diseases. Unfortunately, effective therapies for these diseases are scarce to non-existent. In this chapter, we highlight the clinical and genetic features associated with the rare inherited forms of neurodegenerative diseases, including ataxias, multiple system atrophy, spastic paraplegias, Parkinson's disease, dementias, motor neuron diseases, and rare metabolic disorders.

Keywords Genetic diagnosis • Neuromuscular • Metabolic disorders • Dementia • Ataxia • Movement disorders

25.1 Introduction

Rare diseases are highly heterogeneous life-threatening or chronically debilitating diseases with a low prevalence and a high level of complexity. Most of them are the result of a genetic pathological mutation, a few result from environmental exposures during pregnancy or later in life, often in combination with genetic susceptibility, and the others being rare cancers, auto-immune diseases, congenital malformations, toxic, and infectious diseases. There is also a great diversity in the age at which the first symptoms occur, but half of rare diseases can appear at birth or during childhood.

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Work over the last 25 years has resulted in the identification of genes responsible for ~50% of the estimated 7,000 rare monogenic diseases, and it is predicted that most of the remaining disease-causing genes will be identified by the year 2020. This acceleration in gene discovery is the result of the application of high-throughput next-generation sequencing technologies. We expect to rapidly move into a scenario where most families presenting with a rare disease may have a molecular diagnosis established, allowing adequate clinical follow-up and proper genetic counselling. Also, deciphering the genetic and molecular signatures underlying rare diseases will facilitate the design of new therapies that will hopefully interfere in an efficacious way in those pathogenic pathways.

There is a wide range of diseases that can be classified as neurodegenerative. Some are very rare, but all have a significant impact with a progressively increasing burden of management. Herein, we highlight the clinical and genetic features associated with those rare inherited forms of neurodegenerative diseases, including ataxias, multiple system atrophy, spastic paraplegias, Parkinson's disease, dementias, motor neuron diseases, and rare metabolic disorders.

25.2 Cerebellar Ataxias

Cerebellar ataxias represent a heterogeneous group of disorders characterised by progressive degeneration of the cerebellum often accompanied by a variety of neurological and systemic symptoms. Two main categories are distinguished: sporadic and hereditary ataxias. Sporadic ataxias may be symptomatic or idiopathic. Symptomatic ataxias are due to structural lesions or malformations in the cerebellum, toxics (alcohol; antiepileptic drugs: benzodiazepines; antidepressants: lithium; antineoplastics: cyclosporine; and amiodarone, procainamide, isoniazid, metronidazole, nitrofurantoin, among others; heavy metals: lead and mercury; and chemicals: for instance solvents and pesticides), hypothyroidism, diabetes, malabsortion due to celiac disease, vitamin E or B12 deficiencies, abetalipoproteinemia, paraneoplastic syndromes, demyelinating disorders, Whipple disease and post-viral/immune-mediated ataxia. Symptomatic ataxias can be handled and diagnosed with a detailed medical history and common ancillary tests. Idiopathic ataxias include the so-called idiopathic late-onset cerebellar ataxia (ILOCA) and multiple system atrophy (MSA).

Hereditary ataxias can present with autosomal dominant (SCA), autosomal recessive, X-linked or mitochondrial inheritance. Overall, they comprise about 60–75% of ataxias. They are diagnosed on family history, physical examination, neuroimaging, and genetic testing. This section focuses on hereditary and idiopathic ataxias (ILOSCA and MSA).

25.2.1 Autosomal Dominant Ataxias

Forty-three different genetic subtypes of spinocerebellar ataxia (SCA) are now distinguished. They are conventionally referred as SCAs regardless of whether or not they present with spinal pathology. In addition, the complex form dentatorubral-pallidoluysian atrophy (DRPLA) and eight episodic ataxias (EA) are usually included (Table 25.1; modified from [16, 32]. Together with the autosomal recessive ataxias, the minimum prevalence rate in European descend populations would be 6–7 per 100,000 people, which is comparable to Huntington's disease or motor neuron diseases [32].

25.2.1.1 SCAs

The prevalence of these diseases is not widely known and varies considerably among geographical areas due to founder effects. SCAs 1, 2, 3, 6 and 7 account up to 65% of all SCA worldwide cases [10], being SCA3 the most common subtype worldwide. The genotype still remains elusive in up to 40–50% of SCA families indicating a reservoir of yet to be characterised diseases.

Age of onset is quite variable usually presenting in adulthood, and the disease progresses over decades. Life span is shortened in SCAs 1, 2, 3 and 7 [16] Anticipation is observed in SCAs in which CAG repeat expansion occurs and it is a significant issue to be considered in the genetic counselling process.

Cerebellar dysfunction in SCAs is often associated with other clinical signs such as ophthalmoplegia, polyneuropathy, retinopathy, pyramidal and extrapyramidal features, dementia, chorea, seizures, and lower motor neuron signs. Despite the clinical overlap between different SCA genotypes some distinctive clinical features may help the clinician in pursuing direct genetic testing: marked slow saccades are associated with SCA2; ophthalmoplegia with SCA3; pyramidal signs with SCAs 1 and 3; polyneuropathy with SCAs 1, 4, 8, and 25; pigmentary retinopathy with SCA7; seizures with SCA10; cognitive impairment with SCAs 2, 12, 13, and 17; axial myoclonus with SCA14; chorea with SCA17; dysphonia and early calcification of dentate nucleus with SCA20; and lower motor neuron signs with SCAs 3 and 36 [8]. Conversely, the pure cerebellar phenotype has been mainly associated with SCAs 5, 6, 11, 14, 15/16, and 37 [39, 52].

SCAs are often subdivided into expanded exon-coding CAG repeat ataxias (SCAs 1, 2, 3, 6, 7, 17, and DRPLA); SCAs with mutations in non-coding regions (triplets and pentanucleotide repeat expansions: SCAs 8, 10, 12, 31, and 36); SCAs with conventional mutations in other identified genes, and SCAs with still unidentified loci.

This complex and expanded knowledge in SCAs has not yet led to find the ultimate common pathogenic mechanism. Basic scientific research has identified transcriptional dysregulation, protein aggregation and clearance, autophagy, alterations of calcium homeostasis, mitochondria defects, toxic RNA gain-of-function mecha-

nisms and activation of pro-apoptotic routes, amongst others, as the main mechanisms leading to cerebellar Purkinje cell death [31, 33]. Thus, several identified potential targets open the way to find effective treatments that may act during the early stages of neurodegeneration in SCAs [31, 33, 46, 48].

However, regardless of several trials in cells and animals models, available human therapeutic trials in SCA are scarce and only recently, some positive output has emerged. Valproate, an antiepileptic drug acting as an histone deacetylation inhibitor, improved locomotor function in an open trial in SCA3 [24]; and riluzole, a small-conductance potassium KC2 channel activator showed symptomatic benefits in a double-blind 12-months trial in a few SCAs and FRDA [45]. Nevertheless, no approved treatment to modify neurodegeneration is available yet for these diseases. Piracetam for myoclonus; L-Dopa for dystonia; baclofen and botulin toxin for spasticity; beta-blockers, benzodiazepines and even thalamic stimulation for intention tremor; anticholinergic drugs for hypersalivation; clonazepam for muscle cramps in addition to physical therapy, are commonly used and recommended as symptomatic treatments.

25.2.1.2 Episodic Ataxias (EA)

The episodic occurrence of symptoms differentiates EAs from SCAs [43]. Typically onset of EA occurs in childhood or early adulthood, however in E2, the most common form of EA, the onset may delay up to the fifth decade. Episodic ataxias can be provoked by exercise, emotional stress, startle or change of position. Tremor, muscle cramps, and stiffening may accompany the ataxia. Interictal and subclinical myokimia in face, arms, and legs may be seen in electromyography. Episodic ataxia 1 (EA1) presents with movement-induced attacks of ataxia that lasts less than 15 min and can appear up to 15 times a day. EA1 is caused by mutations in the potassium channel *KCNA1* gene. In contrast, EA2 attacks may last for hours and days and they are often associated with nausea, migraine headache, and sometimes hemiparesis, dystonia and tinnitus; permanent cerebellar interictal signs may develop along the course of EA2, especially nystagmus, followed by a progressive cerebellar syndrome. Emotional and physical stress, caffeine, alcohol, exercise, intercurrent illness and phenytoin may trigger the attacks. EA2 is associated with point mutations in the *CACNA1A* gene whereas missense mutations in the same gene are associated with familial hemiplegic migraine, and CAG repeat expansions with SCA6. Evident clinical overlap exists with EA2, even within families [54]. Acetazolamide is an effective therapy for most patients with EA2 and half of the patients with EA1; phenytoin and carbamazepine are alternative therapies in EA1, whereas valproate, flunarizine, topiramate, and 4-aminopyridine may be an option in case acetazolamide fails in EA2. Episodic ataxias subtypes 3, 4, 5, 6, and 7 represent the minority of phenotypical variations in EA and few patients have been identified. EA5 shows an EA2 phenotype and EA6 additionally presents with seizures [43] (Table 25.1).

25.2.1.3 Other

Other rare autosomal dominant disorders like hereditary spastic ataxia and sensory motor neuropathy with ataxia may also present with ataxia.

25.2.2 Autosomal Recessive Ataxias

The autosomal recessive ataxias constitute a group of heterogeneous and rare disorders involving many genetic defects caused by a myriad of mechanisms of pathogenesis, which are mainly commonly caused by loss of function of the gene products (Tables 25.2 and 25.3).

Friedreich ataxia (FRDA) is the most common recessively inherited ataxia with a prevalence of 1 in 50,000, followed by ataxia telangiectasia (AT) with a prevalence of 1 in 100,000 individuals [6]. Traditionally, neurologists take into account an age of onset of 25 years of age as a cut-off threshold to further screen these patients because only a minority of recessive and metabolic ataxias reveal an adult onset. In addition, all patients with a suspected recessive ataxia and negative screening should also be investigated for SCA.

25.2.2.1 FRDA

FRDA classically presents with ataxia, dysarthria, absent deep tendon reflexes, pyramidal signs, and an early-onset (<25 years). Cardiomyopathy, scoliosis, distal muscle atrophy, deafness, optic atrophy, and diabetes are common variable features. A milder phenotype with late-onset and a phenotype with spastic paraplegia without ataxia or polyneuropathy has also been reported. The underlying mutation consists of a GAA trinucleotide repeat expansion within the *FXN* gene (ranges: normal, 5–33 GAA repeats; mutable normal, 34–65 repeats; FRDA, 66–1,700). The expansion size accounts for less than 50% of the age of onset, and correlates more with the presence of diabetes and cardiomyopathy, particularly for larger alleles. Between 6 and 10% FRDA patients are compound heterozygotes for the GAA expansion. The *FXN* gene encodes for frataxin, a mitochondrial protein related to iron storage and sulphur-iron complexes biogenesis, thus being mitochondrial dysfunction a key feature underlying FRDA pathogenesis. Clinical trials with antioxidants [18, 22, 61], erythropoietin [29] and pioglitazone (ACTFRIE, unpublished data) have failed to prove any benefit.

25.2.2.2 Others

Once FRDA is excluded, an age-dependent screening for recessive ataxic syndromes and metabolic diseases is recommended (Table 25.2). It is important to note that some of these diseases are treatable [1]. Some clinical traits may help to direct the genetic test [6, 16]. Oculomotor apraxia is a common finding in ataxia telangiectasia (AT) and in ataxias presenting with oculomotor apraxia (AOA1, AOA2). Oculocutaneous telangiectases, choreoathetosis, dystonia, immunodeficiency, hypersensitivity to ionizing radiation, and predisposition to malignancy are also specific features for AT. Ataxia telangiectasia is due to mutations in the *ATM* gene, which encodes a protein related to DNA repair. The clinical disparity in AT is partly related to the relative preservation of ATM expression in some *ATM* mutations leading to milder phenotypes. As for AOAs 1 and 2, they both associate with polyneuropathy, and in addition AOA1 may show mild mental retardation. The aprataxin (APTX/AOA1) and the senataxin (SETX/AOA2) genes are both implicated in DNA repair pathways. Polyneuropathy is common in FRDA, vitamin E deficiency, abetalipoproteinemia, Refsum's disease, and late-onset hexosaminidase A deficiency that may present as a FRDA-like phenotype. Retinitis pigmentosa with anosmia, polyneuropathy, cerebellar ataxia, deafness, and ichthyosis is typical of Refsum's disease, while juvenile cataracts are a clinical hallmark of cerebrotendinous xantomatosis (CTX, sterol 27-hydroxylase deficiency) that will also present with tendon xanthomas, chronic diarrhea, ataxia, pyramidal signs, dementia, epilepsy, polyneuropathy, and white matter lesions on magnetic resonance imaging (MRI). In fact, MRI could also contribute to guide genetic testing [6]. White matter lesions are found in mitochondrial diseases and all leukodystrophies, such as the mentioned CTX, metachromatic leukodystrophy (arylsulfatase gene), and Krabbe disease (galactoceribrosidase deficiency).

A few other rare conditions may have an adult onset autosomal recessive ataxia such as Niemann-Pick C, a lipid storage disorder, often associated to dementia or psychiatric symptoms, and GM1 gangliosidosis that may associate with dystonia. Ataxia with a combination of migraine, epilepsy, myoclonus, late-onset ophthalmoplegia, and cognitive decline is presented in the autosomal recessive mitochondrial ataxic syndrome because of mutations in the *POLG* gene [13].

25.2.3 X-Linked Inherited Ataxias

Adult-onset adrenomyeloneuropathy is a mild form of adrenoleukodystrophy that typically presents in adult males (<50 year old) and is characterized by a progressive spastic paraparesia with sphincter and sexual dysfunction. Cerebellar ataxia may be present in up to 10% of these patients [6, 11]. White matter MRI lesions in the parietooccipital regions of the brain are commonly found. An increased level of very long chain fatty acids in plasma is diagnostic and the disease is due to mutations in the *ABCD1* gene. Conversely, in >50 year old males with suspected X-linked

ataxia, the fragile-X-associated tremor ataxia syndrome diagnostic should be considered. The syndrome combines progressive intention tremor, cerebellar ataxia, and white matter disease in the middle cerebellar peduncles. Additional features contributing to the diagnosis include executive function and memory deficits, parkinsonism, and additional MRI findings of global brain atrophy and white matter disease [14]. It has been reported in elderly male carriers of premutation allele (>200 CGG repeats) within the *FMR1* gene, and the diagnostic should be considered in all males with onset of ataxia above 50 years because the carrier frequency is high (1:810 males).

25.2.4 Mitochondrial Cerebellar Ataxia

Cerebellar ataxia is found in most subtypes of mitochondriopathies (MERFF, MELAS, NARP, Kearns-Sayre, Leigh and May-White syndromes). These are all multisystem disorders with involvement of peripheral and central nervous systems, heart, eyes, ears, guts, kidney and bone marrow as well as endocrine dysfunction.

25.2.5 Idiopathic Late-Onset Cerebellar Ataxia (ILOCA)

After exclusion of symptomatic cerebellar ataxia, a hereditary ataxia should be considered in patients younger than 50 even if the family history is negative. Recessive ataxias should be screened followed by SCAs. When all diagnostic tests are negative, the acronym ILOCA should be used.

25.2.6 Multiple System Atrophy (MSA)

MSA is the most common disease causing isolated late-onset cerebellar ataxia (30%) with a prevalence of 1.9–4.9 cases per 100,000 people. Clinical hallmarks include autonomic and urinary dysfunction, Parkinsonism, and cerebellar and corticospinal tract symptoms and signs. Diagnosis is considered possible, probable or definite according to established criteria [62]. It usually starts in the sixth decade with a mean survival of 6–9 years. Some patients show predominant Parkinsonism signs, some of them showing predominant cerebellar signs. MRI show olivopontocerebellar and putaminal atrophy, with hyperintensities of the pons and middle cerebellar peduncles in T2-weighted images. Pathologically, MSA is a α-synucleopathy with glial cytoplasmic inclusions. No effective treatment is available for MSA.

Table 25.1 Genetics of dominantly inherited autosomal spinocerebellar ataxias

Name	Locus	OMIM	Gene	Average onset (range in years)	Distinguishing clinical features
SCA1	6p22.3	164400	*ATXN1*	3rd–4th decade (<10 to >60)	Pyramidal signs, peripheral neuropathy.
SCA2	12q24.12	183090	*ATXN2*	3rd–4th decade (<10 to >60)	Slow saccadic eye movements, peripheral neuropathy, dementia.
SCA3	14q32.12	109150	*ATXN3*	4th decade (10–70)	Pyramidal and extrapyramidal signs, lid retraction, nystagmus, decreased saccade velocity, amyotrophy, fasciculations, sensory loss.
SCA4	16q22.1	600223	Unknown	4th–7th decade (19–72)	Sensory axonal neuropathy, deafness, may be allelic with SCA31.
SCA5	11q13.2	600224	*SPTBN2*	3rd–4th decade (10–68)	Early onset, slow course, first reported in descendant of Abraham Lincoln.
SCA6	19p13.2	183086	*CACNA1A*	5th–6th decade (19–71)	Usually pure phenotype, sometimes episodic ataxia, very slow progression.
SCA7	3p14.1	164500	*ATXN7*	3rd–4th decade (0.5–60)	Visual loss with retinopathy.
SCA8	13q21	608768	*ATXN8OS*	4th decade (1–65)	Slowly progressive, sometimes hyperreflexia, decreased vibration sense; rarely, cognitive impairment.
SCA9	Unknown	612876	Unknown	Unpublished	Ophthalmoplegia, dysarthria, pyramidal and extrapyramidal tract signs, weakness, posterior column signs, parkinsonism, phenotype resembling multiple sclerosis.
SCA10	22q13.31	603516	*ATXN10*	4th decade (12–48)	Occasional seizures, most families are of Native American background.
SCA11	15q15.2	604432	*TTBK2*	Age 30 (15–70)	Usually pure mild phenotype, remain ambulatory.
SCA12	5q32	604326	*PPP2R2B*	4th decade (8–62)	Slowly progressive, hyperreflexia, subtle parkinsonism, cognitive/psychiatric disorder.
SCA13	19q13.33	605259	*KCNC3*	Childhood or adulthood	Mild intellectual disability, short stature.

(continued)

Table 25.1 (continued)

Name	Locus	OMIM	Gene	Average onset (range in years)	Distinguishing clinical features
SCA14	19q13.42	605361	*PRKCG*	3rd–4th decade (3–70)	Early axial myoclonus.
SCA15/ SCA16	3p26.1	606658	*ITPR1*	4th decade (7–66)	Pure ataxia, very slow progression, head tremor in Japanese family.
SCA17/ HDL4	6q27	607136	*TBP*	4th decade (3–55)	Mental retardation, occasional chorea, dystonia, myoclonus, epilepsy.
SCA18	7q22-q32	607458	*IFRD1*	Adolescence (12–25)	Early sensory-motor neuropathy, muscle weakness, atrophy, fasciculation, Babinski response.
SCA19/ SCA22	1p21-q21	607346	*KCND3*	4th decade (10–51)	Slowly progressive, rare cognitive impairment, myoclonus, hyperreflexia.
SCA20	11q12.2-11q13.3	608687	Unknown	5th decade (19–64)	Early dysarthria, spasmodic dysphonia, hyperreflexia, bradykinesia, calcification of the dentate nucleus.
SCA21	7p21.3-p15.1	607454	*TMEM240*	6–30	Mild cognitive impairment.
SCA23	20p13	610245	*PDYN*	5th–6th decade	Dysarthria, abnormal eye movements, reduced vibration and position sense.
SCA24	Unknown	–	Unknown	Unknown	No published data available.
SCA25	2p21-p15	608703	Unknown	1.5–39	Sensory neuropathy.
SCA26	19p13.3	609306	*EEF2*	26–60	Dysarthria, irregular visual pursuit.
SCA27	13q33.1	609307	*FGF14*	11 (7–20)	Early-onset tremor, dyskinesia, cognitive deficit.
SCA28	18p11.21	610246	*AFG3L2*	19.5 (12–36)	Nystagmus, ophthalmoparesis, ptosis, hyperreflexia.
SCA29	3p26	117360	*ITPR1*	Early childhood	Learning deficits.
SCA30	4q34.3-q35.1	613371	Unknown	(45–76)	Hyperreflexia.
SCA31	16q21-q22	117210	*BEAN/TK2*	5th–6th decade	Normal sensation.
SCA32	7q32-33	613909	Unknown	Adulthood	Variable mental impairment, azoospermia.
SCA33	Unknown	–	Unknown	No published data	No published data available.

SCA34	6q14	133190	*ELOVL4*	Cutaneous signs in childhood	Erythrokeratodermia in childhood. Allelic to Stargardt macular dystrophy 3 and autosomal recessive ichthyosis, spastic quadriplegia, and mental retardation.
SCA35	20p13	613908	*TGM6*	Age 43.7 (40–48)	Hyperreflexia, Babinski responses, spasmodic torticollis.
SCA36	20p13	614153	*NOP56*	Age 52.8±4.3	Muscle fasciculations, tongue atrophy, hyperreflexia.
SCA37	1p32	615945	*DAB1*	Age 48 (38–64)	Slowly progressive pure phenotype, early abnormal vertical saccades and pursuit.
SCA38	6p	615957	*ELOVL5*	(34–51)	Usually pure phenotype, slow saccades, few subjects with axonal neuropathy.
SCA39	11q21-11q22.3	–	*44 genes (7.5 Mb)*	40th decade	Ataxia with spasticity and mild mental retardation.
SCA40	14q32.2	616053	*CCDC88C*	4th decade	Ocular dysmetria, impaired vertical gaze, hyperreflexia, spastic paraparesia.
SCA41	4q27	616410	*TRPC3*	38	Gait instability and imbalance.
SCA42	17q21.33	616795	*CACNA1G*	9–78	Dysarthria, saccadic pursuit.
SCA43	3q25.2	617018	*MME*	42–68	Dysarthria, dysmetria, hypometric saccades.
SCA44	6q24.3	617691	*GRM1*	3rd to 6th decade	Gait and limbs ataxia, spasticity, hypermetric saccades.
EA1	12p13.32	160120	*KCNA1*	1st–2nd decade (2–15)	Myokimia, attacks lasting seconds to minutes; startle or exercise induced; no vertigo.
EA2	19p13.2	108500	*CACNA1A*	2–32	Nystagmus; attacks lasting minutes to hours; posture-change induced; vertigo; later, permanent ataxia.
EA3	1q42	606554	Unknown	1–52	Vestibular ataxia, vertigo, tinnitus, and interictal myokymia. Absence of interictal nystagmus.
EA4	Unknown	606552	Unknown	Early adulthood 6th decade	Recurrent attacks of vertigo, diplopia, oscillopsia, and ataxia beginning in early adulthood. Slowly progressive cerebellar ataxia occurred in some.

(continued)

Table 25.1 (continued)

Name	Locus	OMIM	Gene	Average onset (range in years)	Distinguishing clinical features
EA5	2q23.3	613855	*CACNB4*		Recurrent episodes of vertigo and ataxia. Spontaneous downbeat and gaze-evoked nystagmus, mild dysarthria and truncal ataxia.
EA6	5p13.2	612656	*SLC1A3*	Childhood	Allelic with SCA6 and hemiplegic migraine.
EA7	19q13	611907	Unknown	<20	Attacks (hours to days), with weakness and dysarthria, or vertigo, triggered by exercise and excitement; interictal migraine headaches.
EA8	1p36.13-p34.3	616055	Unknown	2	Twitching around the eyes, muscle weakness, intention tremor, myokymia.
ADSA	8p12-q12.1	608984	*RNF170*	28–55	Instability in the dark, Romberg sign, no cerebellar signs, preganglionic posterior columns abnormalities.
SPAX1	12p13	108600	*VAMP1*	1st–7th decades	Initial progressive leg spasticity, involuntary head jerk, dysarthria, dysphagia, ocular movement abnormalities.
ADCADN	6p21-23	604121	*DMNT1*	Adulthood	Deafness, narcolepsy, optic atrophy, primitive reflexes, pseudobulbar signs, incontinence, pyramidal signs, cataracts, nystagmus, ataxia, head tremor, resting tremor, mental deterioration, sensorimotor polyneuropathy.
CIAT/ ADHD	12q13	614306	*SCAN8A*	9–¿? A single pedigree with children and adults	Delayed psychomotor development, attention deficit disorder, esophoria, amblyopia, gaze-evoked nystagmus in childhood. Adult onset with emotional instability and mild cognitive impairment.

SCA Spinocerebellar ataxia, *EA* Episodic ataxia

Table 25.2 Autosomal recessive ataxias to be considered in adults

Name	Locus	OMIM	Gene	Average onset (range in years)	Distinguishing clinical features
FRDA	9q21.11	229300	*FXN*	1st–2nd decade (4–40)	Hyporeflexia, babinski responses, sensory loss, cardiomyopathy.
AT	11q22.3	208900	*ATM*	1st decade	Telangiectasia, immune deficiency, cancer, increased α–fetoprotein.
ATLD1	11q21	604391	*MRE11A*	Early childhood	Oculomotor apraxia, chorea, distal muscle wasting.
ATLD2	20p12.3	615919	*PCNA*	Early childhood	Sensorineural hearing loss, conjunctival and cutaneous telangiectasia.
AVED	8q12.3	277460	*TTPA*	<50 (2–52)	Similar to FA, head titubation.
Abeta lipoproteinemia	4q23	200100	*MTP*	Childhood to young adulthood	Celiac syndrome, retinis pigmentosa, progressive ataxic neuropathy, acanthocytosis, serum cholesterol very low, serum beta lipoprotein absent.
AOA1	9p21.1	208920	*APTX*	Childhood, rare adulthood	Oculomotor apraxia, choreoathetosis, mild intellectual disability, hypoalbuminemia.
AOA2/SCAR1	9q34.13	606002	*SETX*	10–22	Oculomotor apraxia, sensory-motor polyneuropathy.
AOA3	17p13.1	615217	*PIK3R5*	1st decade	Oculomotor apraxia, increased alpha-fetoprotein, axonal sensory polyneuropathy.
AOA4	19q13.33	616267	*PNKP*	1st decade (1–9)	Oculomotor apraxia, distal muscle weakness and atrophy.
Refsum disease	10p13	266500	*PHYH*	1st–6th decade	Neuropathy, deafness, ichthyosis, retinopathy.
PHARC	20p11	612674	*ABHD12*	Full expression in adulthood	Polyneuropathy, hearing loss, ataxia, retinitis pigmentosa, cataract.
MIRAS	15q26.1	607459	*POLG1*	Childhood to young adulthood	Nystagmus, dysarthria, epilepsy.
SANDO	15q26.1	607459	*POLG1*	Childhood to young adulthood	Abnormal eye movements, RRF, myopathy, dysphagia, neuropathy, myopathy.
CTX	2q35	213700	*CYP27A1*	Childhood to young adulthood	Thick tendons, cognitive decline, dystonia, white matter disease, cataract.

(continued)

Table 25.2 (continued)

Name	Locus	OMIM	Gene	Average onset (range in years)	Distinguishing clinical features
Adult Tay-Sachs	15q23	272800	*HEXA*	Young adulthood	Childhood clumsiness, proximal muscle weakness, ataxia, dysarthria, tremor, no cherry red spots, abnormal eye movements.
Adult GM1	3p22.3	230650	*GLB1*	Young adulthood	Variable phenotype. A form with ataxia, mental retardation, vertebral changes, mild visceromegaly.
Niemann-Pick C	18q11.2	257220	*NPC1*	Young adulthood	Mild intellectual impairment, supranuclear vertical gaze paresis, ataxia; later dementia/psychiatric symptoms; variably, seizures and extrapyramidal deficits.
SCAR3	6p21-23	271250	Unknown	Young adulthood, adulthood	Deafness, blindness.
SCAR4	1p36	607317	Unknown	Young adulthood	Pyramidal signs, sensorimotor neuropathy, striking eye movement abnormalities (overshooting horizontal saccades, macrosaccadic oscillations.
SCAR7	11p15	609270	*TPP1*	Childhood to young adulthood	Hyperreflexia, Babinski responses, saccadic pursuit, oculomotor apraxia, impaired neurocognitive function.
SCAR8	6q25.2	610743	*SYNE1*	Childhood to young adulthood	Pure phenotype in adult onset; motor neuron disease in children.
SCAR10	3p22.1-p22.3	613728	*ANO10*	Teenage to young adulthood	Hyperreflexia, mental retardation. Low CoQ10 plasma and muscle levels.
SCAR19/ Lichtenstein-Knorr disease	1p36.11	616291	*SLC9A1*	Childhood or young adulthood	Sensorineural hearing loss, dizziness.
SCAR26	19q13.31	617633	*XRCC1*	28	Oculomotor apraxia, sensory loss, distal polyneuropathy.
SPAX3	2q33.1	611390	*MARS2*	Birth to 59	Spasticity, cerebral palsy, dysarthria.

FRDA Friedreich ataxia, *AT* ataxia telangiectasia, *AOA* ataxia with oculomotor apraxia, *PHARC* polyneuropathy, hearing loss, ataxia, retinitis pigmentosa and cataract, *MIRAS* mitochondrial recessive ataxic syndrome, *SANDO* sensory ataxia, neuropathy, dysarthria and ophthalmoplegia, *CX* cerebrotendinous xanthomatosis, *RRF* ragged red fibers, *SCAR* spinocerebellar ataxia autosomal recessive

Table 25.3 Autosomal recessive ataxias with exclusive or predominantly onset in childhood

Name	Locus	OMIM	Gene	Average onset (range in years)	Distinguishing clinical features
IOSCA Mitochondrial DNA depletion syndrome	10q24.31	271245	*C10ORF2*	Infancy	Finland. Neuropathy, athetosis, optic atrophy, deafness, ophthalmoplegia, seizures.
Marinesco-Sjögren syndrome	5q31.2	248800	*SIL1*	Infancy	Intellectual disability, cataract, hypotonia, short stature, myopathy.
Human Cayman ataxia	19p13.3	601238	*ATCAY*	Early childhood	Marked psychomotor retardation, hypotonia.
ARSACS	13q12.12	270550	*SACS/sacsin*	12–18 months	Dysarthria, spasticity, neuropathy, retinal striation.
SPAX5	18p11.21	614487	*AFG3L2*	Early childhood	Spasticity, oculomotor apraxia, dystonia, myoclonic epilepsy.
CoQ deficiency	1q42.13; 4q21.22-q21.23; 16q13; 10p12; 6q21	612016; 607426; 614654; 614651; 614652	*COQ8A;COQ2;COQ9; PDSS1;PDSS2*	Childhood	Seizures, cognitive decline, pyramidal signs, myopathy.
SCAN1	14q32.11	607250	*TDP1*	Late childhood	Sensory-motor neuropathy (Charcot-Marie-Tooth like)
SCAR2	9q34.3	213200	*PMPCA*	Infancy	Mental retardation.
SCAR5 Galloway-Mowat syndrome	15q25.2	251300	*WDR73*	Infancy	Microcephaly, CNS abnormalities, severe delayed psychomotor development, hiatal hernia, nephrotic syndrome, optic atrophy, seizures.
SCAR6	20q11-q13	608029	Unknown	Infancy	Non-progressive congenital ataxia, spasticity, short stature, pes planus.

(continued)

Table 25.3 (continued)

Name	Locus	OMIM	Gene	Average onset (range in years)	Distinguishing clinical features
SCAR9/ COQ10D4	1q42.13	612016	*ADCK3*	Childhood	Exercise intolerance, seizures, mental retardation.
SCAR11	1q32.2	614229	*SYT14*	Childhood	Psychomotor retardation in childhood; ataxia in fifties.
SCAR12	16q23.1-q23.2	614322	*WWOX*	Infancy	Seizures, mental retardation.
SCAR13	6q24.3	614831	*GRM1*	Infancy	Seizures, mental retardation, pyramidal signs, ophthalmological abnormalities (ptosis, esotropia, abduction deficits, nystagmus, hypometric saccades), short stature.
SCAR14	11q13	615386	*SPTBN2*	Infancy	Delayed psychomotor development, mental retardation, spasticity.
SCAR15	3q29	615705	*K1AA0226/RUBCN*	Infancy	Epilepsy, delayed motor development, cognitive deficits.
SCAR16	16p13.3	615768	*STUB1*	Teenage	Spasticity, sensory neuropathy.
SCAR17	10q24.31	616127	*CWF19L1*	Infancy	Non-progressive congenital cerebellar ataxia.
SCAR18	4q22	616204	*GRID2*	Infancy	Delayed psychomotor development, mental retardation.
SCAR20	6q14.3	616354	*SNX14*	Early infancy	Severely delayed psychomotor development, poor or absent speech, coarse facies.
SCAR21	11q13.1	616719	*SCYL1*	Infancy	Liver failure with liver fibrosis, mild learning disabilities, late neuropathy.

SCAR22	2q21.23	616948	*VWA3B*	Childhood	Normal development followed by intellectual disability, adult-onset ataxia.
SCAR23	6p22.3	616949	*TDP2*	Infancy	Seizures, intellectual disability.
SCAR24	3q22.1	617133	*UBA5*	5–8	Cataract, cerebellar gait and limb, speech disorders
SCAR25	6q21	617584	*ATG5*	Congenital	Inability to read or write, low IQ, truncal ataxia
SPAX4	10p11.23	613672	*MTPAP*	Early childhood	Optic atrophy, learning difficulties, cerebellar and spastic dysarthria
SPAX8	10q26.3	617560	*NKX6-2*	1 month to 5 years	Progressive until CNS myelination is complete, then stable.
CAMRQ1-4	9p24	224050	*VLDLR*	Infancy	Non-progressive congenital cerebellar ataxia, mental retardation, strabismus, seizures, short stature, cataracts.
	17p	610185	*WDR81*		
	8q11	613227	*CA8*		
	13q12	615268	*ATP8A2*		

IOSCA infantile onset spinocerebellar ataxia, *ARSACS* autosomal recessive spastic ataxia Charlevoix-Saguenay type, *SCAN* spinocerebellar ataxia with axonal neuropathy, *SCAR* spinocerebellar ataxia autosomal recessive, *CAMRQ* cerebellar ataxia, mental retardation dysequilibrium syndrome

25.3 Hereditary Spastic Paraplegias

The hereditary spastic paraplegias (HSPs) were first identified by Seeligmüller, Strümpell and Lorrain as an autosomal dominant disease, characterised by progressive spasticity and weakness of the lower limbs, with moderate loss of vibratory sense and bladder dysfunction. At that time, the neuropathological hallmark of the disease was also described as the degeneration of the longest spinal pathways, corticospinal tracts, and medial dorsal columns. The classification of HSPs is difficult and, throughout the years, several proposals have been made based on phenotype, mode of inheritance, and mutated gene (SPGs). All modes of hereditary transmission are found: autosomal dominant (AD), autosomal recessive (AR), X-linked (XL), and mitochondrial inheritance. Clinically, the HSPs have been subdivided into pure and complex forms, according to the presence or absence of other neurological and extra-neurological features.

25.3.1 Clinical Manifestations

The initial symptoms in HSP patients include a feeling of stiffness, muscle cramps, inability to walk rapidly and frequent falls. In early-onset cases the disease is often expressed as delayed gait acquisition. Age-at-onset is highly variable, particularly for pure forms, ranging from the first year of life to the 8th decade, tending to be later in autosomal dominant forms and earlier in recessive ones. At disease onset, spasticity is usually noticeable only while walking. Over time, especially in complex forms, pyramidal signs may affect the upper limbs, though many patients show only tendon hyperreflexia that may include a brisk jaw reflex; weakness or spasticity of the upper limbs is rare, particularly in pure forms. In some patients with complex forms, dysarthria and dysphagia may present as a pseudobulbar state. Other manifestations include cognitive impairment (mental retardation or deterioration), epilepsy, optic atrophy, amyotrophies, neuropathy (usually axonal), ataxia and dystonia [15].

Until now, 89 loci and 75 genes have been identified: 20 autosomal dominant, 57 autosomal recessive, five X-linked, one with mitochondrial inheritance, and 6 with both dominant and recessive transmission (Table 25.4). A recent study has identified HSP mutations in genes associated with Parkinson (*ATP13A2/SPG78*), neuronal ceroid lipofuscinosis (*TPP1*), and the hereditary motor and sensory neuropathy (*DNMT1*), highlighting the genetic, in addition to the clinical, heterogeneity of spastic paraplegia [17].

Table 25.4 Genetics of spastic paraplegias

Name	Locus	OMIM	Gene	Mode of inheritance	Average onset (range in years)	Distinguishing clinical features
SPG1	Xq28	303350	*L1CAM*	X-linked	Infancy	Ataxia, mental retardation, hydrocephalus.
SPG2	Xq22.2	312920	*PLP1*	X-linked	Infancy or childhood	Pure or with cerebellar dysfunction, hypotonia, dementia, seizures, mental retardation.
SPG3A	14q22.1	182600	*ATL1*	AD and AR	Before 10 (1–68)	Pure or rarely axonal neuropathy.
SPG4	2p22.3	182601	*SPAST*	AD	30 (1–80)	Pure or neuropathy, cognitive impairment, agitation.
SPG5A	8q21.3	270800	*CYP7B1*	AR	Variable (1–47)	Pure or cerebellar signs, nystagmus, cognitive impairment.
SPG6	15q11.1	600363	*NIPA1*	AD	16.5 (9–35)	Pure or rarely neuropathy.
SPG7	16q24.3	602783	*SPG7*	AD and AR	30 (25–42)	Pure or optic atrophy, supranuclear palsy, ataxic gait, pyramidal signs.
SPG8	8q24.13	603563	*KIAA0196*	AD	Adult onset (18–60)	Pure or atrophy of shins.
SPG9	10q24.1	601162	*ALDH18A1*	AD and AR	Variable (1–30)	Pure or amyotrophy, cataracts, neuropathy, gastroesophageal reflux.
SPG10	12q13	604187	*KIF5A*	AD	Variable (2–51)	Pure or neuropathy, amyotrophy.
SPG11	15q21.1	610844	*SPG11*	AR	Early variability (1–30)	Pure or amyotrophy, neuropathy, cognitive decline, cerebellar signs.
SPG12	19q13	604805	*RTN2*	AD	6.9 (5–22)	Pure.
SPG13	2q33.1	605280	*HSPD1*	AD	39 (17–68)	Pure or pyramidal signs.
SPG14	3q27-q28	605229	Unknown	AR	30	Pure or mental retardation, distal motor neuropathy.
SPG15	14q24.1	270700	*ZFYVE26*	AR	Infancy or childhood (5–19)	Pure or distal amyotrophy, cerebellar signs, ataxia, cognitive deterioration, axonal neuropathy.

(continued)

Table 25.4 (continued)

Name	Locus	OMIM	Gene	Mode of inheritance	Average onset (range in years)	Distinguishing clinical features
SPG16	Xq11.2	300266	Unknown	X-linked	Infancy	Pure or quadriplegia, motor aphasia, mental retardation, pyramidal signs.
SPG17	11q13	270685	*BSCL2*	AD	Variable (2–60)	Neuropathy, distal limb muscle atrophy and weakness.
SPG18	8p11.2	611225	*ERLIN2*	AR	Infancy (1–6)	Mental retardation, contractures, primary lateral sclerosis.
SPG19	9q33-q34	607152	Unknown	AD	47 (36–55)	Pure.
SPG20	13q12.3	275900	*SPG20*	AR	Early childhood	Troyer syndrome, distal amyotrophy, cerebellar signs.
SPG21	15q22.31	248900	*SPG21*	AR	Adulthood	Mast syndrome, frontotemporal atrophy, pyramidal signs.
SPG22	Xq13.2	300523	*SLC16A2*	X-linked	Infancy	Mental retardation, dystonia, ataxia, quadriplegia.
SPG23	1q32.1	270750	*DSTYK*	AR	Early childhood	Hyperpigmentation, cognitive impairment, peripheral neuropathy.
SPG24	13q14	607584	Unknown	AR	Early onset	Pure.
SPG25	6q23-q24.1	608220	Unknown	AR	Adulthood (30–46)	Sensory or motor neuropathy, pyramidal signs secondary to spinal cord compression.
SPG26	12q13.3	609195	*B4GALNT1*	AR	Childhood (2–19)	Dystonia, ataxia, distal amyotrophy, mental retardation.
SPG27	10q22.1-q24.1	609041	Unknown	AR	Adulthood (25–45)	Pure or sensorimotor polyneuropathy, dysarthria, hyperactive bladder.
SPG28	14q22.1	609340	*DDHD1*	AR	Childhood (7–15)	Pure or pyramidal signs, distal sensory impairment in lower limbs.
SPG29	1p31.1-p21.1	609727	Unknown	AD	Infancy	Neonatal hyperbilirubinemia, auditory neuropathy, hiatal hernia.

SPG30	2q37.3	610357	*KIF1A*	AD/AR	Variable (10–39)	Pure axonal neuropathy or cerebellar signs.
SPG31	2p11.2	610250	*REEP1*	AD	30 (2–45)	Pure distal sensory loss, amyotrophy.
SPG32	14q12-q21	611252	Unknown	AR	Childhood	Mild mental retardation, cerebellar atrophy.
SPG33	10q24.2	610244	*ZFYVE27*	AD	Adulthood (42–50)	Pure.
SPG34	Xq24-q25	300750	Unknown	X-linked	Adulthood (10–25)	Pure.
SPG35	16q23.1	612319	*FA2H*	AR	(3–11)	Dystonia, optic atrophy, ataxia, cognitive decline, seizures.
SPG36	12q23-q24	613096	Unknown	AD	24 (14–33)	Demyelinating motor and sensory neuropathy.
SPG37	8p21.1-q13.3	611945	Unknown	AD	32 (8–60)	Pure.
SPG38	4p16-p15	612335	Unknown	AD	Young adulthood (16–19)	Pure.
SPG39	19p13.2	612020	*PNPLA6*	AR	1st decade	Distal muscle atrophy, axonal motor neuropathy.
SPG40	Reserved	–	–	AD	–	Pure.
SPG41	11p14.1-p11.2	613364	Unknown	AD	Young adulthood (16–19)	Pure.
SPG42	3q25.31	612539	*SLC33A1*	AD	Variable (4–42)	Pure.
SPG43	19q12	615043	*C19orf12*	AR	1st decade	Distal muscle atrophy and weakness, neuropathy.
SPG44	1q42.13	613206	*GJC2*	AR	1st–2nd decade	Cerebellar ataxia, cognitive impairment.
SPG45/ SPG65	10q24.32-q24.33	613162	*NT5C2*	AR	2nd year	Mental retardation, delayed motor development.
SPG46	9p13.3	614409	*GBA2*	AR	Childhood (2–16)	Cerebellar ataxia, cataracts, mental retardation.
SPG47	1p13.2	614066	*AP4B1*	AR	Birth	Mental retardation, seizures, dystonia.

(continued)

Table 25.4 (continued)

Name	Locus	OMIM	Gene	Mode of inheritance	Average onset (range in years)	Distinguishing clinical features
SPG48	7p22.1	613647	*AP5Z1*	AR	Adulthood (2–50)	Pure or complex with cognitive impairment or mental retardation.
SPG49	14q32.31	615031	*TECPR2*	AR	2nd year	Ataxia, brachycephaly, intellectual disability, hypoventilation, areflexia.
SPG50	7q22.1	612936	*AP4M1*	AR	Birth	Mental retardation, seizures, cerebellar atrophy, strabismus.
SPG51	15q21.2	613744	*AP4E1*	AR	Birth	Mental retardation, seizures, cerebellar atrophy, hypotonia.
SPG52	14q12	614067	*AP4S1*	AR	Birth	Mental retardation, microcephaly, axial hypotonia, lack of speech development, stereotypic laughter, shyness.
SPG53	8p22	614898	*VPS37A*	AR	Infancy (1–2)	Kyphosis, cognitive impairment, delayed speech.
SPG54	8p11.23	615033	*DDHD2*	AR	Infancy (0–2)	Mental retardation, short stature, strabismus, telecanthus.
SPG55	12q24.31	615035	*C12orf65*	AR	1st decade	Visual loss, optic atrophy, intellectual impairment, axonal neuropathy.
SPG56	4q25	615030	*CYP2U1*	AR	1st decade (0–8)	Pure or axonal neuropathy, dystonia, cognitive impairment.
SPG57	3q12.2	615658	*TFG*	AR	1st year	Optic atrophy, axonal and demyelinating sensorimotor neuropathy, muscle weakness and atrophy.
SPG58	17p13.2	611302	*KIF1C*	AR	Teenage	Pure or ataxia, dysarthria, distal muscle atrophy.
SPG59	15q21.2	603158	*USP8*	AR	Infancy	Nystagmus, mental retardation.
SPG60	3p22.2	612167	*WDR48*	AR	1st year	Nystagmus, neuropathy.

SPG61	16p12.3	615685	*ARL6IP1*	AR	Infancy	Acropathy, diffuse motor and sensory polyneuropathy.
SPG62	10q24.31	615681	*ERLIN1*	AR	Infancy	Pure
SPG63	1p13.3	615686	*AMPD2*	AR	Infancy	Short stature, amyotrophy.
SPG64	10q24.1	615683	*ENTPD1*	AR	Infancy	Amyotrophy, cerebellar signs, intellectual disability.
SPG66	5q32	610009	*ARSI*	AR	Infancy	Amyotrophy, sensory motor and polyneuropathy.
SPG67	2q33.1	611655	*PGAP1*	AR	Infancy	Amyotrophy.
SPG68	11q13.1	604806	*FLRT1*	AR	Infancy	Optic atrophy, amyotrophy, neuropathy.
SPG69	1q41	–	*RAB3GAP2*	AR	Infancy	Dysarthria, cataract, deafness, intellectual disability.
SPG70	12q13.3	156560	*MARS*	AR	Infancy	Amyotrophy, contractures.
SPG71	5p13.3	615635	*ZFR*	AR	Infancy	Pure.
SPG72	5q31.2	615625	*REEP2*	AD/AR	Infancy	Pure.
SPG73	19q13.33	616282	*CPT1C*	AD	Adulthood (19–48)	Muscle atrophy, urinary dysfunction, delayed central sensory evoked potentials.
SPG74	1q42.13	616451	*IBA57*	AR	1st decade	Optic atrophy, axonal peripheral neuropathy, distal leg muscle atrophy.
SPG75	19q13.12	616680	*MAG*	AR	Early childhood	Optic atrophy, distal muscle atrophy, cognitive impairment, cerebellar signs, peripheral neuropathy.
SPG76	11q13.1	616907	*CAPN1*	AR	28 (19–39)	Cerebellar signs, sensory axonal neuropathy.
SPG77	6p25.1	611592	*FARS2*	AR	Before 5	Pure.
SPG78	1p36.13	617225	*ATP13A2*	AR	Juvenile or adulthood	Cognitive decline, strabismus, sensory-motor polyneuropathy.
SPG79	4p13	615491	*UCHL1*	AR	5–10	Blindness, cerebellar ataxia.

(continued)

Table 25.4 (continued)

Name	Locus	OMIM	Gene	Mode of inheritance	Average onset (range in years)	Distinguishing clinical features
–	19p13.2	602378	*DNM2*	AD	Young Adulthood	Pure.
–	2p25.1	615759	*KIDINS220*	AD	1st year	Intellectual disability, nystagmus, obesity.
SPOAN	11q13.2	609541	*KLC2*	AR	Infancy	Optic atrophy and neuropathy.
–	6p21.1	–	*KLC4*	AR	Infancy	Hearing and vision loss, ataxic gait.
–	1q42.3	606897	*LYST*	AR	Adulthood (48–58)	Cerebellar ataxia, peripheral neuropathy.
–	5p15.2	256840	*CCT5*	AR	Infancy	Mutilating sensory neuropathy.
–	9p13.2	606489	*EXOSC3*	AR	Infancy	Cognitive disability, cerebellar signs, amyotrophy.
–	9q22.31	609797	*BICD2*	AD/AR	Infancy	Spinal muscular atrophy.
–	Mit	516060	*MT-ATP6*	AD	Adulthood (30–50)	Pain, axonal neuropathy.
–	1p36.22	607093	*MTHFR*	AR	Adulthood (29–50)	Polyneuropathy, behavioural changes, cognitive impairment, psychosis, seizures, leukoencephalopathy.
–	19p13.3	602662	*TUBB4A*	AD	Infancy	Pyramidal involvement, ataxia gait, dysdiadochokinesia.

SPG Spastic paraplegia, *AD* Autosomal dominant, *AR* Autosomal recessive

25.3.2 Prevalence

Prevalence of HSP varies widely among studies, probably due to a combination of factors, such as variable diagnostic criteria, epidemiological methodology, and population differences. Reported estimates vary from 0.1 to 9.6/100,000 in different series, 0.5–5.5/100,000 for dominant forms, and 0.0–5.3/100,000 for the recessive ones [9]. The most common dominant spastic paraplegia (SPG) in all series is SPG4, while SPG11 is the most frequent among the recessive HSPs.

25.3.3 Pathogenic Mechanisms

HSPs are among the most genetically heterogeneous diseases (Table 25.4). Many of the proteins involved act in the same cellular processes; nevertheless, the number of cellular mechanisms known to be affected continue growing and include: abnormal mitochondrial function, axonal transport dysfunction, alterations in lipid metabolism, abnormal DNA repair, alterations in membrane trafficking, organelle shaping and autophagy [12, 17]. Currently, no specific treatment exists to prevent, delay, or reverse progressive disability in patients with hereditary spastic paraplegia.

25.4 Inherited Parkinson's Disease

Parkinson's disease (PD) (OMIM 168600) is the second most common neurodegenerative disease after Alzheimer's, albeit the inherited forms are considered rare presenting with a much lower prevalence [21, 25]. PD is characterized by instability, rigidity, bradykinesia, postural tremor, and positive response from Levodopa (30%). Its prevalence is higher than 1% in individuals over 50 years and about 3% in those older than 75. The physiopathology includes loss of dopaminergic neurons in the substantia nigra and the presence of Lewy bodies (LBs), except in a subtype of recessively inherited PD, *PARK2*, that courses without the typical ubiquitinated cell body inclusions. A direct relationship between several gene mutations and Parkinson's disease presenting with an autosomal dominant, recessive, and X-linked modes of inheritance has been demonstrated (Table 25.5).

In many cases there is a confirmed genetic linkage between some loci and Parkinson disease, but the gene has not been isolated as of yet for the following cases: PARK3 (2p13) (602404), PARK10 (1p32) (606852), and PARK11 (2q36) (607688). The PARK12 locus is located on Xq21- q25 (300557) and was the first case presenting with an X-linked mode of inheritance. Two additional genes have been associated with PD: SNCAIP (Synphilin-1, 5q23.1–q23.3) (603779), which codifies for a protein that interacts with α-synuclein. An unique mutation p.R621C within the *SNCAIP* gene in two sporadic cases with PD were identified demonstrating the

involvement of SNCAIP in PD [30]. In addition, a polymorphism within intron 6 of NR4A2 (Nuclear Receptor-related 1: NURR1) (2q22–q23) (601828) is present more frequently in affected patients than in healthy controls [64]. Two different mutations in Parkinson families, but not in sporadic cases [23], demonstrate the implication of NR4A2 in PD. However, other authors have not yet confirmed these findings.

25.4.1 Molecular Genetics Diagnosis

Traditionally the molecular genetics diagnosis in PD included the search for recurrent mutations within the genes implicated in Parkinson disease by DNA sequencing. If this approach was negative then, multiplex ligation-dependent probe amplification is used to look for gene dosage alterations in the *SNCA* gene. In the last years, implementation of next-generation sequencing enables the simultaneous analysis of a myriad of genes implicated in PD thus facilitating diagnosis (Table 25.5).

25.4.2 Autosomal Dominant Parkinson's Disease

25.4.2.1 SNCA/PARK1-4

Mutations in the *SNCA* gene on 4q21–23 coding for alpha-synuclein (OMIM 163890) were the first genetic defects identified causing PD [41]. Nevertheless, mutations within *SNCA* are rare, and thus far, only three different missense mutations as well as duplications and triplications of the entire gene have been reported. The *SNCA* gene contains 6 exons and spans 117 kb. The protein localises in presynaptic terminals and interacts *in vivo* with synphilin-1 resulting in characteristic eosinophilic inclusions. Of the three missense mutations identified to date, p.A53T is by far the most frequent mutation reported. Penetrance of the missense mutations appears to be high, 85% for p.A53T. Increase of the dosage of the *SNCA* gene in familial PD is associated with PARK4 [53]. Other known allelic variants including p.A30P, p.E46K, and the presence of polymorphisms within the gene promoter associate with major susceptibility to develop Parkinson's disease. These and other mutations are reported in the Parkinson's Disease Mutation Database (PDMTD; www.thepi.org/parkinson-s-disease-mutation-database).

25.4.2.2 LRRK2/PARK8

Mutations in the *LRRK2* gene are the most frequent cause of late-onset autosomal dominant and sporadic PD with a mutation frequency ranging from 2 to 40% [5, 36]. LRRK2 parkinsonism is clinically indistinguishable from idiopathic PD.

LRRK2 codifies the leucine-rich repeat kinase 2 Dardarin, a protein with 2,482 amino acids containing a leucine-rich repeat, as well as kinase, Ras, and WD40 domains. The multidomain protein structure supports for a multifactorial role of LRRK2 in the neurodegenerative pathogenesis. The gene contains 51 exons and spans 144 kb. More than 20 mutations over the different protein motifs have been identified. The more prevalent mutations include G2019S, R1441G, and I2020T. To date, the mutations identified in LRRK2 are missense, two of them corresponding to intronic nucleotide changes (source: PDMTD).

25.4.3 Autosomal Recessive Parkinson's Disease (ARPD)

25.4.3.1 PARKIN/PARK2

Parkin was the second identified PD gene and the first gene irrefutably causing an AR form of the disorder. Mutations in this gene trigger a disease onset usually in the third or fourth decade of the patients' life, with slowly progression and an excellent response to dopaminergic treatment. However, some of *Parkin*-mutation carriers have an onset even in childhood, and homozygous mutations in *Parkin* are the most frequent cause of juvenile PD (age of onset ≤21 years). The clinical phenotype of *Parkin*-, *PINK1*-, and *DJ-1*-linked PD is indistinguishable. Reported post-mortem examinations indicate that the substantia nigra shows neuronal loss and gliosis, however, it frequently lacks Lewy bodies. A large number (>100) and wide spectrum of *Parkin* mutations have been identified, including alterations in all 12 exons, across various ethnic groups (PDMTD). *Parkin* is one of the largest genes in the human genome, spanning 1.38 Mb in 12 exons. The gene codifies for a protein involved in the protein degradation pathway by the ubiquitin–proteasome system [20].

25.4.3.2 PINK1/PARK6

Mutations in the phosphatase and tensin homolog (*PTEN*)-induced putative kinase 1 (*PINK1*) gene are the second most common cause of AR early-onset PD (EOPD) after *Parkin* [58] and has been reported in sporadic cases as well. The frequency of *PINK1* mutations is in the range of 1–9%, with considerable variation across different ethnic groups. The gene contains 8 exons and spans 1.8 kb. More than 40 punctual, insertions or deletion mutations have been reported (PDMTD). PINK1 is a 581 amino acid ubiquitously expressed protein kinase. It consists of an amino-terminal 34 amino acid mitochondrial targeting motif, a conserved serine–threonine kinase domain (amino acids 156–509; exons 2–8), and a carboxy-terminal autoregulatory domain. Two-thirds of the reported mutations in PINK1 are loss-of-function mutations affecting the kinase domain, demonstrating the importance of PINK1's enzymatic activity in the pathogenesis of PD. Interestingly, recent studies provide evidence that PINK1 and Parkin function in a common pathway for sensing and

selectively eliminating damaged mitochondria from the mitochondrial network. PINK1 is stabilized on mitochondria with lower membrane potential, and as such, it recruits Parkin from the cytosol. Once recruited to mitochondria, Parkin becomes enzymatically active and initiates autophagic clearance of mitochondria by lysosomes, i.e., mitophagy.

25.4.3.3 DJ-1/PARK7

DJ-1 is the third gene associated with AR PD, and it is mutated in about 1–2% of EOPD cases [4, 37]. Given that *DJ-1*-linked PD seems to be rare, very few patients have been reported in the literature. However, about 10 different point mutations and exonic deletions have been described mostly in the homozygous or compound-heterozygous state. The function of *DJ-1* is not well known, yet it has been implicated as an oncogene and as a regulatory subunit of a RNA binding protein (RBP). The seven coding exons of the *DJ-1* gene encode for a 189-amino acid-long protein that is ubiquitously expressed and functions as a cellular sensor of oxidative stress. The DJ-1 protein forms a dimeric structure under physiologic conditions, and it seems that most of the disease-causing mutants (p.L166P, p.E64D, p.M26I, and p.D149A) heterodimerise with wild-type DJ-1. In addition, the mutated proteins are frequently not properly folded, unstable, and promptly degraded by the proteasome. Thus, their neuroprotective function and antioxidant activity are reduced. There is a genetic and biochemical association between DJ-1 and PINK1. On this regard, an early-onset PD Chinese family presenting with a digenic inheritance of mutations in both genes was identified [57]. It is believed that digenic inheritance occurs because the proteins codified by both genes are functionally related to produce the specific PD phenotype by an epistasis effect. Up to date, more than 25 missense, deletions, frameshift or duplication mutations in *DJ-1* have been reported (PDMTD).

25.4.3.4 ATP13A2/PARK9

Homozygous and compound-heterozygous mutations in *ATP13A2* have been found to cause an AR atypical form of PD named Kufor-Rakeb syndrome [42]. This syndrome has juvenile onset with rapid disease progression, accompanied by dementia, supranuclear gaze palsy, and pyramidal signs. *ATP13A2* is a large gene comprised of 29 exons coding for an 1,180-amino acid protein. The ATP13A2 protein is normally located in the lysosomal membrane and it contains ten transmembrane domains and an ATPase domain. About ten different pathogenic mutations have been identified in the homozygous or compound-heterozygous state, directly or indirectly affecting transmembrane domains. Most of the mutations produce truncated proteins that are unstable and are retained in the endoplasmic reticulum and subsequently degraded by the proteasome. No exonic deletions or deletions or multiplications of the entire gene have been found to date. Several single heterozygous missense mutations are known, but their role in PD pathogenicity is currently unclear.

25.4.4 Parkinsonism-Related Disorders

Neurodegeneration with brain iron accumulation (NBIA) is a genetically heterogeneous disorder characterized by progressive iron accumulation in the basal ganglia and other regions of the brain, resulting in extrapyramidal movements including Parkinsonism and dystonia. Age at onset, severity, and cognitive involvement are highly variable. Associated genes identified include *CP*, *FTL*, C19ORF12, *PLA2G6*, *PLAN*, *PANK2*, *WDR45*, and *COASY*. Mutations in *PANK2* account for most of the NBIA cases.

25.4.5 Mitochondrial Inheritance

Pathogenic mitochondrial DNA (mtDNA) mutations are also associated with PD. MtDNA is a 16,569 base pair length genome that encodes 13 genes for subunit components of the oxidative phosphorylation subunits (OXPHOS) and its own tRNAs and rRNAs. As hundreds to thousands copies of mtDNA reside in virtually each mammalian cell, a state of heteroplasmy arises when different mtDNA genotypes, such as wild type and mutant forms, co-exist within the same cell. Substantia nigra neurons from autopsies of normal aged people and PD patients harbour high levels of mutated mtDNA with large-scale deletions causing mitochondrial dysfunction. Furthermore, mitochondrial disease patients with mutations in polymerase γ, the polymerase responsible for mtDNA replication, excessively accumulate mtDNA mutations and also have an increased risk of developing PD. The many links between mitochondrial dysfunction and the pathogenesis of PD has stimulated interest in the roles of PINK1 and Parkin on mitophagy.

25.4.6 Multifactorial Inheritance

Vaughan et al. [59] proposed that nigral degeneration with the presence of Lewy bodies leading to the several clinical symptoms might represent a common final outcome of a multifactorial process of the disease due to genetic as well as environmental agents [59]. In these regard, it has been observed that the Mendelian inheritance has a major role in PD cases where the disease onset appears in the third or fourth decade of life whereas a polygenic model with a higher environmental participation would account for adult late-onset Parkinson's disease. In this later scenario several genes and their respective polymorphic variations would provide a priori risk contribution. This risk would be posteriorly modulated by acquired environmental circumstances.

Table 25.5 Genetics of Parkinson disease

Name	Locus	OMIM	Gene	Mode of inheritance	Average onset (range in years)	Distinguishing clinical features
PARK1	4q22.1	168601	*α- Synuclein (SNCA)*	AD	Mild to late adulthood	Cognitive decline, depression, dementia may occur.
PARK2	6q26	602544	*Parkin*	AR	Before 40s	Diurnal fluctuations of symptoms, hyperreflexia may occur.
PARK4	4q22.1	605543	α- synuclein *(SNCA)* duplications	AD	45	Hallucinations, paranoia, dementia.
PARK5	4p13	613643	*UCHL-1*	AD	(49–51)	Resting tremor, rigidity, bradykinesia, postural instability.
PARK6	1p36.12	605909	*PINK-1*	AR	(9–68)	Anxiety, diurnal fluctuation, depression.
PARK7	1p36.23	606324	*DJ-1*	AR	Before 40s	Anxiety, psychotic episodes, blepharospasm may occur.
PARK8	12q12	607060	*LRRK2*	AD	Reduced penetrance (50–65)	Hyposmia, neurofibrillary MAPT (tau)-positive tangles.
PARK9	1p36.13	606693	*ATP13A2*	AR	13	Hallucinations, psychotic episodes, supranuclear gaze palsy, atrophy of pyramids.
PARK13	2p13.1	610297	*HTRA2*	AD	57 (49–77)	Bradykinesia, tremor, muscular rigidity.
PARK14	22q13.1	612953	*PLA2G6*	AR	Young adulthood	Personality changes, eyelid opening apraxia, frontotemporal dementia, variable severity.
PARK15	22q12.3	260300	*FBXO7*	AR	Adolescence or young adulthood	Pyramidal and extrapyramidal signs, spasticity, mainly in the lower limbs.
PARK17	16q11.2	614203	*VPS35*	AD	(50–52)	Motor fluctuation, cramps, akinesia.
PARK18	3q27.1	614251	*EIF4G1*	AD	Late onset (50–80)	Lewy bodies, rigidity.
PARK19	1p31.3	615528	*DNAJC6*	AR	1st decade	Masked facies, mental retardation, seizures.
PARK20	21q22.11	615530	*SYNJ1*	AR	Early twenties	Eyelid apraxia, supranuclear gaze palsy, dysarthria.
PARK21	3q22.1	616361	*DNAJC13*	AD	Late-adult onset	Postural instability, Lewy bodies.
PARK22	7p11.2	616710	*CHCHD2*	AD	56.2 (10–61)	Asymmetry at onset, bradykinesia, rigidity, and gait disturbance.
PARK23	15q22.2	616840	*VPS13C*	AR	Young-adult onset	Incontinence, cognitive decline, axial symptoms.
PARK-RAB39B	Xq28	–	*RAB39B*	X-linked	Early infancy (2–52)	Delayed psychomotor development.

AD Autosomal dominant, *AR* Autosomal recessive

25.5 Inherited Dementias

The term dementia encompasses a group of cognitive, psychological, and memory problems which ultimately render an individual unable to carry-out daily functions involving social interactions, assessment of the environment and consequences of events, reasoning, and problem solving. There are 47.5 million people with dementia worldwide, and 8 million new cases diagnosed every year according to the most recent data published by the World Health Organization [63]. Genetics *per se* contributes to a small proportion of all dementia cases and thus familiar forms are considered rare. Alzheimer's disease (AD) is the most common cause of dementia accounting for 60–80% of all cases, followed by vascular dementia responsible for 25%, Lewy Body dementia (LBD) for 15%, and frontotemporal dementia lobar degeneration forms by less than 5%. Other genetically linked dementia include Niemann-Pick, Creutzfeldt-Jakob disease (CJD), Gerstmann-Straussler disease (GSD), and Huntington's disease [26]. Most individuals with dementia present the late-onset form starting after the age of 65 making up 90–95% of all cases. Although there are greater numbers of individuals with familial history of early-onset dementia, 95% of all cases are of unknown aetiology. Early-onset AD is 5–10% of all cases of which only 10% is familial [7]. Therefore, most recent efforts in dementia research have focused on finding the genetic factors causing Mendelian inheritance of dementia or can be one of the contributing factors to genetically complex diseases of which dementia forms part of the symptoms (Table 25.6).

25.5.1 Alzheimer's Disease (AD)

The most common symptoms of Alzheimer's disease include difficulty remembering recent events and conversations, often accompanied with apathy and depression followed by poor judgement, personality changes, disorientation, impaired communication, difficulty speaking, swallowing, and walking. AD is currently considered a disease of slow progression starting well before the presentation of symptoms. The major neuropathological hallmarks are the beta-amyloid protein fragment plaques and the tau protein tangles in addition to neuronal damage and loss. Some of the affected individuals express a mutation in one of three genes: the amyloid precursor protein gene (*APP*) and two presenilin genes (*PSEN1* and *PSEN2*). These mutations show dominant inheritance with low prevalence (1 in 1,000 people) and result in early-onset dementia (EOD) with presentation of symptoms as early as the third decade of life. On the other hand, AD presenting after the age of 65 is considered late-onset (LOAD), which is more common than EOAD and exhibits a complex inheritance. No specific gene has been identified to cause LOAD but rather a number of genes increasing the risk. The best known of such risk genes and the one with the highest effect is apolipoprotein E (APOE), found on chromosome 19. Specifically, one of its isoforms, APOE ε4 is present in about 25% of the total

population and is associated with the highest risk for developing AD. Less than 2% of the population carry two copies of the *APOE ε4* which increases their chances tenfold for developing AD, although it does not predict whether they will have AD symptoms in their lifetime. Some of the functions of the proteins encoded by the mutated genes associated with EOAD have been described. APP is known to function as a receptor on the surface of neurons to regulate neurite growth, neuronal adhesion, and axonogenesis. A buildup of amyloid-beta APP fragment has been linked to AD although not exclusively, since elderly people with identified build-up did not exhibit AD symptoms. Both PSEN1 and PSEN2 appear to function as catalytic subunits of gamma-secretase complex responsible for the intramembrane cleavage of the receptors NOTCH and APP. The specific roles of the mutation effects and the risk factors on the pathogenesis are still unclear.

25.5.2 Vascular Dementia

Vascular dementia is the most frequent EOD, being the second most common form of dementia in the general population and younger people [35]. It often results following many small strokes that restrict blood flow to the brain. It is a progressive condition affecting speech, memory, language, and learning. Recent studies support a role for APOE ε4 as a risk factor for vascular dementia, but with much less impact than in AD. Other known risk factors include high cholesterol levels, high blood pressure, and diabetes. In general, genes appear to play a much lesser role in the common forms of vascular dementia compared to familial Alzheimer. However, a rare form of vascular dementia known as cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is found to be caused by the dominant inheritance of mutations in the notch homolog protein 3 gene (*NOTCH3*). Affected individuals experience migraines and temporary loss of vision and numbness followed by progressive cognitive problems around the age of 50. The *NOTCH3* gene encodes a receptor for membrane-bound ligands, and is mostly expressed in vascular smooth muscle cells regulating cell fate during development. The mutation is thought to alter its ligand-binding site resulting in dysfunction of the vascular muscle.

25.5.3 Dementia with Lewy Bodies (DLB)

Ten percent of individuals with dementia with early-onset have dementia with Lewy body (DLB) also known as Lewy body disease. Some of the clinical symptoms are generally common to other dementias such as difficulty with attention, spatial awareness and memory. In addition, some individuals suffer with hallucinations and movement problems resembling Parkinson's disease (PD). DLB is the second more prevalent form of age related dementia affecting approximately 5% of people over

age 85. The hallmark neuropathological finding of the DLB affected individuals is the presence of diffuse Lewy bodies in the cortical and subcortical regions. Genetic analysis identified a mutation in the alpha-synuclein gene (*SNCA*) that co-segregated with the disease phenotype and two different heterozygous mutations in the beta-synuclein gene (*SNCB*) in unrelated individuals [34]. It has been proposed that the mutations may alter the ability of beta-synuclein to inhibit the toxic alpha-synuclein fibril formation. Moreover, the expression of synuclein specific isoforms are differentially altered in brains of patients with DLB compared to PD [3]. Heterozygous mutations in the glucosylceramidase gene (*GBA*) have also been identified and shown to enhanced susceptibility to the disease. GBA is a lysosomal enzyme involved in glycolipid metabolism. Mutations result in the accumulation of glucocerebrosides in the lysosome leading to cell damage.

25.5.4 Frontotemporal Dementias (FTD)

Frontotemporal dementia (FTD) is a group of neurological disorders caused by damage to the cells of the frontal and temporal lobes of the brain. These disorders are also referred to, by the pathological finding, frontotemporal lobar degeneration diseases (FTLD). The frontal lobe controls the emotions, behaviour, and personality, and is required for language. Most cases occur at ages between 45 and 65 with almost half of the affected individuals having a family history and being caused by a mutation in a single gene [2]. Several subtypes of FTD have been classified by the most prominent clinical symptoms which differ depending on the region of the frontal and temporal lobes affected and mostly restricted by the presence of pathologic inclusions [19]. Clinical symptoms include obsessive, and aggressive behaviours, loss of inhibitions and/or speech difficulties. The FTD subtypes include the behavioural variant (bvFTD), and the language variants primary progressive aphasia (PPA), which include the progressive non-fluent aphasia (PNFA), semantic dementia (SD) and logopenic progressive aphasia (LPA). The most common form is bvFTD. It is characterized by progressive atrophy of the frontal and anterior region of the brain resulting in deficits in complex thinking and planning, and changes in behaviour and personality mostly stemming from behavioural disinhibition, apathy, loss of empathy, and compulsive behaviours. In contrast, the clinical features of PPA include difficulty speaking, word errors, and loss of word retrieval in PNFA, SD, and LPA subtypes respectively. Unlike other types of dementia, memory and executive functions are not affected in the early stages, many times causing patients to become frustrated and depressed as they become aware of their deficits.

The frontotemporal lobar degenerations diseases (FTLD) have been classically grouped by the neuropathological findings after post-mortem examination, mainly the presence of tau-positive inclusions (FTLD-tau) or those with ubiquitin-positive inclusions most of which are also TAR-DNA-binding protein 43 (TDP-43) positive (FTDLD-TDP43) [28]. Other neuropathological subtypes include those with positive inclusions for the RNA-binding protein FUS or for ubiquitinated proteasome

system components [55]. Most recently, the identification of genetic mutations associated with the inheritance of these conditions is helping to link both the pathology and clinical features of these disorders. The most common mutations involve genes encoding for the proteins tau (MAPT), progranulin (*GRN*), and a gene called chromosome 9 open reading frame 72 (*C9orf72*). Less frequent associated mutations include chromatin-modifying protein 2b (*CHMPB2*), TAR-DNA-binding protein (*TARDBP*), the valosin-containing protein (*VCP*) genes, coiled-coil-helix-coiled-coil-helix domain-containing protein 10 (*CHCHD10*), sequestosome 1 (*SQSTM1*), tank-binding kinase 1 (*TBK1*), and fused in sarcoma (*FUS*) genes (Tables 25.6 and 25.7).

The most common clinical subtype bvFTD, with or without motor symptoms resembling Parkinson's disease (PD), is associated with mutations in the tau gene (*MAPT*). More than 50 mutations in tau have been identified associated with hereditary FTD. These mutations can disrupt the function of tau in the maintenance of the neuronal structure and the axonal transport and result in the accumulation and clumping of this protein within neurons. Neuropathological post-mortem findings in these individuals show FTLD-tau positive inclusions. The mutations in the progranulin (*GRN*) gene are responsible for 5–10% of all cases of FTLD and 13–25% of familial cases. *GRN* mutations are associated with bvFTD, PNFA, and rarely with amyotrophic lateral sclerosis (ALS). The missense mutations in *GRN* result in reduced progranulin levels and the formation of TDP-43 and ubiquitin positive inclusions. Likewise, mutations in the *TARDBP* gene encoding the TDP-43 protein have been identified in individuals with sporadic and familial ALS lead to accumulation of ubiquitin and TDP-43 inclusions. Progranulin is involved in cell growth, TDP-43 regulates the protein expression, and ubiquitin helps to clear out the cellular waste products particularly damaged proteins. Mutations in the *C9orf72* gene consisting of a hexanucleotide repeat expansion (GGGGCC) are present in approximately 60% of hereditary FTD with ALS (FTDALS1). Affected individuals show TDP-43 positive inclusions. The protein encoded from the *C9orf72* gene is enriched in neurons and appears to function in membrane trafficking and in the nucleus in RNA homeostasis. The most recent model proposes a role for both, an arginine-rich protein and a repeat-containing RNA in the *C9orf72* mutation induced pathogenesis. Mutations in the *VCP* gene has shown a 100% association with an autosomal dominant condition called inclusion body myopathy associated with Paget disease of bone (PDB) and/or FTD (IBMPFD). *VCP* mutations potentially disrupting the proteins role in the ubiquitin pathway cause the accumulation of inclusions made of ubiquitin rarely TDP-43 or VCP, but not tau. Mutations in the *CHMP2B* gene have only been detected in a single Danish family and lead to ubiquitin, but not TDP-43 positive inclusions in the brain. The protein encoded by the *CHMP2B* gene is involved in the recycling or destroying cell surface proteins or receptors. Because of low casuistic, genetic diagnosis based on mutations in *TARDBP* and *CHMP2B* genes is mostly done on a research basis only. Mutations in *CHCHD10* underlie FTD with ALS (FTDALS2). The *CHCHD10* gene encodes a small mitochondrial protein proposed to be involved in maintaining the morphology of the mitochondrial cristae and in oxidative phosphorylation. Expression of the *CHCHD10*

mutations in cells result in mitochondria fragmentation and dysfunction. The *SQSTM1* gene underlying FTDALS3 encodes a scaffolding protein involved in NFKB signalling and ubiquitin-mediated autophagy. Mutations in the *TBK1* gene are associated with FTDALS4, which encodes a serine/threonine kinase involved in inflammatory responses. The *FUS* gene encodes a nuclear protein involved in DNA and RNA metabolism including repair, transport, as well as transcription. Mutations in this gene are associated in ALS6 with or without FTD.

25.5.5 Progressive Supranuclear Palsy (PSP) and Corticobasal Syndrome (CBS)

Two movement disorders, progressive supranuclear palsy (PSP) and corticobasal syndrome (CBS), are also related to FTD and they share some common symptoms. PSP is the second most frequent cause of degenerative Parkinsonism and results in progressive damage to the neurons controlling eye movement. In addition to supranuclear gaze palsy, the clinical symptoms include early postural instability and cognitive decline. The most prominent neuropathological feature is the abundance of neurofibrillary tangles in both neurons and glia in subcortical regions while in Alzheimer's disease these are prominent in the cortex and detected in neurons. Several mutations in the *MAPT* gene, some of which appear to increase tau expression, have been associated with PSP. These mutations often result in particular difficulty with spelling, writing, or math skills. CBS is characterized by progressive neurodegeneration of the cerebral cortex and the basal ganglia beginning in people from 50 to 70 years of age. The prominent symptoms include Parkinsonism, Alien hand syndrome, apraxia, aphasia and cognitive dysfunction. Some individuals are particularly difficult to diagnose since they also experience behavioural and other symptoms resembling Alzheimer's or Parkinson's disease. Recently, two new loss-of-function mutations in the *GRN* gene have been differentially associated with CBS, but not with FTLD diagnosed individuals [56].

25.5.6 Niemann-Pick Disease

Niemann-Pick disease encompasses a group of metabolic disorders characterised by the accumulation of sphingomyelin within lysosomes. Most of the affected individuals are children (70%) and the remainder of individuals having a disease onset during early adolescence (30%). The disease course could be severe, fatal during early childhood or milder resulting in a somewhat normal life span. The most pronounced symptoms result from the organs with the most abnormal accumulation of sphingomyelin such as in the liver, spleen, bone marrow or the nervous system. The later results in ataxia, dysarthria, dysphagia and dystonia, and seizures and

dementia. The symptoms may first present while in early adulthood, at which time the psychiatric illness may appear as schizophrenia or bipolar disorder. Mutations in the *SMPD1* gene produce deficient sphingomyelinase activity and underlie Niemann–Pick disease types A and B (NPCA and NPCB). Mutations in the NPC1 and NPC2 encoding proteins intracellular cholesterol transporter proteins 1 and 2, involved in lipid transport cause Niemann–Pick disease type C (NPC). Type D delineates a common ancestry from Nova Scotia with NPC.

25.5.7 Inherited Prion Diseases

The Creutzfeldt-Jakob disease (CJD) is the most common human form of the rare fatal brain disorders called prion diseases affecting both people and several other mammals. The incidence of all forms of CJD is 0.5–1.5 per million per year of which 15% are familial cases. Unlike the familial CJD, the variant CJD commonly referred to as "mad cow disease" occurs in cattle, and has been transmitted to people mostly through consumption of affected tissue. Likewise, the Gerstmann-Straussler disease (GSD), also known as PRNP-related cerebral amyloid angiopathy, is a prion disease with an autosomal inheritance. GSD is associated with mutations in the prion protein gene (PRNP). It is characterized by memory loss, dementia, ataxia, and pathologic deposition of amyloid-like plaques in the brain. This disease first presents with truncal ataxia, dysarthria, and cognitive decline in the third and fourth decade of life. The fatal familial insomnia (FFI) disorder is another familial disease caused by mutations in the *PRNP* gene. The pathological changes appear localized to the anterior and dorsomedial thalamus. The Asp-178->Asn mutation in the *PRNP* gene (D178N) when the amino acid at position 129 is a methionine, is the only mutation associated with FFI described to date. However, the D178N mutation accompanied by the M129 V mutation in the *PRNP* gene has been shown associated with CJD. GSD is distinguished from CJD and FFI in that it normally has a longer disease course and shows prominent cerebellar ataxia.

25.5.8 Huntington's Disease (HD) and Other Choreas

Huntington's disease (HD), also known as Huntington's chorea, is an inherited autosomal dominant neurodegenerative disease characterised by motor, psychiatric, and cognitive dysfunction. Most commonly, the symptoms first present from the third to the fifth decade. Early symptoms include loss of short-term memory and their planning and organisational skills. The classic signs of the disorder are progressive chorea, rigidity, and dementia accompanied by caudate nucleus atrophy. The clinical features develop progressively with severe increase in choreic

movements and dementia. HD is one of the most common dementia. However, because it can sometimes present without chorea it is difficult to recognize particularly in young patients with dementia. Early onset or juvenile Huntington's disease, typically beginning by 20 years of age, is approximately less than 10% of all HD cases. The genetic cause of HD is an abnormal expansion of a CAG repeat in the *HTT* gene encoding a polyglutamine tract in the N- terminus of huntingtin [27]. The juvenile form is associated with very large number of CAG repeats (more than 60) in the *HTT* gene. It is usually transmitted through an affected father due to the genetic phenomenon of anticipation and male transmission bias. Huntingtin is a ubiquitously expressed protein, which can translocate to the nucleus where it has been shown to regulate transcription. It also has roles in the cytoplasm where its functions include axonal transport [50]. The toxicity of the expanded repeat protein appears to be increased upon cleavage by enhancing the altered conformation and aberrant protein interactions of the mutant protein fragments [47, 49]. A toxic gain-of-function of the mutant protein rather than a loss-of-function mutation has been proposed to be responsible for the pathogenesis in HD.

Some individuals with similar symptoms to HD negative for the *HTT* mutation were further investigated for distinguishing clinical features and potential alternate genetic causes. This led to the description of three Huntington disease-like (HDL1-3) disorders and the categorisation of SCA17 as HDL4. HDL1 presents with chorea, cognitive decline, dementia, ataxia, rigidity, cell loss and gliosis in the basal ganglia, kuru and multicentric plaques in the cerebellar cortex. It is an autosomal dominant disease caused by insertion of 8 additional octapeptide repeats in the prion protein gene (*PRNP*). It distinguishes from other prion disorders by the prominence of psychiatric symptoms and the long progression of the disease course. Huntington disease-like 2 (HDL2) presents chorea and also dementia. It is associated with a heterozygous expanded CAG/CTG repeat in the junctophilin-3 gene (*JPH3*). While normal alleles contain 6–28 repeats, the pathogenic alleles contain over 41 repeats. JPH3 protein mediates the interaction between the endoplasmic reticulum and the plasma membrane thereby mediating the regulation between the cell surface and the intracellular ion channels. It has been proposed that a toxic RNA gain-of-function effect underlies the pathogenesis caused by this mutation since expression of the RNA is sufficient to cause toxicity in cells. Unlike HLD1 and HDL2, HDL3 shows autosomal recessive inheritance which was described in children (onset age 3–4 years old) presenting with Huntington disease-like prominent seizures, rapid course, speech disturbances such as mutism. The identification of the associated mutation is still in progress.

Choreoacanthocytosis (CHAC) and McLeod neuroacantocitosis syndrome are rare movement disorders characterized by progressive basal ganglia neurodegeneration with red cell acanthocytosis, showing variable age of onset typically in the third to fifth decade of life. These are caused by mutations in the *VSP13A* and *XK* genes respectively. The *VSP13A* gene encodes chorein protein while the *XK* gene encodes the membrane transport protein XK, both membrane-bound proteins.

Table 25.6 Genetics of inherited dementias

Name	Locus	OMIM	Gene	Mode of inheritance	Average onset (range in years)	Distinguishing clinical features
Alzheimer´s disease						
AD 1	21q21.3	104300	*APP*	AD	Early onset	Presenile and senile dementia, parkinsonism, long tract signs.
AD 2	19q13.32	104310	*APOE*	AD	Late onset	Presenile and senile dementia, parkinsonism, long tract signs.
AD 3	14q24.2	607822	*PSEN1*	AD	20–30	Progressive, memory loss, behavioural and personality changes, gait disturbances, apraxia, extrapyramidal signs.
AD 4	1q42.13	606889	*PSEN2*	AD	35–60	Presenile dementia, sleep-wake cycle disturbance.
Vascular dementia						
CADASIL	19p13.12	125310	*NOTCH3*	AD	3th decade	Vasculopathy, leukoencephalopathy, gait abnormalities.
Dementia with Lewy Bodies						
Dementia with Lewy Bodies	4q22.1	127750	*SNCA*	AD	60–70	Parkinsonism, fluctuations in consciousness, visual hallucinations.
Dementia with Lewy Bodies	5q35.2		*SNCB*			
Dementia with Lewy Bodies	1q22		GBA			
Frontotemporal dementia						
Dementia, familial, nonspecific	3p11.2	600795	*CHMP2B*	AD	57	Mutism, abnormal gait, pyramidal signs, aggressiveness, personality changes.
FTDALS1	9p21.2	105550	*C9orf72*	AD	Adulthood	Muscle atrophy, quadriparesis, parkinsonism, extrapyramidal signs.
FTDALS3	5q35.3	616437	SQSTM1	AD	Late Adulthood	Orofacial apraxia, muscle weakness, mutism.
FTDALS4	12q14.2	616439	*TBK1*	AD	Adulthood	Bulbar weakness, muscle weakness, mutism,
FTD with or without parkinsonism	17q21.31	600274	*MAPT*	AD	45	Frontal lobe dementia, motor symptoms may be present, personality changes.

FTLD with ubiquitin-positive inclusions	17q21.31	607485	*GRN*	AD	62 (45–79)	Dysnomia, mutism, apraxia, personality changes hallucinations.
Inclusion body myopathy with early-onset Paget disease and FTD1	9p13.3	167320	*VCP*	AD	57	Winged scapulae, hip pain, muscle weakness, gait abnormalities.
FTLD, TARDBP-related	1p36.22	612069	*TARDBP*	AD	(25–78)	Tongue hypotrophy, muscle weakness, pyramidal signs, disinhibition.
ALS6, with or without frontotemporal dementia	16p11.2	608030	*FUS*	AD/AR	Adulthood	Bulbar onset, motor neuron loss.
Progressive Supranuclear palsy	17q21.31	601104	*MAPT*	AD	66	Diplopia, Supranuclear gaze palsy, Parkinsonism, Forgetfulness, Dysarthria
Niemann-Pick disease						
Niemann-Pick disease, type A	11p15.4	257200	*SMPD1*	AR	Infancy	Short stature, granular-appearing maculae, xanthomas, Muscle weakness.
Niemann-Pick disease, type B	11p15.4	607616	*SMPD1*	AR	Infancy or Childhood	Dyspnea.
Niemann-Pick disease, type C1	18q11.2	257220	*NPC1*	AR	Early childhood	Vertical supranuclear gaze palsy, hypotonia, developmental delay, ataxia.
Niemann-Pick disease, type C2	14q24.3	607625	*NPC2*	AR	Variable	Vertical supranuclear gaze palsy, hypotonia, developmental delay, ataxia.
Prion Diseases						
Creutzfeldt-Jakob Disease	20p13	123400	*PRNP*	AD	38 – 45	Loss of facial expression, Supranuclear gaze paralysis, Gait ataxia, Hallucinations,
Gerstmann-Straussler disease	20p13	137440	*PRNP*	AD	30s (30–60)	Cerebellar ataxia, parkinsonism, psychosis.
Fatal Familial Insomnia (FFI)	20p13	600072	*PRNP*	AD	18–54	Insomnia, Thalamic, medial dorsal nucleus, neuron loss,
Huntington´s disease	4p16.3	143100	*HTT*	AD	40s (10–70)	Abnormal eye movement, chorea, bradykinesia.

25.6 Motor Neuron Diseases (MND)

Motor neuron diseases (MND) are classified according to whether they are inherited or sporadic, these being the most common, and to whether degeneration affects upper motor neurons (UMNs), lower motor neurons (LMNs), or both. In adults, the most common MND is amyotrophic lateral sclerosis (ALS or Lou Gehri disease), characterised by progressive skeletal muscle weakness, amyotrophy, spasticity, and fasciculations as a result of degeneration of the upper and lower motor neurons, culminating in respiratory paralysis. It has inherited and sporadic forms and can affect the arms, legs, or facial muscles. Most ALS cases are sporadic, and only 5–10% of cases are considered to be familial. Mutations in the *C9orf72* gene are responsible for 30–40% of familial ALS cases in the United States and Europe. Worldwide, approximately 20% of cases of familial ALS are due to a mutation in the Cu/Zn superoxide dismutase–1 gene (*SOD1*). Western Pacific ALS occurs on the islands of Guam (Guam ALS), on the Kii peninsula of Japan, and in Western New Guinea. It is now clear that a subset of ALS cases shows features of frontotemporal lobar degeneration (FTLD) (ie, FTLD-MND/ALS) (Tables 25.6 and 25.7).

Primary lateral sclerosis (PLS) is a rare neurodegenerative disorder that primarily involves the UMNs, resulting in progressive spinobulbar spasticity. Because substantial numbers of cases initially diagnosed as PLS would be reclassified as ALS as the disease progresses, a disease duration of at least 3 years is required to render this diagnosis clinically. There is still debate regarding whether PLS is a distinct pathologic entity or whether it represents one end of a clinical spectrum of ALS.

Progressive bulbar palsy (PBP) is a progressive degenerative disorder of the motor nuclei in the medulla specifically involving the glossopharyngeal, vagus, and hypoglossal nerves, that produces atrophy and fasciculations of the lingual muscles, dysarthria, and dysphagia. In adults, because most of the cases presenting with these pure bulbar symptoms represent so-called bulbar-onset ALS and eventually develop widespread symptoms typically seen in ALS, some authors consider this disorder to be a subset of ALS. Infantile PBP is a rare disorder that occurs in children and presents as the following two phenotypically associated forms: Brown-Vialetto-Van Laere syndrome (pontobulbar palsy with deafness) and Fazio-Londe disease. Brown-Vialetto-Van Laere syndrome is characterised by bilateral sensorineural deafness that is followed by CNs VII, IX, and XII palsies, whereas Fazio-Londe disease causes progressive bulbar palsy without deafness. Both disorders are genetically heterogeneous (Table 25.7).

Table 25.7 Molecular genetics of MNDs

Name	Locus	Gene/Locus	OMIM	Mode of inheritance	Average onset (range in years)	Distinguishing clinical features
Amyotrophic lateral sclerosis (ALS)						
ALS1	21q22.11	*SOD1*	105400	AD/AR/SP	Variable	
ALS2	2q33.1	*ALS2*	205100	AR	First decade	ALS2-related disorders.
ALS3	18q21	–	606640	AD		
ALS4	9q34.13	*SETX*	602433	AD	Less than 6 years	UMN and LMN.
ALS5	15q21.1	*SPG11*	602099	AR	Juvenile (<25)	UMN and LMN, slowly progressive.
ALS6	16p11.2	*FUS/TLS*	608030	AD/AR	4th decade	LMN, with or without FTD.
ALS7	20p13	–	608031	AD		
ALS8 (SMAIV or Finkel type SMA)	20q13.32	*VAPB*	608627	AD	31–45 years	Slow progression.
ALS9	14q11.2	*ANG*	611895	AD		UMN and LMN, with or without parkinsonism or FTD.
ALS10	1p36.22	*TARDBP*	612069	AD	Adult onset	With or without FTD.
ALS11	6q21	*FIG4*	612577	AD	Adult onset	Allelic of CMT4J,
ALS12	10p13	*OPTN*	613435	AD/AR	30–60 years	
ALS13	12q24.12	*ATXN2*	183090	AD	Adult	Susceptibility to ALS.
ALS14	9p13.3	*VCP*	613954	AD	37–53 years	UMN, LMN, with or without FTD.
ALS15	Xp11.21	*UBQLN2*	300857	XLD	16–71 years	With or without FTD.
ALS16	9p13.3	*SIGMAR1*	614373	AR	1–2 years	Early lower limb spasticity with hyperreflexia and weakness.
ALS17	3p11.2	*CHMP2B*	614696	AD	Adult	LMN, bulbar signs, respiratory insufficiency.
ALS18	17p13.2	*PFN1*	614808	AD	30s–40s	

(continued)

Table 25.7 (continued)

Name	Locus	Gene/Locus	OMIM	Mode of inheritance	Average onset (range in years)	Distinguishing clinical features
ALS19	2q34	*ERBB4*	615515	AD	60–70	UMN, LMN, no cognitive impairment.
ALS20	12q13.13	*HNRNPA1*	615426	AD	Adult	
ALS21	5q31.2	*MATR3*	606070	AD	30–55 years	UMN, LMN with or without myopathy or dementia.
ALS22	2q35	*TUBA4A*	616208	AD	48–71	With or without FTD.
ALS/FTD	9p21.2	*C9orf72*	105550	AD	40–62 years	With FTD.
ALS/FTD	22q11.23	*CHCHD10*	615911	AD	Adult	With FTD.
ALS/FTD	5q35.3	*SQSTM1*	616437	AD	Adult	UMN, LMN, FTD.
ALS/FTD	12q14.2	*TBK1*	616439	AD	Adult or late	Cognitive impairment, behavioral abnormalities, and speech apraxia and/or UMN and LMN signs.
ALS with dementia	–	–	205200	–	Juvenile	Progressive.
Primary lateral sclerosis (PLS)						
Infantile-onset ascending spastic paralysis	2q33.1	*ALS2*	607225	AR	First years	
Juvenile (PLSJ)	2q33.1	*ALS2*	606353	AR/SP	Infantile/Juvenile	
Adult (PLSA1)	4p16	–	611637	AD/SP	Adult	UPN, corticospinal, corticobulbar.
Progressive bulbar palsy						
Brown-Vialetto-Val Laere Syndrome 1	20p13	*SLC52A3*	211530	AR	Childhood	Progressive bulbar palsy with sensorineural deafness.
Brown-Vialetto-Val Laere Syndrome 2	8q24.3	*SLC52A2*	614707	AR	Childhood	
Fanzio-Londe Disease	20p13	*SLC52A3*	211500	AR	Childhood	Without sensorineural deafness.

Spinal muscular atrophy						
SMA type 1 (Werdnig-Hoffmann disease)	5q13.2	*SMN1*	253300	AR	Childhood	
SMA type 2	5q13.2	*SMN1*	253550	AR	3–15 months	
SMA type 3 (Kugelberg-Welander Syndrome)	5q13.2	*SMN1/2*	253400	AR	2–17 years	
SMA type 4	5q13.2	*SMN1*	271150	AR	20s–40s	
Spinal and bulbar muscular atrophy	Xq12	*AR Receptor*	313200	XLR	3rd–5th decade	Kennedy disease.

LMN lower motor neurons, *UMN* upper motor neurons, *AD* autosomal dominant, *AR* autosomal recessive, *SP* sporadic, *XLD* X-linked dominant, *XLR* X-linked recessive

25.7 Rare Metabolic Neurodegenerative Diseases

Inborn errors of metabolism can be defined as genetic disorders that interfere with chemical reactions that the body uses to maintain life, including energy production. They are an important cause of neurodegenerative processes, and in a recent epidemiological study, they represent up to 60% of progressive neurological deterioration cases, being the most frequent, mitochondrial disorders, mucopolysaccharidosis, and neuronal ceroid lipofuscinosis (NCL) [60]. In this clinical context, they must be considered early in the diagnosis algorithm, as many of them are treatable disorders while in turn a specific diagnosis is crucial for genetic counselling, prenatal diagnosis and assessment of family members.

25.7.1 Classification of Rare Metabolic Neurodegenerative Diseases

According to the mechanisms responsible for their pathophysiology, Saudubray proposed three main groups of metabolic diseases (Table 25.8) [51]:

Group I including those diseases associated with the accumulation of toxic substances because of the defect in the function of an enzyme or transport protein. The main examples are disorders of protein metabolism including aminoacidopathies, organic acidemias and urea cycle disorders. These disorders usually present as an acute encephalopathy and start at young age or even in the neonatal period.

Group II includes diseases where a defect of energy production is implicated in the deficient cellular functioning. The major disorders included in this group are respiratory chain diseases (OXPHOS), beta-oxidation, glycogen storage, and creatine metabolism disorders. They present with either a slowly progressive course and/or intermittent metabolic crises precipitated by stress.

Group III comprises disorders of cellular organelles in which there are storage of large molecules causing progressive dysfunction. Lysosomal storage diseases, peroxisomal disorders, and congenital disorders of glycosylation (CDG) are included among others.

25.7.2 Main Clinical Symptoms

Metabolic diseases are usually multiorganic, albeit in many cases there are predominant features [40]. Global developmental delay can be the main symptom in adenylosuccinate lyase deficiency, lysosomal storage disorders, CDG, but also in

urea cycle disorders, creatine metabolism diseases, mild forms of non-ketotic hyperglycinemia (NKH), homocystinuria, and cerebrotendinous xanthomatosis. Refractory epilepsy starting in the neonatal period or infancy should raise suspicion of possible pyridoxine-dependent seizures, pyridoxamine-5′-phosphate oxidase (PNPO) deficiency, GLUT-1 deficiency syndrome, serine or folate deficiencies, creatine disorders or NKH. Instead, the progressive appearance of pyramidal signs associated sometimes with cognitive decline, movement disorders or ataxia is characteristic of leukodystrophies. Dystonia can be seen in mitochondrial diseases, Segawa disease, late-onset tyrosine hydroxylase deficiency, and in organic acidurias (OAs) like glutaric aciduria type I following episodes of acute decompensation, whereas late forms of GLUT-1 deficiency syndromes can manifest as paroxysmal exercise-induced dyskinesia that improves with rest or administration of sugar. Intermittent ataxia is a main feature in disorders of protein metabolism and mitochondrial disorders, while chronic ataxia appears in mitochondrial disorders (Leigh syndrome, Kearns-Sayre, CoQ10 deficiency), vitamin E deficiency, Refsum disease, CDG, GM2 and Niemann-Pick type C. Finally, autism can be a predominant manifestation of Smith-Lemli-Opitz syndrome, mitochondrial disorders or creatine, folate or biotinidase deficiencies.

25.7.3 Diagnosis

A family history of consanguinity, unexplained hydrops foetalis, sibling deaths or developmental delay must raise the suspicion of a metabolic disease. Similarly, the presence of cerebral palsy of unknown origin or coexistence of neurological and non-neurological features should always raise suspicion of a metabolic disorder. At the neurological level, to differentiate whether the predominant involvement is in the white matter (hypotonia or spasticity and visual impairment) or grey matter (dementia, personality changes, seizures) can be helpful to guide complementary exams. Another important point is to consider treatable disorders first and the most frequent according to the age of onset of symptoms.

Most of neurometabolic disorders are autosomal recessive (Table 25.9), whereas maternal transmission might suggest an X-linked or mitochondrial mode of inheritance. Sporadic cases with de novo mutations are frequent.

In acute metabolic decompensations, studies including lactate/pyruvate ratio, NH3, blood gases, plasma amino acids, urine organic acids, and acylcarnitines are recommended. However, in slowly progressive processes testing for urine glycosaminoglycans, white cell enzymes activity, studies in muscle biopsy, transferrin isoelectric focusing, VLCFA, and 7-dehydrocholesterol may be needed.

In other cases, CSF studies may be undertaken in order to demonstrate high lactate levels in mitochondrial disorders, low glucose CSF/plasma ratio in GLUT1 deficiency and for neurotransmitter analysis [44]. Magnetic resonance imaging (MRI) is important to detect white matter abnormalities, which can have a very characteristic pattern in some leukodystrophy patients, but also signs of cortical or cerebellar atrophy or basal ganglia abnormalities. MR spectroscopy may uncover a low creatine/phosphocreatine ratio, a high lactate peak in mitochondrial disorders, or elevated concentration of N-acetylaspartate in Canavan disease [38].

In recent years, newborn screening (NBS) has been implemented in many countries, allowing early detection of several metabolic disorders before clinical manifestations appear. On the other hand, performance of next generation sequencing (NGS) studies can help in confirmation of molecular basis and guide genetic counselling.

25.7.4 Treatment

In acute metabolic encephalopathies, emergency treatment based on glucose infusions to reverse catabolism and medications or haemofiltration to remove toxins is crucial in order to avoid irreversible brain damage.

In some metabolic disorders there are specific treatment options: enzyme replacement treatment (ERT) have been developed for some lysosomal storage diseases including Gaucher, MPS type I, II, IV, VI, VII, Pompe and Fabry disease; substrate reduction with miglustat has been used in Gaucher disease type 1 and to delay Niemann-Pick C (NPC) progression; ketogenic diet in patients with GLUT1 deficiency syndromes or with refractory epilepsy; and early haematopoietic stem cell transplantation for X-linked adrenoleukodystrophy, Hurler syndrome (MPS I), Maroteaux Lamy (MPS VI) and Sly (MPS VII) syndromes. For most mitochondrial disorders there is no specific treatment, with the exception of coenzyme Q10 and riboflavin responsive complex I deficiency, although some antioxidant molecules have also been used. Creatine deficiency syndromes caused by L-arginine:glycine amidinotransferase (AGAT) or guanidinoacetate methyltransferase (GAMT) enzymatic defects can be successfully treated by creatine and arginine supplements. In the last years, therapy with small molecules chaperones is being investigated in some lysosomal disorders such as Fabry disease, whereas there has been significant progress in the development of gene therapy for several diseases, with currently ongoing clinical trials on Pompe's disease, MLD, and MPS IIIA.

Table 25.8 Classification of the main neurometabolic disorders

Main disorder	Main clinical features	Metabolic tests
Intoxication		
Aminoacidurias	First months (symptom free interval). Metabolic crisis (lethargy, vomiting, seizures, liver failure) precipitated by intercurrent illness or food intake. Chronic (failure to thrive, developmental delay).	Plasma AA, urine OA, acylcarnitine
Organic acidurias		
Urea cycle disorders		Plasma NH3
Metal intoxication (Wilson, Menkes), Fe, Mn	Seizures, movement disorders.	Cu, ceruloplasmin, Fe, Mn.
Neurotransmitter diseases	Dystonia, tremor, parkinsonism, pyramidal signs, autonomic, neuropsychiatric.	CSF neurotransmitters.
Energy deficiency		
Mitochondrial diseases and congenital lactic acidemias (PC, PDH, Alpers, Kearns-Sayre, Leigh, MERRF, MELAS, NARP syndromes), syndromes of mtDNA depletion	Any age. Multisystemic. Global developmental delay, epilepsy, ptosis, external ophthalmoplegia, proximal myopathy, peripheral neuropathy, ataxia, stroke-like episodes, cardiomyopathy, sensorineural hearing loss, retinitis pigmentosa, renal tubular insufficiency, diabetes mellitus, liver dysfunction.	Plasma/CSF lactate and pyruvate, muscle biopsy, molecular studies
Deficiencies creatine metabolism	Intellectual disability, language developmental delay behavioural difficulties and epilepsy.	Creatine/creatinine (u), guanidinoacetate (p,u). MRS creatine peak.
Glycogen storage diseases	Hypoglicemia, hepatomegaly, cardiomegaly, weakness.	Hypoglycemia. Liver or muscle biopsy
Fatty acid oxidation defects	Lethargy and encephalopathy during fasting. Hepatomegaly sometimes.	Hypoglycemia with absent ketosis, liver dysfunction.

(continued)

Table 25.8 (continued)

Main disorder	Main clinical features	Metabolic tests
Complex molecules		
Lysosomal	**MPS**: macrocephaly, developmental delay, dwarfism, bony deformity, organomegaly.	Urinary GAG (MPS). Enzymatic analysis. Molecular studies.
	Tay-Sachs: weakness, startle, seizures, spasticity.	
	Gaucher: anemia, trombocitopenia, HEM, ocular and neuromotor dysfunction**.**	
	Pompe: hypertrophic cardiomyopathy, muscle weakness.	
	Neuronal ceroid lipofuscinosis: seizures, dementia, visual loss, and/or cerebral atrophy.	
Peroxisomal	Hypotonia, skeletal dysplasia, sensory deficits, liver dysfunction.	Plasma VLCFA.
	Zellweger: dysmorphic features, macrocephaly, seizures.	
	X-ALD: leukodystrophy, developmental regression, spasticity, adrenal failure.	
Congenital disorders of glycosylation	Developmental delay, seizures, hypotonia, liver disease, coagulopathy, dystonia.	Sialotransferrin isoelectric focusing.
Disorders of complex lipids metabolism	Spastic paraparesias, neurodegeneration with iron brain accumulation, peripheral neuropathy, muscular/cardiac, ichtyosis, retinal dystrophies, bone dysplasias, segmental overgrowth, liver, renal and immune presentations.	Next generation sequencing. Lipidomics

AA amino acids, *CDG* congenital disorders of glycosylation, *GAG* glycosaminoglycans, *MELAS* mitochondrial encephalomyopathy, lactic acidosis, stroke, *MERRF* myoclonus epilepsy, ragged-red fibers, *OA* organic acids, *PC* pyruvate carboxylase deficiency, *PDH* pyruvate dehydrogenase deficiency, *VLCFA* very-long-chain fatty acids, *X-ALD* X-linked adrenoleukodystrophy

Table 25.9 Genes identified associated with the main neurometabolic conditions

Condition name	Locus	Gene	OMIM
Batten disease/ Neuronal ceroid lipofuscinosis (NCL)	1p34.2	*PPT1*	256730
	11p15.4	*TPP1*	204500
	20q13.33	*DNAJC5*	162350
	13q22.3	*CLN5*	256731
	15q23	*CLN6*	601780
	4q28.2	*MFSD8*	610951
	8p23.3	*CLN8*	600143
	11p15.5	*CTSD*	610127
	17q21.31	*GRN*	614706
	1p36.13	*ATP13A2*	606693
	11q13.2	*CTSF*	615362
	7q11.21	*KCTD7*	611726
Niemann-Pick disease	11p15.4	*SMPD1*	257200 / 607616,
	18q11.2	*NPC1*	257220
	14q24.3	*NPC2*	607625
Pelizaeus-Merzbacher disease	Xq22.2	*PLP1*	312080
Canavan disease	17p13.2	*ASPA*	271900
Fabry disease	Xq22.1	*GLA*	301500
Gaucher disease	1q22	*GBA*	608013, 230800, 230900, 231000, 231005
Hunter syndrome (MPS II)	Xq28	*IDS*	309900
Hurler syndrome (MPS I)	4p16.3	*IDUA*	607014, 607015, 607016
Krabbe disease	14q31.3	*GALC*	245200
Lesch-Nyhan syndrome	Xq26.2-q26.3	*HPRT1*	300323
Menkes and related syndromes	Xq21.1	*ATP7A*	309400
Ornithine transcarbamylase (OTC) deficiency	Xp11.4	*OTC*	311250
Phenylketonuria (PKU)	12q23.2	*PAH*	261600
Sandhoff disease	5q13.3	*HEXB*	268800
Sanfilippo Syndrome (MPS III)	17q25.3	*SGSH*	252900
	17q21.2	*NAGLU*	252920
	8p11.2-p11.1	*HGSNAT*	252930
	12q14.3	*GNS*	252940
Tay-Sachs disease	15q23	*HEXA*	272800
Wilson disease	13q14.3	*ATP7B*	277900
X-linked adrenoleukodistrophy	Xq28	*ABCD1*	300100

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References

1. Albin RL (2003) Dominant ataxias and Friedreich ataxia: an update. Curr Opin Neurol 16:507–514. https://doi.org/10.1097/01.wco.0000084230.82329.d5
2. Bang J, Spina S, Miller BL (2015) Frontotemporal dementia. Lancet (London, England) 386:1672–1682. https://doi.org/10.1016/S0140-6736(15)00461-4
3. Beyer K, Munoz-Marmol AM, Sanz C, Marginet-Flinch R, Ferrer I, Ariza A (2012) New brain-specific beta-synuclein isoforms show expression ratio changes in Lewy body diseases. Neurogenetics 13:61–72. https://doi.org/10.1007/s10048-011-0311-8
4. Bonifati V, Rizzu P, van Baren MJ, Schaap O, Breedveld GJ, Krieger E, Dekker MCJ, Squitieri F, Ibanez P, Joosse M, van Dongen JW, Vanacore N, van Swieten JC, Brice A, Meco G, van Duijn CM, B a O, Heutink P (2003) Mutations in the DJ-1 gene associated with autosomal recessive early-onset parkinsonism. Science 299:256–259. https://doi.org/10.1126/science.1077209
5. Brice A (2005) Genetics of Parkinson's disease: LRRK2 on the rise. Brain 128:2760–2762. https://doi.org/10.1093/brain/awh676
6. Brusse E, Maat-Kievit JA, van Swieten JC (2007) Diagnosis and management of early- and late-onset cerebellar ataxia. Clin Genet 71:12–24. https://doi.org/10.1111/j.1399-0004.2006.00722.x
7. Cacace R, Sleegers K, Van Broeckhoven C (2016) Molecular genetics of early-onset Alzheimer's disease revisited. Alzheimers Dement 12:733–748. https://doi.org/10.1016/j.jalz.2016.01.012
8. Corral-Juan M, Matilla-Dueñas A, Corral-Juan M, Corral J, Nicolás S, Héctor VV, Matilla-Dueñas A (2011) Genetics of the autosomal dominant spinocerebellar ataxias. Encycl Life Sci. https://doi.org/10.1002/9780470015902.a0006076
9. Coutinho P, Ruano L, Loureiro JL, Cruz VT, Barros J, Tuna A, Barbot C, Guimarães J, Alonso I, Silveira I, Sequeiros J, Marques Neves J, Serrano P, Silva MC (2013) Hereditary ataxia and spastic paraplegia in Portugal: a population-based prevalence study. JAMA Neurol 70:746–755. https://doi.org/10.1001/jamaneurol.2013.1707
10. Durr A (2010) Autosomal dominant cerebellar ataxias: Polyglutamine expansions and beyond. Lancet Neurol 9:885–894. https://doi.org/10.1016/S1474-4422(10)70183-6
11. Engelen M, Kemp S, de Visser M, van Geel BM, Wanders RJ, Aubourg P, Poll-The BT (2012) X-linked adrenoleukodystrophy (X-ALD): clinical presentation and guidelines for diagnosis, follow-up and management. Orphanet J Rare Dis 7:51. https://doi.org/10.1186/1750-1172-7-51
12. Lo Giudice T, Lombardi F, Santorelli FM, Kawarai T, Orlacchio A (2014) Hereditary spastic paraplegia: clinical-genetic characteristics and evolving molecular mechanisms. Exp Neurol 261:518–539. https://doi.org/10.1016/j.expneurol.2014.06.011
13. Van Goethem G, Luoma P, Rantamäki M, Al Memar A, Kaakkola S, Hackman P, Krahe R, Löfgren A, Martin J-JJ, De Jonghe P, Suomalainen A, Udd B, Van Broeckhoven C (2004) POLG mutations in neurodegenerative disorders with ataxia but no muscle involvement. Neurology 63:1251–1257. https://doi.org/10.1212/01.WNL.0000140494.58732.83

14. Hagerman PJ, Hagerman RJ (2015) Fragile X-associated tremor/ataxia syndrome. Ann N Y Acad Sci 1338:58–70. https://doi.org/10.1111/nyas.12693
15. Hensiek A, Kirker S, Reid E (2014) Diagnosis, investigation and management of hereditary spastic paraplegias in the era of next-generation sequencing. J Neurol 262:1601–1612. https://doi.org/10.1007/s00415-014-7598-y
16. Jayadev S, Bird TD (2013) Hereditary ataxias: overview. Genet Med 15:673–683. https://doi.org/10.1038/gim.2013.28
17. Kara E, Tucci A, Manzoni C, Lynch DS, Elpidorou M, Bettencourt C, Chelban V, Manole A, Hamed SA, Haridy NA, Federoff M, Preza E, Hughes D, Pittman A, Jaunmuktane Z, Brandner S, Xiromerisiou G, Wiethoff S, Schottlaender L, Proukakis C, Morris H, Warner T, Bhatia KP, Korlipara LVP, Singleton AB, Hardy J, Wood NW, Lewis PA, Houlden H (2016) Genetic and phenotypic characterization of complex hereditary spastic paraplegia. Brain 139:1904–1918. https://doi.org/10.1093/brain/aww111
18. Kearney M, Orrell RW, Fahey M, Pandolfo M (2012) Antioxidants and other pharmacological treatments for Friedreich ataxia. Cochrane Database Syst Rev 4:CD007791. https://doi.org/10.1002/14651858.CD007791
19. Kertesz A (2003) Pick complex: an integrative approach to frontotemporal dementia: primary progressive aphasia, corticobasal degeneration, and progressive supranuclear palsy. Neurologist 9:311–317. https://doi.org/10.1097/01.nrl.0000094943.84390.cf
20. Kitada T, Asakawa S, Hattori N, Matsumine H, Yamamura Y, Minoshima S, Yokochi M, Mizuno Y, Shimizu N (1998) Mutations in the parkin gene cause autosomal recessive juvenile parkinsonism. Nature 392:605–608. https://doi.org/10.1038/33416
21. Klein C, Westenberger A (2012) Genetics of Parkinson's disease. Cold Spring Harb Perspect Med 2:a008888. https://doi.org/10.1101/cshperspect.a008888
22. Lagedrost SJ, Sutton MSJ, Cohen MS, Satou GM, Kaufman BD, Perlman SL, Rummey C, Meier T, Lynch DR (2011) Idebenone in Friedreich ataxia cardiomyopathy-results from a 6-month phase III study (IONIA). Am Heart J 161:639–645. https://doi.org/10.1016/j.ahj.2010.10.038
23. Le W-D, Xu P, Jankovic J, Jiang H, Appel SH, Smith RG, Vassilatis DK (2003) Mutations in NR4A2 associated with familial Parkinson disease. Nat Genet 33:85–89. https://doi.org/10.1038/ng1066
24. Lei L-F, Yang G-P, Wang J-L, Chuang D-M, Song W-H, Tang B-S, Jiang H (2016) Safety and efficacy of valproic acid treatment in SCA3/MJD patients. Parkinsonism Relat Disord 26:55–61. https://doi.org/10.1016/j.parkreldis.2016.03.005
25. Lin MK, Farrer MJ (2014) Genetics and genomics of Parkinson's disease. Genome Med 6:48. https://doi.org/10.1186/gm566
26. Loy CT, Schofield PR, Turner AM, Kwok JBJ (2014) Genetics of dementia. Lancet 383:828–840. https://doi.org/10.1016/S0140-6736(13)60630-3
27. MacDonald M, Ambrose CM, Duyao MP, Myers RH, Lin C, Srinidhi L, Barnes G, Taylor SA, James M, Groot N, MacFarlane H, Jenkins B, Anderson MA, Wexler NS, Gusella JF, Bates GP, Baxendale S, Hummerich H, Kirby S, North M, Youngman S, Mott R, Zehetner G, Sedlacek Z, Poustka A, Frischauf A-M, Lehrach H, Buckler AJ, Church D, Doucette-Stamm L, O'Donovan MC, Riba-Ramirez L, Shah M, Stanton VP, Strobel SA, Draths KM, Wales JL, Dervan P, Housman DE, Altherr M, Shiang R, Thompson L, Fielder T, Wasmuth JJ, Tagle D, Valdes J, Elmer L, Allard M, Castilla L, Swaroop M, Blanchard K, Collins FS, Snell R, Holloway T, Gillespie K, Datson N, Shaw D, Harper PS (1993) A novel gene containing a trinucleotide repeat that is expanded and unstable on Huntington's disease chromosomes. Cell 72:971–983. https://doi.org/10.1016/0092-8674(93)90585-E
28. Mackenzie IRA, Neumann M, Bigio EH, Cairns NJ, Alafuzoff I, Kril J, Kovacs GG, Ghetti B, Halliday G, Holm IE, Ince PG, Kamphorst W, Revesz T, Rozemuller AJM, Kumar-Singh S, Akiyama H, Baborie A, Spina S, Dickson DW, Trojanowski JQ, Mann DMA (2010) Nomenclature and nosology for neuropathologic subtypes of frontotemporal lobar degeneration: an update. Acta Neuropathol 119:1–4. https://doi.org/10.1007/s00401-009-0612-2

29. Mariotti C, Nachbauer W, Panzeri M, Poewe W, Taroni F, Boesch S (2013) Erythropoietin in Friedreich ataxia. J Neurochem 126:80–87. https://doi.org/10.1111/jnc.12301
30. Marx FP, Holzmann C, Strauss KM, Li L, Eberhardt O, Gerhardt E, Cookson MR, Hernandez D, Farrer MJ, Kachergus J, Engelender S, Ross CA, Berger K, Schöls L, Schulz JB, Riess O, Krüger R (2003) Identification and functional characterization of a novel R621C mutation in the synphilin-1 gene in Parkinson's disease. Hum Mol Genet 12:1223–1231. https://doi.org/10.1093/hmg/ddg134
31. Matilla-Dueñas A, Ashizawa T, Brice A, Magri S, McFarland KN, Pandolfo M, Pulst SM, Riess O, Rubinsztein DC, Schmidt J, Schmidt T, Scoles DR, Stevanin G, Taroni F, Underwood BR, Sánchez I (2014) Consensus paper: pathological mechanisms underlying neurodegeneration in spinocerebellar ataxias. Cerebellum 13:269–302
32. Matilla-Dueñas A, Corral-Juan M, Volpini V, Sánchez I (2012) The spinocerebellar ataxias: clinical aspects and molecular genetics. Adv Exp Med Biol 724:351–374. https://doi.org/10.1007/978-1-4614-0653-2_27
33. Matilla-Dueñas A, Sánchez I, Corral-Juan M, Dávalos A, Alvarez R, Latorre P (2010) Cellular and molecular pathways triggering neurodegeneration in the spinocerebellar ataxias. Cerebellum 9:148–166. https://doi.org/10.1007/s12311-009-0144-2
34. Meeus B, Theuns J, Van Broeckhoven C (2012) The genetics of dementia with Lewy bodies: what are we missing? Arch Neurol 69:1113–1118. https://doi.org/10.1001/archneurol.2011.3678
35. O'Brien JT, Thomas A (2015) Vascular dementia. Lancet 386:1698–1706. https://doi.org/10.1016/S0140-6736(15)00463-8
36. Paisán-Ruíz C, Jain S, Evans EW, Gilks WP, Simón J, Van Der Brug M, De Munain AL, Aparicio S, Gil AM, Khan N, Johnson J, Martinez JR, Nicholl D, Carrera IM, Peña AS, De Silva R, Lees A, Martí-Massó JF, Pérez-Tur J, Wood NW, Singleton AB (2004) Cloning of the gene containing mutations that cause PARK8-linked Parkinson's disease. Neuron 44:595–600. https://doi.org/10.1016/j.neuron.2004.10.023
37. Pankratz N, Pauciulo MW, Elsaesser VE, Marek DK, Halter CA, Wojcieszek J, Rudolph A, Shults CW, Foroud T, Nichols WC, Parkinson Study Group – PROGENI Investigators (2006) Mutations in DJ-1 are rare in familial Parkinson disease. Neurosci Lett 408:209–213. https://doi.org/10.1016/j.neulet.2006.09.003
38. Patay Z, Blaser SI, Poretti A, Huisman TAGM (2015) Neurometabolic diseases of childhood. Pediatr Radiol 45:473–484. https://doi.org/10.1007/s00247-015-3279-y
39. Paulson HL (2009) The spinocerebellar ataxias. J Neuroophthalmol 29:227–237. https://doi.org/10.1097/WNO0b013e3181b416de
40. Pierre G (2013) Neurodegenerative disorders and metabolic disease. Arch Dis Child 98:618–624. https://doi.org/10.1136/archdischild-2012-302840
41. Polymeropoulos MH, Lavedan C, Leroy E, Ide SE, Dehejia A, Dutra A, Pike B, Root H, Rubenstein J, Boyer R, Stenroos ES, Chandrasekharappa S, Athanassiadou A, Papapetropoulos T, Johnson WG, Lazzarini AM, Duvoisin RC, Di IG, Golbe LI, Nussbaum RL (1997) Mutation in the α-Synuclein gene identified in families with Parkinson's disease. Science 276:2045–2047. https://doi.org/10.1126/science.276.5321.2045
42. Ramirez A, Heimbach A, Gründemann J, Stiller B, Hampshire D, Cid LP, Goebel I, Mubaidin AF, Wriekat AL, Roeper J, Al-Din A, Hillmer AM, Karsak M, Liss B, Woods CG, Behrens MI, Kubisch C (2006) Hereditary parkinsonism with dementia is caused by mutations in ATP13A2, encoding a lysosomal type 5 P-type ATPase. Nat Genet 38:1184–1191. https://doi.org/10.1038/ng1884
43. Riant F, Vahedi K, Tournier-Lasserve E (2011) Hereditary episodic ataxia. Rev Neurol (Paris) 167:401–407. https://doi.org/10.1016/j.neurol.2010.10.016
44. Rice GM, Steiner RD (2016) Inborn errors of metabolism (metabolic disorders). Pediatr Rev 37:3–17. https://doi.org/10.1542/pir.2014-0122
45. Romano S, Coarelli G, Marcotulli C, Leonardi L, Piccolo F, Spadaro M, Frontali M, Ferraldeschi M, Vulpiani MC, Ponzelli F, Salvetti M, Orzi F, Petrucci A, Vanacore N, Casali C, Ristori G (2015) Riluzole in patients with hereditary cerebellar ataxia: a randomised, double-blind, placebo-controlled trial. Lancet Neurol 14:985–991. https://doi.org/10.1016/S1474-4422(15)00201-X

46. Sánchez I, Balagué E, Matilla-Dueñas A (2016) Ataxin-1 regulates the cerebellar bioenergetics proteome through the GSK3β-mTOR pathway which is altered in spinocerebellar ataxia type 1 (SCA1). Hum Mol Genet. https://doi.org/10.1093/hmg/ddw242
47. Sánchez I, Mahlke C, Yuan J (2003) Pivotal role of oligomerization in expanded polyglutamine neurodegenerative disorders. Nature 421:373–379. https://doi.org/10.1038/nature01301
48. Sánchez I, Piñol P, Corral-Juan M, Pandolfo M, Matilla-Dueñas A (2013) A novel function of Ataxin-1 in the modulation of PP2A activity is dysregulated in the spinocerebellar ataxia type 1. Hum Mol Genet 22:3425–3437. https://doi.org/10.1093/hmg/ddt197
49. Sánchez I, CJ X, Juo P, Kakizaka A, Blenis J, Yuan J (1999) Caspase-8 is required for cell death induced by expanded polyglutamine repeats. Neuron 22:623–633
50. Saudou F, Humbert S (2016) The biology of huntingtin. Neuron 89:910–926. https://doi.org/10.1016/j.neuron.2016.02.003
51. Saudubray JM, Sedel F, Walter JH (2006) Clinical approach to treatable inborn metabolic diseases: an introduction. J Inherit Metab Dis 29:261–274. https://doi.org/10.1007/s10545-006-0358-0
52. Serrano-Munuera C, Corral-Juan M, Stevanin G, San Nicolás H, Roig C, Corral J, Campos B, de Jorge L, Morcillo-Suárez C, Navarro A, Forlani S, Durr A, Kulisevsky J, Brice A, Sánchez I, Volpini V, Matilla-Dueñas A (2013) New subtype of spinocerebellar ataxia with altered vertical eye movements mapping to chromosome 1p32. JAMA Neurol 70:764–771. https://doi.org/10.1001/jamaneurol.2013.2311
53. Singleton AB, Farrer M, Johnson J, Singleton A, Hague S, Kachergus J, Hulihan M, Peuralinna T, Dutra A, Nussbaum R, Lincoln S, Crawley A, Hanson M, Maraganore D, Adler C, Cookson MR, Muenter M, Baptista M, Miller D, Blancato J, Hardy J, Gwinn-Hardy K (2003) Alpha-Synuclein locus triplication causes Parkinson's disease. Science 302:841. https://doi.org/10.1126/science.1090278
54. Sinke RJ, Ippel EF, Diepstraten CM, Beemer FA, Wokke JHJ, van HBJ, Knoers NVAM, van AHKP, Kremer HPH (2001) Clinical and molecular correlations in spinocerebellar ataxia type 6. Arch Neurol 58:1839–1844
55. Snowden JS, Hu Q, Rollinson S, Halliwell N, Robinson A, Davidson YS, Momeni P, Baborie A, Griffiths TD, Jaros E, Perry RH, Richardson A, Pickering-Brown SM, Neary D, Mann DMA (2011) The most common type of FTLD-FUS (aFTLD-U) is associated with a distinct clinical form of frontotemporal dementia but is not related to mutations in the FUS gene. Acta Neuropathol 122:99–110. https://doi.org/10.1007/s00401-011-0816-0
56. Taghdiri F, Sato C, Ghani M, Moreno D, Rogaeva E, Tartaglia MC (2016) Novel GRN mutations in patients with Corticobasal syndrome. Sci Rep 6:22913. https://doi.org/10.1038/srep22913
57. Tang B, Xiong H, Sun P, Zhang Y, Wang D, Hu Z, Zhu Z, Ma H, Pan Q, Xia J-H, Xia K, Zhang Z (2006) Association of PINK1 and DJ-1 confers digenic inheritance of early-onset Parkinson's disease. Hum Mol Genet 15:1816–1825. https://doi.org/10.1093/hmg/ddl104
58. Valente EM, Abou-Sleiman PM, Caputo V, Muqit MMK, Harvey K, Gispert S, Ali Z, Del Turco D, Bentivoglio AR, Healy DG, Albanese A, Nussbaum R, González-Maldonado R, Deller T, Salvi S, Cortelli P, Gilks WP, Latchman DS, Harvey RJ, Dallapiccola B, Auburger G, Wood NW (2004) Hereditary early-onset Parkinson's disease caused by mutations in PINK1. Science (New York, NY) 304:1158–1160. https://doi.org/10.1126/science.1096284
59. Vaughan JR, Davis MB, Wood NW (2001) Genetics of parkinsonism: a review. Ann Hum Genet 65:111–126. https://doi.org/10.1017/S0003480001008557
60. Verity C, Winstone AM, Stellitano L, Will R, Nicoll A (2010) The epidemiology of progressive intellectual and neurological deterioration in childhood. Arch Dis Child 95:361–364. https://doi.org/10.1136/adc.2009.173419
61. Weidemann F, Rummey C, Bijnens B, Störk S, Jasaityte R, Dhooge J, Baltabaeva A, Sutherland G, Schulz JB, Meier T (2012) The heart in Friedreich ataxia: definition of cardiomyopathy, disease severity, and correlation with neurological symptoms. Circulation 125:1626–1634. https://doi.org/10.1161/CIRCULATIONAHA.111.059477

62. Wenning GK, Colosimo C, Geser F, Poewe W (2004) Multiple system atrophy. Lancet Neurol 3:93–103. https://doi.org/10.1016/S1474-4422(03)00662-8
63. Winblad B, Amouyel P, Andrieu S, Ballard C, Brayne C, Brodaty H, Cedazo-Minguez A, Dubois B, Edvardsson D, Feldman H, Fratiglioni L, Frisoni GB, Gauthier S, Georges J, Graff C, Iqbal K, Jessen F, Johansson G, JÖnnsson L, Kivipelto M, Knapp M, Mangialasche F, Melis R, Nordberg A, Rikkert MO, Qiu C, Sakmar TP, Scheltens P, Schneider LS, Sperling R, Tjernberg LO, Waldemar G, Wimo A, Zetterberg H (2016) Defeating Alzheimer's disease and other dementias: a priority for European science and society. Lancet Neurol 15:455–532. https://doi.org/10.1016/S1474-4422(16)00062-4
64. P-Y X, Liang R, Jankovic J, Hunter C, Zeng Y-X, Ashizawa T, Lai D, Le W-D (2002) Association of homozygous 7048G7049 variant in the intron six of Nurr1 gene with Parkinson's disease. Neurology 58:881–884. https://doi.org/10.1212/WNL.58.6.881