CHAPTER

27

Molecular basis of movement disorders

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27.1 Introduction

Movement disorders form a broad phenomenological spectrum of conditions including tremor, myoclonus, dystonia, chorea, parkinsonism, and ataxia, as well as spanning both neurodevelopmental and neurodegenerative fields. Huntington's disease (HD), a neurodegenerative choreiform disorder, was one of the first movement disorders for which an underlying genetic cause was identified. Following this, disease-causing gene discovery predominantly focused on linkage analysis in large, multigenerational families where multiple family members were affected with the same disorder. However, it is the advent of next-generation sequencing that has led to the rise in disease-causing genes being identified for movement disorders, which in some cases has facilitated further understanding of disease mechanisms and provided insights for future therapeutic development. In this chapter, we will discuss the genetically determined forms of parkinsonism, dystonia, ataxia, and other movement disorder types identified to date as well as the likely mechanisms by which mutations in these genes lead to the disorder phenotype.

27.2 Parkinson's disease

A summary of the disease-causing genes in Parkinson's and their associated clinical phenotypes can be summarized in Table 27.1.

27.2.1 Epidemiology and pathophysiology

Parkinson's disease is characterized by alpha-synuclein deposition and dopaminergic neuronal degeneration in the substantia nigra. The classical clinical signs of parkinsonism include bradykinesia, a resting tremor, and rigidity. Parkinson's is age-related with 1% of the population affected at 65 years of age, increasing to 4%–5% by the age of 85 [1]. Although the cause of Parkinson's disease is unknown, there seems to be an interplay between genetic and environmental factors. Environmental factors associated with an increased risk of Parkinson's include pesticide use, rural living, well-water consumption, and occupational exposure, for example, mining. Protective agents against the development of Parkinson's disease include smoking, alcohol consumption, and caffeine intake [1]. Six genes, namely, *SNCA*, *LRRK2*, *Parkin*, *PINK1*, *DJ1*, and *VPS35*, with Mendelian patterns of inheritance have been identified as causing Parkinson's disease when carrying pathogenic mutations.

27.2.2 Genetics

27.2.2.1 Autosomal dominant inheritance

27.2.2.1.1 SNCA/PARK1: alpha-synuclein gene

Located on chromosome 4q21-22, the *SNCA* gene gives rise to the alpha-synuclein protein. Little is known about the normal function of *SNCA*; however, roles in regulating the release of neurotransmitters, synaptic

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TABLE 27.1 Genetic and clinical characteristics of Parkinson's disease.

Disorder (MIM number)	Epidemiology	Inheritance	Causative gene (locus)	Protein product	Proposed impact of mutation	Clinical phenotype	
						Motor	Nonmotor
168601/ 605543	2.5% of unrelated affected carriers	AD	SNCA/ PARK1/4 (4q22.1)	Alpha-synuclein	Toxicity caused by aggregates of mutated protein	Parkinsonism Dysarthria	Dementia
607060	0.5%–2% sporadic cases and 5% familial cases in Caucasians. 18%–30% in Ashkenazi Jews/North African Barbar	AD	LRRK2/ PARK8 (12q12)	Leucine-rich repeat serine/ threonine-protein kinase 2	Impaired autophagy	Tremor-dominant parkinsonism, dystonia	Depression
614203	Rare	AD	VPS35/ PARK17 (16q11.2)	Vacuolar protein sorting-associated protein 35	Protein aggregation, mitochondrial dysfunction, increased ROS production	Parkinsonism, dystonia, dyskinesia	Memory impairment
600116	2.5%–8.2% <45 years	AR	Parkin/ PARK2 (6q26)	E3 ubiquitin-protein ligase parkin	Impaired mitophagy	Parkinsonism, early-onset dystonia, hyperreflexia, slower progression of disease	Depression, constipation
605909	1%–2% of early-onset	AR	PINK1/ PARK6 (1p36.12)	Serine/ threonine-protein kinase PINK1	Impaired mitophagy	Early-onset parkinsonism	Depression
606324	<1% of early-onset parkinsonism	AR	DJ1/ PARK7 (1p36.23)	Protein/ nucleic acid deglycase DJ-1	Exposure to oxidative stress causing neurotoxicity	Early-onset parkinsonism, slower progression	Psychosis

AD, Autosomal dominant; *AR*, autosomal recessive; *ROS*, reactive oxygen species.

function, and neural plasticity have been suggested. The majority of mutations are missense mutations, with less frequent forms including gene multiplication (duplication or triplication). *SNCA* mutations result in increased expression and/or aggregation of alpha-synuclein with formation of oligomers, fibrils, and protofibrils thought to be toxic to glia, implicated in mitochondrial damage and affecting membrane permeability [2].

27.2.2.1.2 LRRK2/PARK8: leucine-rich repeat kinase 2

Case report

A 70-year old gentleman of North African descent presented with a 5-year history of disturbed sleep involving acting out of vivid dreams, vocalizations and involuntary limb movements. Over the same time period, he also noticed a deterioration in his sense of smell. Three years later, he became aware of an asymmetric upper limb tremor, predominantly involving his right hand, most evident when sitting quietly. He had also noticed increasing difficulty with fine motor tasks such as doing buttons, zips, and cleaning his teeth. Over the same time period his family described his mobility as having generally slowed, with a tendency to fall backward. They also described him as being lower in mood than would normally be typical for him, and some short-term memory difficulties were becoming increasingly evident in the family home. Following initial review with a neurologist he was started on levodopa (62.5 mg tds), noting an improvement to his dexterity and mobility, which further increased with higher doses of the medication.

LRRK2 mutations are the most common type of disease-causing parkinsonian mutations in Caucasian populations, accounting for 0.5%–2% of sporadic cases and 5% of familial cases, rising to 18%–30% of cases in Ashkenazi Jewish and North African Barbar populations [1,3]. *LRRK2* encodes a 2527 amino acid protein, with the most common pathogenic mutation being the missense G2019S (p. Gly2019Ser) mutation. The protein is expressed in neurons, astrocytes, and microglia, but expression is low in the dopaminergic neurons of the substantia nigra. Although a multidomain protein, mutations generally tend to be found in the central region of the

protein, affecting the Ras of complex (Roc) GTPase protein domain and kinase domain, as well as the carboxy-terminal of Roc sequence. However, the mechanisms by which these changes give rise to pathogenicity remains poorly understood.

27.2.2.1.3 VPS35/PARK17

A rare, highly penetrant, cause of autosomal-dominant Parkinson's disease is the VPS35 D620N mutation. A component of a retromer complex (membrane-associated protein), *VPS35* mediates retrieval of membrane proteins via endosomes and the Golgi apparatus. Mutations in this gene impair autophagy, which may manifest as protein aggregation, mitochondrial abnormality formation, increased production of reactive oxygen species, and enhanced susceptibility to cell death [4].

27.2.3 Autosomal recessive inheritance

27.2.3.1 Parkin/PARK2

Case report

A 50-year old woman was reviewed in the neurology outpatient clinic. She first developed symptoms in her early 20s with right lower limb dystonia and a rest-tremor involving her right upper limb. These symptoms had slowly progressed over the subsequent 30 years, with some general slowing of mobility and increased difficulty with fine motor tasks. Clinical examination found evidence of a rest-tremor, bradykinesia and generalized hyperreflexia. Within a few years of symptom onset, she was started on low-dose levodopa treatment (62.5 mg tds, with a good response, although dyskinetic movements had developed over the preceding 5–10 years. There were no reports of marked cognitive impairment nor mood change, and no preceding anosmia or symptoms of rapid eye movements (REM)-sleep behavioral disorder.

Parkin (PARK2) is responsible for half of all cases of early-onset Parkinson's (under 45 years of age) and a significant proportion of sporadic cases. The typical clinical phenotype includes early-onset dystonia, hyperreflexia, and slower disease progression [5]. *Parkin* is believed to function as an E3-ligase, responsible for protein degradation, as well as mediating mitophagy (autophagic removal of damaged organelles within the mitochondria), likely involved in Parkinson's pathogenesis. A variety of mutation types have been identified to date, including missense mutations (most common form) and copy number variants (deletions and duplications).

27.2.3.2 PINK1/PARK6: PTEN-induced kinase 1

PINK1 mutations have been identified in 1%–2% of early-onset disease cases. The *PINK1* gene encodes a PTEN-induced kinase protein containing a protein kinase domain and a mitochondrial-targeting motif [6]. *PINK1* shares a number of overlapping functions and mechanistic pathways with other known Parkinsonian genes, principally *Parkin* and *DJ1*. In physiological form, PINK1 accumulates on the outer membrane of dysfunctional mitochondria and its kinase activity is required for Parkin to be translocated into damaged mitochondria to facilitate mitophagy [7].

27.2.3.3 DJ1/PARK7: protein deglycase

DJ1 mutations are a rare cause of Parkinson's disease, accounting for <1% of early-onset parkinsonism, with missense mutations and deletions being most common [8,9]. Located on chromosome 1p36, DJ1 is a redox sensor of oxidative stress and is likely to play a role in protecting neurons from oxidative stress-induced damage [10,11].

27.2.3.4 Glucocerebrosidase mutations

Although normally associated with Gaucher's disease (a lysosomal storage disorder) in its homozygous form, heterozygous glucocerebrosidase (*GBA*) mutations are a strong risk factor for Parkinson's. Located on chromosome 1p22, *GBA* encodes a lysosomal enzyme that hydrolyzes glucocerebroside in glycolipid metabolism. It is thought that glucosidase activity helps modulate alpha-synuclein processing, with mutations causing accumulation of glycolipid metabolism intermediates, which then mediate cell damage [10]. *GBA* mutations are twice as common in early-onset versus late-onset Parkinson's and are associated with higher prevalence of cognitive impairment [10,12].

27.2.3.5 Other genes implicated in Parkinson's

Several other autosomal dominantly inherited genes have also been implicated in Parkinson's pathogenesis. *DNAJC13* encodes a chaperone protein that is thought to regulate protein trafficking and has mostly been found in those of Dutch-German-Russian Mennonite ancestry [13]. *CHCHD2* encodes a mitochondrial protein and has been found in a small cohort of Japanese families. Finally, links with *EIF4G1* have also been identified, although little is known of its function.

27.2.4 Treatment of Parkinson's disease

Treatment of both the motor and nonmotor symptoms in Parkinson's is symptomatic, with the overall emphasis being to increase the levels of midbrain dopamine. The two main groups of treatments for the management of motor symptoms include levodopa, also used in combination with a DOPA-decarboxylase inhibitor, and dopamine agonists, which target striatal dopaminergic neurons [13]. Other medications include monoamine oxidase type B inhibitors (e.g., selegiline), catechol-*O*-methyltransferase inhibitors (e.g., entacapone), amantadine, and anticholinergics [13]. In addition to oral medical therapy, treatment for Parkinson's can also be given via continuous infusion (e.g., apomorphine) or further down the gastrointestinal tract (e.g., jejunal duodopa). In eligible patients with refractory disease or the development of drug-induced dyskinesias, deep brain stimulation (DBS) provides a surgical means of symptoms management [14,15].

27.2.5 Parkinson's disease: key learning points

- There is a broad clinical phenotypic spectrum observed in genetically determined forms of Parkinson's disease.
- Autosomal-dominant inheritance of *LRRK2* mutations represent the most common form of genetically inherited Parkinson's disease.
- Common mechanistic pathways have been identified in *Parkin*, *PINK1*, and *DJ1* mutations.
- Heterozygous GBA mutations represent a risk allele for the development of parkinsonian symptoms but are not currently recognized as being directly responsible in giving rise to the disease phenotype.

27.3 Dystonia

27.3.1 Clinical characteristics

Dystonia is a movement disorder characterized by sustained or intermittent muscle contractions causing abnormal, often repetitive, movements, postures or both [16]. There is widespread variation in the clinical presentation of dystonia, with childhood, adolescent, and adult-onset forms, and muscle involvement ranging from single isolated groups (e.g., cervical dystonia) to more generalized forms. Many forms of dystonia have associated features, encompassing other movement disorders (such as parkinsonism), other neurological symptoms (such as peripheral neuropathies), and nonmotor associations. The association of psychiatric conditions is a specific common phenotype across dystonia disorders, for example, individuals with myoclonus dystonia (DYT11) demonstrate higher rates of generalized anxiety disorder, obsessive compulsive disorder, social phobia, and alcohol dependence compared to controls [17].

The most recent classification system aims to take into account diagnosis, treatment, underlying pathophysiology, and mechanism, organizing the dystonias according to two main features: clinical characteristics and etiology:

- Clinical features includes age at onset, regions of the body affected, temporal pattern of symptoms, presence of other movement disorders and other associated neurological features.
- Etiological categorization considers pathological nervous system findings (degeneration, structural nondegenerative lesions or neither) and inheritance pattern.

Dystonia is also divided into inherited, acquired, and idiopathic types. Acquired types are those noninherited forms with a known cause, such as dystonic cerebral palsy caused by brain injury in the perinatal period, and medication-induced forms. The idiopathic dystonias are those with no identified cause but may represent sporadic or currently unidentified genetic causes. The third category, which will form the focus of this section, are

the genetic dystonias. These are subdivided by mode of inheritance into autosomal dominant, autosomal recessive, X-linked recessive, and mitochondrial forms. Within the inherited dystonias, the DYT classification of diseases according to the locus of gene mutation can be helpful for subclassifying types.

27.3.2 Genetics of dystonia

With the use of next-generation genetic sequencing techniques, there has been a significant increase in the number of disease-causing genes identified for dystonia, with over 20 now recognized as having a role in disease pathogenesis. However, even within genetically homogeneous groups, there is substantial intra- and interfamilial variability in clinical phenotype and response to treatment. A number of genes linked with dystonia also demonstrate pleiotropic effects. An example of this is the gene implicated in paroxysmal kinesigenic dyskinesia, *PRRT2*. Encoding the proline-rich transmembrane protein 2, mutations in this gene locus are responsible for benign familial infantile epilepsy, infantile convulsions with choreoathetosis, and hemiplegic migraine. Even individuals within the same family group can exhibit phenotypical heterogeneity, with multiple different clinical conditions [18].

Dystonia genes demonstrate autosomal dominant, autosomal recessive, and X-linked inheritance patterns, with several of the dominantly inherited genes also displaying incomplete penetrance, such as *TorsinA* (DYT1), *THAP1* (DYT6), and *SGCE* (DYT11). The cause for this variation in penetrance of DYT1 (30%) and DYT6 (60%) remains largely unknown, although in DYT1 mutation carriers evidence is the emergence of additional genetic factors that may be of influence. A polymorphism in the cDNA at nucleotide 646, with a guanosine to cytosine substitution, encoding histidine rather than aspartate has been identified in 15% of cohorts. While no functional consequences directly relating to this have been identified, individuals carrying both mutation types have a higher likelihood of developing dystonia that those with the DYT1 mutation alone. *SGCE* (DYT11) also demonstrates variable penetrance via maternal imprinting mechanisms. Here, maternally inherited pathogenic mutations are silenced due to imprinting mechanisms, although may be subsequently expressed in later generations. In contrast, paternally inherited *SGCE* mutations are fully penetrant in demonstrating the disease phenotype [19].

27.3.3 Pathophysiology of dystonia

The pathophysiology of dystonia remains largely unknown; however, dystonia is widely considered to be a circuit-based disorder with disruption at the synaptic level impacting pathways, circuits, and networks. Evidence to date suggests that two circuits may be of particular importance, the basal ganglia-thalamo-cortical and cerebello-thalamo-cortical pathways, with imaging studies suggesting that disruption to these pathways may be critical in giving rise to dystonia [20]. The functioning of these connections are of particular importance, with diffusion tensor imaging demonstrating disrupted connections between motor cortical regions and subcortical connecting areas in those with focal dystonia. In addition, animal models have demonstrated reversible induced movement disorders including dystonia with pharmacological lesions of the basal ganglia [21]. On a cellular level, disruption to neurotransmitter function is also likely to contribute, particularly with the number of dystonia genes with direct links to the dopamine synthetic pathway, for example, dopa-responsive dystonia (DYT5, *GCH1* mutations). There is also accumulating evidence for the importance of cholinergic interneurons from animal models of dystonia, and disruption to serotonin metabolic pathways in human studies [22].

27.3.4 Targeted molecular diagnosis and therapy of dystonia

The clinical and genetic characteristics of the genetically determined forms of dystonia are summarized in Table 27.2.

27.3.5 Diagnosis of dystonia

The diagnosis of dystonia remains clinical; however, genetic testing can be used to provide greater specificity of diagnosis, further aiding management and genetic counseling. The majority of dystonia genes are now available for testing as gene panels, facilitating simultaneous testing of multiple potential causative genes and reducing the waiting time for patients to receive a genetic outcome [23].

TABLE 27.2 Clinical and genetic description of dystonic disorders where the disease-causing gene has been identified.

Disorder (MIM number)	Epidemiology	Inheritance	Causative gene (locus)	Protein product	Proposed impact of mutation	Clinical phenotype	
						Motor	Nonmotor
DYT1 (605204)	0.17/100,000 mutation frequency	AD, 30% penetrance	TOR1A (9q32-q34)	Torsin1A	Torsin1A loss of function and increased degradation	Varies from focal to generalized dystonia. Usually early onset	Increased rate recurrent major depression
DYT2 (224500)	Unknown	AR	Likely HPAC (1p35.1)	Unknown	altered regulation of voltage-dependent calcium channels	Childhood or adolescent onset initially distal limb dystonia, slowly progressive	
DYT3 XDP/Lubag's disease (313650)	High rates in Philippine populations	X-linked	TAF1 (X13.1)	TAF1	Impaired cellular transcription-progressive neostriatal neuronal loss	Torsion dystonia. Progressive, severe. parkinsonian features	Increased rates of depression and anxiety
DYT4 Whispering dysphonia (602662)	Unknown	AD	TUBB4A (19p)	Tubb4a	Brain specific interference with assembly of tubulin subunits	Second to third decade progressive laryngeal dysphonia followed by generalization	Some alcohol and propranolol responsiveness Thin face and body habitus
DYT 5a Segawa's disease (600225)	0.5/1,000,000 More females than males	AD	GCH1 (14q22.1−22.2)	GTP cyclohydrolase 1	Reduced dopamine levels in substantia nigra	Young onset progressive limb dystonia. Improved by sleep, worse in evenings. Associated parkinsonism	Levodopa responsiveness. Neuropsychiatric features including depression, anxiety and OCD
DYT 5b (605407)	rare	AR	TH (11p15.5)	Tyrosine hydroxylase	Altered regulation of dopamine production	Two phenotypes: (1) perinatal severe encephalopathy with diurnal variation, (2) First year onset progressive generalized dystonia, hypokinesis, rigidity	Autonomic disturbances
DYT 5b (612716)	Rare	AR	SPR (2p13.2)	Sepiapterin reductase	Defect in BH4 synthesis causing severe deficiencies in dopamine and seratonin	Usually starts in lower limbs. Diurnal fluctuation, levodopa responsive. Parkinsonism. Ataxia	Cognitive delay. Psychiatric and behavioral abnormalities
DYT6 (609520)	Unknown	AD, ~60% penetrance	THAP1 (8p11.1)	THAP domain encoding protein	Involved in endothelial cell proliferation and proapoptotic processes	Early craniofacial involvement with secondary generalization. Laryngeal dystonia common	
DYT8 Paroxysmal non-kinesigenic Dyskinesia (609023)	Rare	AD	MR1 (2q35)	MR-1L	?altered glutathione related detoxification in neuronal cells	Onset infancy or childhood. Episodic dystonia, choreoathetosis, ballism. Precipitated by stress, caffeine, alcohol, exertion, ovulation, and menstruation	

DYT10 Paroxysmal kinesigenic dyskinesia (614386)	1/150,000	AD, incomplete penetrance	PRRT2 (16p11.2-q12.1)	Proline-rich transmembrane protein 2	Protein highly expressed in brain and spinal cord, interacts with a synaptosomal membrane	Childhood onset, brief attacks of dystonia, chorea, and athetosis. Improves with age and carbamazepine	Depressive and behavioral disorders
DYT 11 Myoclonus dystonia (604149)	Rare	AD, incomplete penetrance-maternal imprinting	SGCE (7q21.3)	Epsilon-sarcoglycan	Reduced expression at the cell surface membrane. Potential role in synaptic plasticity	Childhood/Adolescent onset, dystonia affects mainly neck, trunk and arms. Myoclonic jerks. Improved by ethanol and clonazepam	Neuropsychiatric disorders including depression, OCD, personality disorder
DYT12 Dystonia-parkinsonism (182350)	Rare	AD	ATP1A3 (19q13.2)	Alpha 3 subunit of Na/K ATPase	Impaired activity of enzyme involved in regulation of neuronal activity, expressed in regions including basal ganglia, hypocampus, and cerebellum	Young adults. Sudden onset, asymmetrical dystonia and parkinsonism	Neuropsychiatric disorders including psychosis, anxiety, and depression
DYT16 (603424)	Reported in two Brazilian families	AR	PRKRA (2q31.2)	Interferon-inducible double-stranded RNA-dependent protein kinase activator A	?disrupted cellular stress response	Early-onset dystonia and parkinsonism	Aggression. Cognitive impairment
DYT18 GLUT1 Deficiency Syndrome 2 (138140)	1 in 90,000	AD	SLC2A1 (1p34.2)	GLUT1	Impairment of glucose transport into the brain	Episodic dyskinesia, mainly distal lower limb dystonia/choreoathetosis. Triggers include hunger, exercise. Can get ataxia, spacticity, seizures, encephalopathy	Associated with hemolytic anemia. Improves with a ketotic diet
DYT23 (614860)	Reported in one German family and one Dutch family	AD	CACNA1B (9q34.3)	CACNA1B	Alteration in neurotransmitter release at synapses	Adult-onset cervical dystonia, tremor of head and limbs one family. Myoclonic dystonia the other family	
DYT24 (615034)	Unknown	AD	ANO3 (11p)	Anoctmin-3	A transmembrane calcium activated protein channel, highly expressed in putamen. Reduced intracellular calcium signaling	Adult-onset cervical dystonia, upper limb tremor, and laryngeal involvement	
DYT25 (615073)	Unknown	AD	GNAL (18p)	G-protein G alpha subunit	Highly expressed in basal ganglia, mutations related to abnormality in dopamine D1 receptor activity	Adult onset, focal cranial and cervical dystonia	
DYT26 (616398)	Unknown	AD	KCTD17 (22q12.3)	Potassium channel tetramerization-domain containing proteins	Highly expressed in putamen. ?role in dopaminergic dysfunction and cellular calcium homeostasis	Onset of mild upper limb dystonia, progressive. Myoclonic jerks	
DYT28 (617284)	Unknown	AD	KMT2B (19p13), reduced penetrance	Histone-lysine N methyltransferase 2B	Involved in regulation of transcription	Childhood onset, progressive	Elongated face, bulbous nose. Developmental delay and intellectual disability

(*Continued*)

TABLE 27.2 (Continued)

Disorder (MIM number)	Epidemiology	Inheritance	Causative gene (locus)	Protein product	Proposed impact of mutation	Clinical phenotype	
						Motor	Nonmotor
Aromatic-L-amino acid decarboxylase deficiency (608643)	Rare	AR	DDC (7p12)	Aromatic L-amino acid decarboxylase	Deficiency of protein that catalyzes dopamine synthesis	Onset in infancy or childhood of hypotonia, dystonia, oculogyric crises, developmental delay	Irritability and emotional lability
Dopamine transporter deficiency syndrome (613135)	Rare	AR	SLC6A3 (5p15.33)	Sodium-dependent dopamine transporter	Defective presynaptic dopamine reuptake	Onset in infancy or childhood of parkinsonism and dystonia	Irritability

AD, Autosomal dominant; *AR*, autosomal recessive; *OCD*, obsessive compulsive disorder.

27.3.5.1 *DYT1: TorsinA mutations*

Case report

An 8-year old girl was referred to the pediatric neurology out-patient clinic by her general practitioner, attending with her parents. She was born at term, at the end of an uneventful pregnancy. There was no report of perinatal injury or anoxic insult, and no developmental delay in infancy or early childhood. Two years prior to presentation she had begun to develop pain and cramping in her right foot, progressing to abnormal posturing, particularly inversion and rotation of the foot. During this time, walking became more difficulty, with a tendency to walk on the outer aspect of her foot. Over the preceding 6 months similar symptoms had begun to develop in the left lower limb and to a lesser extent the right upper limb. There was no immediate family history of similar symptoms, although her paternal grandfather had had lifelong mobility difficulties, similar posturing of the limbs and symptoms of major depression in adult life. Cerebral imaging and routine blood tests (including copper and caeruloplasmin) were within normal limits, with no evidence of focal pathology.

DYT1 dystonia is caused by mutations to the *TOR1A* gene, resulting in loss of function of the encoded protein, Torsin1A. The most common mutation type is a three base pair deletion (GAG) at the c.907_909 locus, with this accounting for 16%–53% of all types of early-onset dystonia in non-Jewish populations, and 80%–90% in Ashkenazi Jewish populations. No genotype–phenotype correlation has been identified to date, although the link with the guanosine to cytosine genetic variant described earlier provides some evidence of the genetic underpinning of the observed variable penetrance. Murine and *Drosophila* models of this disorder suggest that *TOR1A* mutations result in a loss of function of the Torsin1A protein, primarily due to destabilization and premature degradation, resulting in failure of its expression. In addition, although no focal areas of pathology have been identified, animal models carrying this mutation have demonstrated some evidence of abnormal nuclear membranes in postmigratory neurons.

27.3.5.2 *DYT5:* GCH1 *mutations (dopa-responsive dystonia)*

Case report

An 11-year old boy was referred to the pediatric neurology out-patient department, attending with both of his parents. He had been born at term, at the end of a normal pregnancy and without any perinatal complications. There were no reports of developmental delay in infancy, and no history of recurrent hospital admissions during this period. At the age of 6 years, he began to develop abnormal posturing of his right foot, with evidence of inversion and a tendency to walk on the outer aspect of his foot. This became more pronounced with running and was impacting his ability to partake in sporting activities at school. Over the past 5 years these symptoms had generalized to involve his remaining limbs and trunk, limiting all activities of daily living. These symptoms tended to be worse toward the end of the day and improved after sleep (diurnal variation). This boy had three siblings, one, his younger sister having developed a similar spectrum of symptoms. Six months prior to this appointment he had been started on levodopa treatment with a dramatic improvement to his limb posturing and general mobility.

Dopa-responsive dystonia (DYT5) can be caused by mutations to the *GCH1*, *TH*, and *SPR* genes. Mutations in the *GCH1* gene (previously referred to as Segawa's disease) are the most common and are inherited in an autosomal-dominant fashion. *GCH1* encodes the GTP cyclohydrolase 1 enzyme, critical in the catalysis of the first step in the synthesis of tetrahydrobiopterin (TH4). Tetrahydrobiopetrin itself is an essential cofactor in amino acid processing and neurotransmitter synthesis. This latter role includes monoaminergic neurotransmitters, and in particular dopamine. Pathological studies have demonstrated a reduction of dopamine levels in the substantia nigra of patients with DYT5 dopa-responsive dystonia in the absence of any neurodegeneration, and normal levels of tyrosine hydroxylase activity.

27.3.5.3 *DYT6:* THAP1 *mutations*

Case report

A 20-year old man was seen in the movement disorders outpatient clinic with a 2-year history of spasms and unusual movements involving the face, and in particular his eyes. He described these as being involuntary with no preceding warning and would frequently cause the muscles around his eyes and mouth to contract and "spasm." The symptoms involving the eyes were particularly pronounced with excess blinking and periods of sustained eye closure. These symptoms had progressed over the past 12 months to involve his speech and swallow. The phonation of his speech had become more variable and on occasion sounded as though he was breathless, while he had also begun to choke when drinking liquids. In the 6 months leading up to the appointment he had also noted cramping in his right hand and forearm when writing.

THAP1 mutations are inherited in autosomal-dominant fashion but with only ~60% penetrance, the cause for this being unknown. *THAP1* itself encode the THAP1 protein that functions as a DNA-binding transcriptional

regulator that regulates endothelial cell proliferation and G1/S-cell cycle progression. It is also thought that it may have some proapoptotic activity, aiding cell apoptosis and degradation. Functional cellular studies have suggested that *THAP1* mutations impair protein stability, reducing the amount of function THAP1 protein that is available to bind to DNA, and therefore reducing its cellular function.

27.3.5.4 *DYT10: paroxysmal kinesigenic dyskinesia*

Case report

A 10-year old boy attended the neurology out-patient clinic with his parents. Over the preceding 6 months he had begun to develop "attacks" of abnormal movements. These tended to occur after a sudden movement, for example, standing up quickly from a chair, or suddenly starting to run in the school playground. The attacks involved abnormal posturing of his lower limbs bilaterally, with a tendency of his feet to invert. He also described cramping and pain in his lower limbs during these events. Each attack would last 30–40 s, and could occur up to 40–50 times per day dependent upon the activities undertaken. There was no reported loss of consciousness during the events. The patient's father also described similar, less frequent attacks, involving his upper limbs the description of which was more in keeping with chorea. On examination there was no evidence of a focal neurological deficit in either the patient or his father. The young boy had been prescribed Carbamazepine by his general practitioner, with a significant improvement to his symptoms.

Paroxysmal kinesigenic dyskinesia is caused by mutations to the proline-rich transmembrane protein 2 (*PRRT2*), which are inherited in an autosomal-dominant manner. *PRRT2* mutations demonstrate pleiotropy, giving rise to a number of distinct clinical disorders including infantile convulsions and choreoathetosis Syndrome, benign familial infantile convulsions, and hemiplegic migraine. The proline-rich transmembrane protein 2 itself is predicted to include two transmembrane segments. Its function in the brain remains unknown; however, it is believed to interact with the synaptosomal-associated protein 25 (SNAP25), with a suggestion that it may play a role in the fusion of synaptic vesicles to the plasma membrane. Patients with *PRRT2* mutation positive paroxysmal kinesigenic dyskinesia often respond well to treatment with carbamazepine and phenytoin, resulting in a significant reduction to the number of events experienced.

27.3.5.5 *DYT11:* SGCE *mutations*

Case report

A 7-year old girl is reported to have developed jerks involving her upper body at the age of 3 years. These were most evident when feeding or drawing. There was no evidence that these were stimulus sensitive and were not associated with a loss of consciousness or awareness. The jerks had remained relatively stable over the preceding 4 years, with no spread to other body regions. More latterly she had also begun to develop some abnormal posturing of her neck and upper limbs, again more pronounced when undertaking tasks. Her parents described some anxiety-related symptoms, particularly in relation to unfamiliar social settings. Both of her parents were well with no evidence of a movement disorder. However, her maternal grandmother had developed similar symptoms in childhood that had persisted into adult life. Her motor symptoms were highly alcohol responsive, almost completely resolving after a few glasses of wine. In addition, she also had diagnoses of obsessive-compulsive disorder and generalized anxiety disorder and was reviewed regularly by the local psychiatry department.

Myoclonus dystonia is caused by mutations to the epsilon-sarcoglycan (*SGCE*) gene located on chromosome 7 and encoding the epsilon-sarcoglycan protein, a single-pass transmembrane protein. The role of the epsilon-sarcoglycan protein in brain remains unknown, but in peripheral tissue forms part of the dystrophin-associated glycoprotein complex. Hypothetical models have suggested that the epsilon-sarcoglycan protein may be preferentially located on the postsynaptic membrane and play a role in postsynaptic receptor clustering or function. Mutations in the *SGCE* gene result in degradation of the protein by the ubiquitin-proteasome system, and failure of its expression at the cell surface membrane. Postmortem tissue analysis has demonstrated that the highest levels of epsilon-sarcoglycan protein are expressed in the basal ganglia and cerebellum, with evidence from cerebral imaging demonstrating a positive correlation between dystonia severity and gray matter volume, as well as reduced striatal dopamine-2-receptor binding in those with *SGCE* mutations.

27.3.6 *Therapy of dystonia*

The currently available treatment for dystonia involves physical therapy, oral medication, localized neurotoxin injections, and DBS.

27.3.6.1 Physiotherapy

Physiotherapy is used to aid symptomatic management in dystonia, helping with control of pain, improvement of posturing of the affected area, and aiding of day-to-day functioning. Techniques used include passive mobilization and stretching of affected areas, and training aimed at improving voluntary control and functionally relevant activities.

27.3.6.2 Oral medication

Medical treatment of dystonia focuses on the neurotransmitter systems implicated in dystonia pathophysiology. These systemic forms of treatment are predominantly used in the more generalized dystonia phenotypes rather than for focal dystonias where more targeted treatments are usually utilized. Anticholinergic medications such as trihexyphenidyl, with their action as postsynaptic antagonists of muscarinic receptors, provide symptomatic treatment in some, although potential side effects include a dry mouth, urinary retention, constipation, impairment in concentration and memory, and confusion. Benzodiazepines impact gamma amniobutyric acid (GABA) neurotransmission by binding to $GABA_A$ receptors, increasing the opening of chloride channels and resulting in enhancement of inhibitory neurotransmission. Clonazepam is a commonly used benzodiazepine in dystonia management due to its long half-life. Side effects include sedation, disinhibited behavior, depression, and drooling. In the specific case of dopa-responsive dystonia (DYT5, *GCH1* mutations) a large and sustained improvement can be seen with administration of levodopa. Dopamine reducing medications also improve symptoms in dystonia. Examples of these include tetrabenazine, which reduces dopamine presynaptically; and clozapine that acts on the postsynaptic membrane to block dopamine uptake.

27.3.6.3 Botulinum toxin

Botulinum toxin therapy forms the first-line treatment for those with focal dystonia, in particular cervical dystonia. The botulinum toxin is injected into the affected area, exerting its effects locally by preventing presynaptic acetylcholine release and so relaxing the injected muscle. The effects of this treatment gradually wane, typically over a 12-week period, requiring repeated treatment for sustained effect.

27.3.6.4 Deep brain stimulation

DBS is indicated in those with generalized or segmental dystonia and complex cervical dystonia, where botulinum toxin treatment is ineffective or its effect has waned. It is a surgical procedure involving the insertion of electrodes, which can apply stimulation in functionally relevant brain areas. The globus pallidus interna, a subsection of the basal ganglia, represents the most commonly targeted area for stimulation, while evidence also supports the stimulation of the thalamus and subthalamic nucleus. Using MRI guidance, the electrodes are placed bilaterally in the target location, together with an implantable pulse generator, placed below the left clavicle, acting as a pacemaker for the electrical stimulation. The intensity of stimulation can gradually be increased to reach a level that optimizes benefit but avoids side effects. It takes several months before the beneficial effects are experienced. Risks of the procedure are similar to those inherent in all neurosurgical procedures, including bleeding, infection, and adverse effects on other functional brain regions [24].

27.3.7 Dystonia: key learning points

- Dystonia is often described according to its clinical distribution, including generalized, segmental, and focal forms.
- Proposed pathophysiological mechanisms include disrupted synaptic neurotransmission impacting neuronal circuits and networks.
- Genetically determined forms of dystonia can be inherited in autosomal dominant, autosomal recessive, X-linked recess, and via mitochondrial mutations
- Several of those with autosomal-dominant inheritance demonstrate reduced penetrance (e.g., DYT1, DYT6, and DYT11).
- Within dystonia genetics, there are some examples of pleiotropy, that is, mutations to the same gene result in distinct clinical disorders, for example, *PRRT2* mutations.

27.4 Ataxia

Ataxia describes a loss of coordination of movement, which can affect the limbs and trunk [25]. There are many heritable forms of ataxia, where in addition to the loss of coordination additional clinical characteristics may also be present. A summary of the clinical, genetic and proteomic characteristics of genetically determined forms of ataxia can be seen in Table 27.3 (spinocerebellar ataxias) and Table 27.4 (other forms of ataxia).

TABLE 27.3 Clinical and genetic description of the spinocerebellar ataxias (SCA).

Disorder (MIM number)	Epidemiology	Inheritance	Causative gene (locus)	Protein product	Proposed impact of mutation	Clinical phenotype
SCA1 (164400)	rare	AD	*ATXN1* (6p22) (CAG repeat expansion)	Ataxin-1	Disrupted transcriptional regulation	Pyramidal signs, peripheral neuropathy, chorea
SCA2 (183090)	Unknown. Cuba Holguin Province 43/100,000	AD	*ATXN2* (12q24.12) (CAG repeat expansion)	Ataxin-2	Role of ataxin-2 in RNA metabolism	Slowed saccades, parkinsonism, and dementia
SCA3 Machado–Joseph disease (109150)	Commonest SCA	AD	*ATXN3* (14q32.12) (CAG repeat expansion)	Ataxin-3	Protein misfolding, accumulation of disease protein in neuron inclusions	Cerebellar ataxia, pyramidal and extrapyramidal signs, fasciculations, oculomotor apraxia
SCA5 (600224)	Rare	AD	*SPTBN2* (11q13.2)	Beta-III spectrin	Calcium-mediated alteration of transcription	Slowly progressive. Eye movement abnormalities, tremor, impaired vibration sense
SCA6 (183086)	<1/100,000	AD	*CACNA1A* (CAG repeat expansion)	Alpha 1a subunit voltage-gated calcium channel	Disrupted calcium channel function	Predominantly cerebellar symptoms. Slow progression
SCA7 (164500)	Rare	AD	*ATXN7* (CAG repeat expansion)	Ataxin-7	Impaired transcription. Development of neuronal nuclear inclusions	Visual loss (cone-rod dystrophy), slow saccades
SCA8 (608768)	Unknown	AD	*ATXN8/ATXN80S* (13q21) (CTG repeat expansion)	Ataxin-8	RNA-related neurotoxicity	Cognitive dysfunction, psychiatric disorders. Pyramidal and sensory signs
SCA10 (603516)	unknown	AD	*ATXN10* (22q13.31) (ATTCT pentanucleotide expansion)	Ataxin-10	RNA processing abnormality	Slowly progressive cerebellar symptoms and epilepsy. Mild pyramidal signs, peripheral neuropathy
SCA11 (604432)	Rare	AD	*TTBK2* (15q15.2)	Tau tubulin kinase	Reduction of tau protein phosphorylation, causing tau deposition	Slowly progressive cerebellar symptoms and eye movement abnormalities. Occasional hyperreflexia, dystonia and parkinsonism
SCA12 (604326)	Unknown/Rare	AD	*PPP2R2B* (5q32) (CAG repeat expansion)	Serine/Threonine-protein phosphatase		Mild ataxia. Action tremor. Pyramidal and extrapyramidal signs. Dementia

(*Continued*)

TABLE 27.3 (Continued)

Disorder (MIM number)	Epidemiology	Inheritance	Causative gene (locus)	Protein product	Proposed impact of mutation	Clinical phenotype
SCA13 (604259)	Unknown	AD	*KCNC3* (19q13.33)	Voltage gated potassium channel	Disrupted voltage gated potassium channel function. Altered neuronal excitability	Childhood onset: developmental delay, mild ataxia. Short stature. Late development: dysphagia, bradykinesia, and urinary urgency
SCA14 (605361)	Rare	AD	*PRKCG* (19q13.42)	Protein kinase C γ	Aggregation of abnormal protein in Purkinje cells	Variable age at onset hyperreflexia, reduced vibration sensation
SCA15 (606658)	Unknown	AD	*ITPR1* (3p26.1)	IP3 receptor	Disruption to calcium channel function impacting synaptic signaling	Slowly progressive. Head tremor
SCA17 (607136)	Unknown	AD	*TBP* (6q27) (CAG repeat expansion)	TATA binding protein	Impaired transcriptional regulation.	Dementia, parkinsonism, dystonia, epilepsy, chorea, spasticity, and psychiatric disorders
SCA19/22 (607346)	Unknown	AD	*KCND3* (1p13.2)	Potassium channel	Voltage gated potassium channel dysfunction	Myoclonus, postural tremor, cognitive impairment
SCA21 (607454)	Unknown	AD	*TMEM240* (1p36.33)	Transmembrane protein 240	Unknown	Parkinsonism, mild cognitive impairment
SCA23 (610245)	Unknown	AD	*PDYN* (20p13)	Proenkephalin-B	Increased NMDA receptor signaling leading to cellular dysfunction and death	Slowing of saccades, ocular dysmetria, dysarthria, and hyperreflexia
SCA26 (609306)	Reported in one American family	AD	*EEF2* (19p13.3)	Elongation factor 2	Impaired translocation	Slowly progressive. Nystagmus and impaired pursuit
SCA27 (609307)	Rare	AD	*FGF14* (13q33.1)	Fibroblast growth factor 14	Abnormality of presynaptic calcium channel regulation	Tremor, dyskinesia
SCA28 (610246)	Rare	AD	*AFG3L2* (18p11.22)	AFG3-like protein 2	Purkinje degeneration	Juvenile onset, slow progression. Later pyramidal signs, ptosis, slowing of saccades, ophthalmoparesis
SCA29 (117360)	Unknown	AD	*ITPR1* (3p26.1)	Inositol 1,4,5-triphosphate receptor type 1	Abnormalities of membrane channel function	Onset at birth, slow or no progression
SCA31 (117210)	Rare	AD (incomplete penetrance)	*BEAN1* (16q21)	Protein BEAN1	RNA abnormalities	Eye movement abnormalities
SCA35 (613908)	Reported in 3 Chinese families	AD	*TGM6* (20p13)	Transglutamase 6	Reduction of intranuclear TG6, accumulation in perinuclear region	Hyperreflexia, extensor plantars, and spasmodic torticollis
SCA36 (614153)	Unknown	AD	*NOP56* (20p13)	Nucleolar protein 56	RNA function abnormality, toxic effect	Hearing loss, tongue atrophy, fasciculations, and peripheral neuropathy

AD, Autosomal dominant; *AR*, autosomal recessive.

TABLE 27.4 Clinical and genetic description of other forms of inherited ataxia.

Disorder (MIM number)	Epidemiology	Inheritance	Causative gene (locus)	Protein product	Proposed impact of mutation	Clinical phenotype
Friedreich ataxia (229300)	Commonest autosomal recessive ataxia	AR	*FXN* (9q21.11) (GAA repeat expansion)	Frataxin, mitochondrial	Mitochondrial iron accumulation leading to oxidative stress.	Limb weakness, absent lower limb reflexes, upgoing plantars. Dysarthria, pes cavus, scoliosis, visual impairment, and cardiomyopathy
DRPLA (125370)	Most common in Japan	AD	*ATN1* (12p13.31) (CAG repeat expansion)	Atrophin 1	Reduced transcription of fat tumor suppressor gene, leading to neuronal degeneration	Onset <20 years: myoclonic epilepsy and intellectual disability Onset >40 years: choreoathetosis, dementia
EA1 (160120)	unknown	AD	*KCNA1* (12p13.32)	Potassium voltage-gated channel subfamily A member 1	Reduction of potassium channel function leading to increased neuronal excitability.	Brief episodes of ataxia. Myokymia, episodic muscle contractions
EA2 (108500)	Unknown	AD	*CACNA1A* (19p13.13)	Voltage-dependent P/Q-type calcium channel subunit alpha 1A	Abnormal function of calcium channel heavily expressed in the cerebellum	Episodic ataxia. Nystagmus, vertigo, migraines
EA5 (613855)	Single French-Canadian family	AD (incomplete penetrance)	*CACNB4* (2q23.3)	Voltage-dependent L-type calcium channel subunit beta-4	Calcium channel dysfunction	Episodic vertigo and ataxia. Nystagmus between episodes
EA6 (612656)	Three unrelated families identified	AD	*SLC1A3* (5p13.2)	Excitatory amino acid transporter 1	Reduced glutamate transport	Episodic and progressive ataxia. Hemiplegia, seizures
Cerebellar ataxia, deafness and narcolepsy (604121)	Reported in four families	AD	*DNMT1* (19q13.2)	DNA (cytosine-5)-methyltransferase 1	Abnormal DNA methylation	Deafness, narcolepsy, dementia. Sometimes optic atrophy, sensory neuropathy, depression, psychosis
Ataxia-telangiectasia (208900)	1/40,000−300,000	AR	*ATM* (11q22.3)	Serine-protein kinase ATM	Lack of repair of damaged DNA and increased oxidative stress	Childhood onset, oculomotor apraxia, cutaneous telangiectasia, immune deficiency, hypogonadism, and hematological malignancies
Ataxia with vitamin E deficiency (277460)	Unknown	AR	*TTPA* (8q12.3)	Alpha-tocopherol transfer protein	Low levels of vitamin E, increased oxidative stress	Childhood onset, progressive. Dysarthria, peripheral neuropathy, loss of lower limb reflexes, retinitis pigmentosa
Ataxia with oculomotor apraxia type 1 (208920)	Unknown	AR	*APTX* (9p21.1)	Aprataxin	Impaired DNA repair	Childhood onset. Oculomotor ataxia, axonal peripheral neuropathy, hypoalbuminaemia
Ataxia with oculomotor apraxia type 2 (606002)	Unknown	AR	*SETX* (19q34.13)	Probable helicase senataxin	Implicated in DNA repair	Choreoathetosis, dystonic posturing, and oculomotor ataxia
Cerebrotendinous xanthomatosis (213700)	Rare	AR	*CYP27A1* (2q35)	Sterol 26-hydroxylase, mitochondrial	Defective bile acid biosynthesis	Onset early childhood. Spinal cord involvement, dementia, tendon xanthomas, juvenile cataracts, and early atherosclerosis

AD, Autosomal dominant; *AR*, autosomal recessive.

27.4.1 Genetics of ataxia

Hereditary ataxias demonstrate a range of inheritance patterns including autosomal dominant, autosomal recessive, X-linked, and inheritance of mitochondrial mutations. Within these groups, a large number constitute trinucleotide repeat disorders, where there is an expansion of a three nucleotide repeat, for example, CAG, to pathogenic levels. As with other trinucleotide repeat disorders, these disorders demonstrate genetic anticipation, in which the size of the repeat increases with successive generations with a progressively earlier age at onset.

27.4.1.1 Gene transcription and RNA

Many of the proteins expressed by the mutated genes in the hereditary ataxias have a role in regulating gene expression (e.g., SCA1, SCA2, and SCA7) with a subsequent impact on neuronal cell function and ultimately degeneration. Trinucleotide repeat segments are commonly found within transcription regions, with several lines of evidence suggesting that theses transcription regions impact histone acetylization, subsequently affecting chromatin regulation and gene expression [26]. One such example is SCA7, in which the ataxin protein typically forms part of the histone acetyltransferase complex, increasing acetylation of the histone H3, which in turn causes downregulation of transcription. Similarly, a polyglutamine expansion of the TATA box-binding protein in SCA17 results in protein dysfunction and subsequent disruption of the transcription initiation process [27]. Mutations in noncoding regions are also observed among the genetically determined ataxias. One such example is Friedreich's ataxia, caused by a GAA repeat expansion within an intronic region of the *frataxin* gene. Several mechanisms have been proposed for the resultant failure of transcription of this gene, including the physical obstruction of the DNA-polymerase II in unwinding DNA as well as that the abnormal expansion behaves like heterochromatin (chromatin too tightly bound to be translated effectively), which acts to silence the expression of neighboring regions.

27.4.1.2 Intranuclear inclusions

A common neuropathological finding among the hereditary ataxias is neuronal accumulation of misfolded proteins, predominantly in the nucleus, and to a lesser extent in the cytoplasm of cells. Frequently these protein aggregates will include not only the pathological protein, but other proteomic elements such as transcription factors, which with the additional impairment of the ubiquitin-proteasome system, accumulate due to the failure of abnormal protein degradation. A more specific example of this is SCA3, where the ataxin-3 protein interacts with the ubiquitin-proteasome system, with accumulation of pathogenic ataxin-3 resulting in impairment to its normal function [28].

27.4.1.3 Transmembrane channel abnormalities

Several types of ataxia involve mutations in genes encoding transmembrane channels, including voltage-gated calcium channels (SCA6); voltage-gated potassium channel (SCA13, EA1, and SCA19); ligand-gated calcium channels (SCA15); and active transporters (EA6). Overall, this disruption to channel function impacts neuronal excitability and subsequent neuronal activity [29].

27.4.1.4 Neuronal calcium homeostasis

Synaptic neurotransmission requires maintenance of calcium homeostasis for normal function, with disruption to these processes implicated in the pathogenesis of some forms of hereditary ataxia. Calcium homeostasis abnormalities can be the direct result of calcium channel abnormalities (such as a mutation in the *IP3R1* smooth endoplasmic reticulum (ER) calcium channel in SCA15), or result indirectly from impaired calcium signaling, such as with SCA1. Calcium homeostasis is also important in intracellular signaling pathways, which in turn impact transcriptional regulation [29].

27.4.1.5 Mitochondrial dysfunction

Many conditions caused by inheritance of mitochondrial DNA mutations involve ataxia as part of a broader phenotype, for example, Kearns–Sayres and myoclonic epilepsy with ragged red fibers. Several of the autosomal recessively inherited forms of ataxia also interfere with mitochondrial function, such as infantile onset spinocerebellar ataxia. Mitochondria function in the production of adenosine triphosphate (ATP), failure of which results in a deficit in cellular energy production with neurological sequalae including cerebellar dysfunction [29].

27.4.2 Cerebellar degeneration

The mechanisms discussed both directly and indirectly ultimately lead to cell death, with particular involvement of cerebellar Purkinje cell neurons via both apoptosis and necrotic mechanisms. Atrophy of the cerebellum, as well as other brain regions, is a notable feature of the hereditary ataxias, particularly the autosomal dominantly inherited forms. There is evidence that this selective degeneration may be related to cerebellar Purkinje cells being particularly vulnerable due to their high metabolic activity and the balance of protein production and degradation mechanisms [30] (Table 27.5).

27.4.3 Targeted molecular diagnosis and therapy

27.4.3.1 Diagnostic testing

27.4.3.1.1 Blood plasma tests

For some forms of ataxia a blood plasma test can be used to measure pathological levels of specific substrates (Table 27.6).

27.4.3.1.2 Genetic testing

Molecular genetic testing is available for both the trinucleotide repeat disorders and the other forms of inherited ataxias. Due to the clinical overlap of many of the autosomal-dominant spinocerebellar ataxias, gene panel testing of several of the disorders simultaneously is frequently used. When a trinucleotide repeat disorder is confirmed, the length of the repeats is quantified to determine if this is within normal, intermediate, or pathogenic ranges. In some cases the size of the trinucleotide repeat may be too large to be determined using this technique, in which case Southern blotting would be used for further analysis.

27.4.4 Freidreich's ataxia

Case report

A 20-year old man attended the neurology outpatient clinic following a referral by his general practitioner. Five years ago he had begun to develop what was initially described as clumsiness, followed by increased difficulties with coordination, frequent falls and worsening of his mobility. Over this time, friends and family had noticed that his speech had become more slurred and that he was more difficult to understand. He also reported occasional episodes of breathlessness, although these were present only on exertion. On examination there was evidence of increased tone and sustained clonus in the lower limbs bilaterally. Examination of power demonstrated proximal limb weakness involving both the upper and lower limbs, deep tendon reflexes were absent throughout and plantar responses were upgoing bilaterally. There was also evidence of spinal scoliosis involving the lumbosacral region of the spine, and pes cavus deformities of the feet bilaterally. Cognitive examination identified no marked evidence of impairment. Echocardiogram and electrocardiogram recordings were both suggestive of hypertrophic cardiomyopathy. There was no reported family history of similar symptoms.

Freidreich's ataxia is caused by mutations to the *frataxin (FXN)* gene, inherited in an autosomal recessive manner. The *frataxin* gene encodes the frataxin protein, which is important in the normal functioning of mitochondria. Freidreich's ataxia is a trinucleotide repeat disorder, with expansion of the GAA repeat beyond the normal limits (normal range: 5–33 repeats). Typically >66 GAA repeats is seen in Friedreich's ataxia, with fewer repeats correlating with a later onset of motor symptoms. In the pathological setting, there is reduced production of the frataxin protein that leads to degeneration of sensory neurons at the dorsal root ganglion, with subsequent involvement of the spinal cord and cerebellum. Currently, there are no disease-modifying or curative therapies available for Freichreich's ataxia, with treatment principally being supportive and including walking aids, prostheses, and cardiac monitoring.

27.4.5 Spinocerebellar ataxia 2

Case report

A 30-year old man presented with a 2-year history of progressive loss of coordination, balance difficulties and falls. Approximately 12 months after onset of these symptoms he also began to develop difficulties with his speech and swallow, resulting in approximately a stone of weight loss. He also described sensory disturbance in his hands and feet, reporting both numbness and a "pins and needles" sensation, as well as a bilateral upper limb tremor. Three other family members were

TABLE 27.5 Clinical and genetic description of other neurodegenerative movement disorders.

Disorder (MIM number)	Epidemiology	Inheritance	Causative gene (locus)	Protein product	Proposed impact of mutation	Clinical phenotype	
						Motor	Nonmotor
Huntington's disease 143100	Prevalence 5-7/100,000 in Caucasian population	AD	HTT (4p16.3)	Huntingtin	Medium spiny neuron damage	Chorea, dystonia	Cognitive impairment, psychosis
Wilson's disease 277900	30/1,000,000	AR	ATP7B (13q14.3)	Copper-transporting ATPase 2	Toxicity secondary to copper accumulation	Parkinsonism	Psychosis, depression, liver failure, hemolytic anemia
PKAN 234200	Rare	AR	PANK2 (20p13)	Protein Pantothenate kinase 2	?disordered CoA biosynthesis	Parkinsonism, dystonia, dysarthria, spasmodic dysphonia	Pigmentary retinopathy, mood lability, impulsivity, abnormal eye movements
PLAN 610217	Rare	AR	PLA2G6 (22q13.1)	Calcium-independent phospholipase A2	Uncertain	Dystonia, parkinsonism, spastic tetraparesis	Developemental regression, optic atrophy
Mitochondrial MPAN 614298	Rare	AR	C19orf12 (19q12)	Protein C19orf12	Possible dysfunctional mitochondrial autophagy and increased apoptosis	Dystonia of distal limbs, spasticity	Optic atrophy, cognitive impairment
BPAN 300894	Rare	X-linked dominant	WDR45 (Xp11.23)	WD repeat domain phosphoinositide-interacting protein 4	Possible impaired autophagy	Dystonia, parkinsonism	Developmental delay, seizures
FAHN 612319	Rare	AR	FAH2 (16q23.1)	Fatty acid 2-hydroxylase	Reduced 2-OH production	Gait disorder, spasticity	Frequent falls, cognitive decline, seizures, optic atrophy
CoPAN 615643	Rare	AR	COASY (17q21.2)	Bifunctional coenzyme A synthase	CoA deficiency	Dystonia, dysarthria	Cognitive decline
Neuroferritinopathy 606159	Rare	AD	FtL (19q13.33)	Ferritin light chain	Ferritin precipitation and aggregation	Action-induced and orofacial dystonia, parkinsonism, chorea	Cognitive decline
Aceruloplasminemia 604290	Rare	AR	CP (3q24-q25)	Ceruloplasmin	Iron toxicity	Facial dystonia	Diabetes, macrocytic anemia, cognitive decline
Woodhouse–Sakati syndrome 241080	Rare	AR	DCAF17 (2q31.1)	DDB1- and CUL4-associated factor 17	Uncertain	Parkinsonism	Hypogonadism, diabetes mellitus, alopecia totalis
Kufor Rakeb 606693	Rare	AR	ATP13A2/PARK9 (1p36.13)	Cation-transporting ATPase 13A2	Lysosomal dysfunction	Parkinsonism, supranuclear gaze palsy, dystonia	Cognitive decline, visual hallucinations
Niemann–Pick type C 257220	<1/120,000 births	AR	NPC1/NPC2 (18q11.2)	Niemann–Pick C1 protein	Free cholesterol and glycosphingolipid accumulation	Ataxia	Hepatosplenomegaly, seizures
DRPLA 125370	0.2–0.7/100,00 in Japanese population	AD	ATN-1 (12p13.31)	Atrophin-1	ATN-1 accumulation	Cerebellar ataxia, choreoathetosis	Dementia, seizures

AD, Autosomal dominant; *AR*, autosomal recessive; *BPAN*, beta-propellar protein-associated neurodegeneration; *CoPAN*, COASY protein-associated neurodegeneration; *DRPLA*, dentarubral–pallidyluysian atrophy; *FAHN*, fatty acid hydroxylase-associated neurodegeneration; *MPAN*, membrane protein-associated neurodegeneration; *PKAN*, pantothenate kinase-associated neurodegeneration; *PLAN*, phospholipase A2-associated neurodegeneration.

TABLE 27.6 Blood plasma tests associated with specific forms of genetically determined ataxia.

Disorder	Serum test
Ataxia telangiectasia	Alpha-fetoprotein (raised)
Ataxia with oculomotor apraxia type 2	Alpha-fetoprotein (raised)
Ataxia with vitamin E deficiency	Vitamin E (reduced)
Cerebrotendinous xanthochromatosis	Cholestinol (raised)
Oculomotor apraxia type 1	Albumin (reduced)

reported to be similarly affected; his mother, a maternal uncle and his son. On examination, there was evidence of impaired horizontal saccades and bilateral sixth cranial nerve palsies. He was dysarthric, although the majority of his speech was intelligible. Examination of the limbs demonstrated some generalized wasting and increased tone throughout. There was evidence of ataxia with both finger–nose and heel–shin testing. His gait was moderately broad based and ataxic, and he was unable to heel–toe walk.

Spinocerebellar ataxia 2 (SCA2) is caused by autosomal-dominant inheritance of CAG repeat expansions to the *ATXN2* gene. Typically, approximately 22 repeats are observed, with pathological signs and symptoms evident when >32 repeats are present. The number of repeats appear to be linked with age at onset, with those with >45 repeats frequently developing symptoms in their teens. *ATXN2* encodes the ataxin-2 protein whose function remains largely unknown; however, it appears to be predominantly present in cellular cytoplasm and may play a role in RNA processing through interaction with the ER. Treatment is supportive with encouragement of regular exercise to maintain muscle mass and a healthy weight. With progressive ataxia walking aids are frequently required, and computerized devices are often used to aid communication with more severe dysarthria.

27.4.6 Spinocerebellar ataxia type 3: Machado–Joseph disease

Case report

A 50-year old woman was receiving ongoing follow-up in the neurology department. She had initially presented 10 years earlier with a subacute onset of progressive clumsiness and unsteadiness. This had progressed to involve speech and swallowing difficulties, such that she now had a modified, thickened diet. During this time, she had also reported blurring of her vision, which had later progressed to a horizontal diplopia. There were reports of disturbed sleep, with vocalizations and acting out of vivid dreams. Several other family members were affected, including her paternal grandfather, father, and several uncles. However, onset of their symptoms had been at least a decade later than hers. On examination, there was evidence of horizontal nystagmus and reported diplopia on the extremes of gaze. Examination of the limbs demonstrated increased tone throughout, most marked in the lower limbs, and a generalized hyperreflexia. Finger–nose testing in the upper limbs and heel–shin testing in the lower limbs found evidence of an intention tremor and dysmetria. Her gait was broad based, and she was unable to heel–toe walk.

SCA3 (previously known as Machado–Joseph disease) is caused by autosomal dominantly inherited mutations in the ataxin-3 gene (*ATXN3*). This is a trinucleotide repeat disorder caused by an expansion of the CAG repeat (normal range: 12–43 repeats). SCA3 also demonstrates anticipation, with those <75 repeats tending to develop symptoms in mid-adulthood where as individuals with ~80 repeats tend to present in their teenage years. The encoded ataxin-3 protein functions in removing ubiquitin from proteins undergoing degradation as part of the ubiquitin-proteasome system, freeing up the ubiquitin for future use. Pathological CAG expansions result in an abnormally long ataxin-3 enzyme, causing a loss of function with the combined protein, ubiquitin and ataxin-3 complex aggregating in the nucleus. The mechanism by which this results in neurodegeneration is not fully understood, but atrophy is initially prominent in the brainstem and cerebellum, with later involvement of the spinal cord.

27.4.7 Spinocerebellar ataxia type 7

Case report

A 50-year old man described a 10-year history of progressive symptoms. These began with visual loss, initially involving his central vision, but progressing such that he was now registered as being blind. A few years later, he noticed difficulties

with coordination, a general clumsiness and increased number of falls. Over the preceding 12 months, he found that people were having greater difficulty understanding what he was saying, and he was having trouble swallowing solid food. On examination, there was evidence of some mild cognitive difficulties. Eye movement examination revealed generally slow saccades in both horizontal and vertical planes. There was loss of coordination in both upper and lower limbs, resulting in past-pointing, intention tremor, and dysdiadochokinesis. Five other family members had developed similar symptoms including the patient's older sister, his mother, and maternal grandfather.

SCA7 is caused by a trinucleotide repeat (CAG) expansion in the *ATXN7* gene, resulting in production of a pathological form of the ataxin-7 protein. As with SCA6 this is thought to lead to nuclear accumulation of protein aggregates resulting in neuronal loss. Cerebral imaging demonstrates preferential atrophy of the cerebellum and pons, with more generalized atrophy as the disease progresses.

27.4.8 Ataxia-telangiectasia

Case report

A 10-year old boy was initially seen in the pediatric clinic at the age of 4 years with a 2-year history of balance difficulties. He had been born at term, at the end of a normal pregnancy. He had initially met all of his developmental milestones, but from the age of 2-years he had begun to fall more frequently and had difficulty with coordinated activities. Over this time period, he had had a number of hospital admissions due to respiratory and middle ear infections, many of which required prolonged courses of antibiotics. When he started school (aged 5 years), his teachers described a tendency for his gaze to flit between objects, often moving his head to be able to focus. Over the past 5 years the balance difficulties had progressed, such that he needed multiple walking aids to be able to mobilize short distances. On examination, there was evidence of enlarged blood vessels in the sclerae bilaterally, as well as on areas of sun exposed skin (telangiectasia). There was evidence of oculmotor apraxia (loss of co-ordinated head and eye movements) as well as upper and lower limb ataxia. He was unable to walk even short distances unaided. There was no reported family history of similar symptoms.

Ataxia-telangiectasia is caused by autosomal recessive inheritance of mutations in the *ATM* gene. The ATM protein is thought to be involved in regulating cellular responses to stress, including the repair of DNA in the context of double-strand breaks. Under normal circumstances the ATM protein would halt the cell cycle and recruit repair proteins to the site, facilitating a regulated repair process. In the presence of *ATM* mutations, these repair mechanisms are impaired, resulting in genomic instability and an increased risk of malignancy, especially leukemia and lymphoma. As well as genetic testing, other clinical investigations include cerebral imaging (cerebellar atrophy), serum alpha-fetoprotein (elevated) and serum immunoglobulins (reduced).

27.4.8.1 Therapy of ataxia telangiectasia (AT)

Few disease-modifying therapies are available in the treatment of the hereditary ataxias, although treatments do exist for reversible forms, for example, replacement of vitamin E in vitamin E−deficient ataxia, replacement of fat-soluble vitamins and a low-fat diet in abetalipoproteinemia, and oral chenodeoxycholic acid to prevent accumulation of metabolites in cerebrotendinous xanthomatosis [31].

27.4.9 Potential future targets for molecular therapy

As several of the genetically determined forms of ataxia are caused by over or under gene expression rather than altered protein product, potential future therapies include the direct targeting of gene expression, such as in Friedreich's ataxia where there is reduced production of the frataxin protein. Another potential mechanism of treatment is the targeting of abnormal protein aggregates, for example, heat shock protein 70, involved in protein quality control pathways, is reduced in SCA7. Activators of this protein could potentially be utilized therapeutically to improve protein regulation and reduce aggregation. Oxidative stress has also been implicated in ataxia pathophysiology, where mitochondrial iron accumulation and impaired respiratory chain electron transport lead to free radical formation, oxidative stress, and DNA damage. Preclinical testing of antioxidant treatment has shown some promising results, although these are yet to progress to clinical trials. Therapies aimed at modulating calcium signaling pathways have also been proposed, for example, the abnormal ataxin-2 protein in SCA2 interacts with the inositol 1,4,5-triphosphate receptor resulting in increased intracellular release of calcium; enzymes that reduce level of the receptor substrate (inositol 1,4,5-triphosphate) have been shown to improve motor function in mice [29,32].

27.5 Ataxia: key learning points

- Several of the inherited ataxias are trinucleotide repeat disorders demonstrating anticipation of clinical symptom onset with successive generations.
- Clinical characteristics often involve impaired bulbar function (speech and swallow) as well as loss of limb coordination.
- Key processes likely to be involved in pathogenesis are DNA repair mechanisms, mitochondrial dysfunction and free radical accumulation, and loss of calcium homeostasis.
- No disease-modifying or curative therapies exist to date, although future treatment may involve gene therapy aimed at altering levels of gene expression.

27.6 Other movement disorders

27.6.1 Huntington's disease

Case report

A 45-year old gentleman presented with a 5-year history of depressive symptoms requiring ongoing treatment from the local psychiatry department. Over the past 2 years, family members had reported memory difficulties, particularly short-term memory impairment and increasing difficulty managing day-to-day living. This gentleman's GP had referred him to the neurology department after noticing persistent, fidgety limb and facial movements during a routine consultation. On examination, this gentleman was low in mood and had poor eye contact throughout the consultation. There was evidence of generalized choreiform movements, particularly involving the eyes, mouth, and limbs. He had difficulty performing tasks such as water pouring and writing a sentence. Further discussion with the patient and his accompanying family members revealed that five other family members were affected with similar symptoms. The patient's grandfather developed symptoms in his 70s, two of his four uncles developed a movement disorder in their mid-50s, and his cousin had presented to his local neurology department a few years earlier.

HD is an autosomal dominantly inherited neurodegenerative disorder and is most common among Caucasian individuals, with a prevalence of 5–7/100,000 [33]. Clinically it is characterized by motor abnormalities, such as chorea and dystonia, and neuropsychiatric symptoms, including cognitive decline and personality changes. It is caused by a CAG repeat expansion in the *Huntingtin* gene, encoding a prolonged polyglutamine repeat in the huntingtin protein, and resulting in a toxic gain of function. Repeat lengths of >36 are considered pathogenic with the mutations demonstrating anticipation, that is, accumulation of increased CAG repeats in successive generations results in an earlier age at onset, with CAG repeats of >55 typically associated with the juvenile form of the disease. Although the number of CAG repeats account for the majority of the variation in age at onset, a recent genome wide association study (GWAS) demonstrated the likely role of DNA repair pathways, and in particular mutations in the *FAN1* gene [34]. It is the GABAergic striatal medium spiny neurons that are most vulnerable in HD, resulting in prominent atrophy of the caudate and putamen nuclei. The nuclear accumulation of mutant huntingtin, also known as intraneuronal nuclear inclusions, has been found in the brains of patients with HD, with protein misfolding and inadequate protein clearance suggested as potential pathogenic mechanisms.

27.6.1.1 Treatment of Huntington's disease

The treatment of HD is symptomatic, with no disease-modifying or curative therapies available at present. The chorea observed in HD can be treated with dopamine-depleting agents such as tetrabenazine to varying effect. In those patients with dystonia, botulinum toxin injections may aid in reducing symptoms of abnormal posture and pain. Neuropsychiatric manifestations are common throughout the course of disease and atypical neuroleptics may be used to treat psychotic symptoms, while selective serotonin reuptake inhibitors (e.g., citalopram) can help in the management of depression, anxiety and obsessive–compulsive behavior.

27.6.2 Wilson's disease

Wilson's disease is caused by autosomal recessive inheritance of mutations in the *ATP7B* gene [35]. The ATP7B protein is responsible for incorporating copper into ceruloplasmin, and is among a group of proteins that utilize ATP to transfer metals into and out of cells. Mutated *ATP7B* results in changes to the copper-binding

domains of the ATP7B protein expressed in hepatocytes, resulting in hepatic copper accumulation with subsequent systemic release, leading to its deposition in the brain, kidneys, and cornea. In addition to genetic testing, the investigation of Wilson's disease typically includes the measurement of ceruloplasmin, and serum and urinary copper levels. Neuroimaging usually demonstrates changes to the basal ganglia with increased density visualized on CT head and hyperintensity on T2-weighted MRI. The clinical presentation is typically either hepatic in adolescence, or in later life with neuropsychiatric symptoms. Those with early-onset Wilson's disease tend to present with acute liver failure and/or hemolytic anemia. The presentation of neurological signs is predominantly extrapyramidal, including bradykinesia, tremor, and rigidity, while neuropsychiatric presentations include psychosis and depression. In addition, a classical feature of Wilson's is the appearance of Keyser–Fleischer rings, with copper deposition in the Decemet's membrane between the cornea and the sclera. Treatment is mainly by chelating agents to reduce copper levels, such as d-penicillamine, with hepatic transplantation considered in those with end-stage liver disease.

27.6.3 Neurodegeneration with brain iron accumulation

Neurodegeneration with brain iron accumulation is a rare (prevalence of <1/1,000,000) neurodegenerative disorder characterized by extrapyramidal signs, intellectual disability, and iron deposition within the basal ganglia. Ten genetically determined forms have been identified: eight autosomal recessive, one autosomal dominant, and one X-linked dominant [36].

27.6.3.1 Pantothenate kinase-associated neurodegeneration

Case report

A 6-year old girl developed speech difficulties, followed by problems with balance and mobility resulting in a number of falls. Her parents also reported that her neck and limbs had begun to adopted unusual postures, and that she felt very "stiff" and "rigid" when they were helping her to dress in the morning. There were also reports of increasing difficulty with vision at night, and an apparent reduction in peripheral vision, with a tendency to bump into furniture at home. On examination, there was marked dysarthria and evidence of significant weight loss. There was a generalized spasticity, particularly involving the lower limbs, with brisk reflexes and bilateral upgoing plantar responses. Cervical dystonia was evident, with abnormal posturing of the neck and shoulder-girdle region. A recent review by an ophthalmologist had confirmed evidence of retinal degeneration. There was no history of a similar disorder affecting immediate family members.

Pantothenate kinase-associated neurodegeneration (PKAN) is an autosomal recessive disorder caused by a mutation in the *PANK2* gene, which encodes the pantothenate kinase 2 enzyme, responsible for the phosphorylation of components involved in the first key regulatory step of coenzyme A biosynthesis. Two forms of PKAN have been described: the classical form usually affects those <6 years old with a predominant lower limb dystonia, upper motor neuron signs, and frequent falls. Visual problems include pigmentary retinopathy and abnormal pursuit and saccadic eye movements. General decline follows with speech and swallowing difficulties presenting toward the latter stages of disease. The atypical form tends to progress more slowly, and presentation is more heterogeneous. Symptoms are generally age-dependent, with adolescents experiencing higher levels of dystonia, while adults tend to be affected by symptoms of parkinsonism (bradykinesia and rigidity). PKAN has a classical appearance on MRI with T2-weighted imaging demonstrating globus pallidus hypointensity with an anteromedial-placed region of hyperintensity, known as the "eye of the tiger" sign. Treatment is generally symptomatic, with therapy aimed at reducing symptoms of dystonia and spasticity with the use of anticholinergics, baclofen, botulinum toxin injections, benzodiazepines, and DBS.

27.6.3.2 Phospholipase A2-associated neurodegeneration

Phospholipase A2-associated neurodegeneration (PLAN), an autosomal recessive disorder caused by a mutation in the calcium-independent phospholipase A gene, *PLA2G6*, presents in early childhood with developmental delay. There are three phenotypes. The first is an infantile neuroaxonal dystrophy that typically presents between 6 months and 3 years of age with developmental regression, hypotonia with subsequent progression to spastic tetraparesis. An atypical neuroaxonal dystrophy presents in later childhood with slower progression, dystonia, and spastic tetraparesis. The third phenotype consists of a *PLA2G6*-related dystonia-Parkinsonism, which normally presents in late adolescence/early adulthood [37]. Affected individuals develop truncal hypotonia, ocular involvement (optic atrophy and nystagmus), and cerebellar atrophy on cerebral imaging.

27.6.3.3 Mitochondrial membrane protein-associated neurodegeneration

Mitochondrial membrane protein-associated neurodegeneration (MPAN) is an adult-onset, autosomal recessively inherited disorder, although autosomal-dominant inheritance has been reported in one family. It is caused by mutations in the *C19orf12* gene, the function of which is poorly understood but is likely to be involved in fatty acid metabolism. Proposed mechanisms of pathogenesis include impaired mitochondrial autophagy and increased apoptosis [38,39]. Symptoms include dystonia (mainly of the hands and feet), optic atrophy, corticospinal tract signs such as spasticity and extensor plantars, behavioral difficulties, and cognitive impairment. MPAN is slowly progressive, with lower motor neuron signs manifesting as the disease progresses. Neuroimaging demonstrates iron accumulation within the pallidum and substantia nigra.

27.6.3.4 Beta-propeller protein-associated neurodegeneration

Beta-propeller protein-associated neurodegeneration is caused by X-linked dominant inheritance of mutations to the *WDR45* gene, resulting in abnormalities in the beta-propeller protein [40]. Females normally exhibit a heterogeneous *WDR45* germline pathogenic variant, whereas males either have a hemizygous WDR45 pathogenic variant or a partial deletion of *WDR45*. The *WDR45* gene normally encodes a WD repeat domain phosphoinositide-interacting protein 4 (WIPI4), which is thought to play a role in autophagy, although its exact role remains unclear. Clinical features include developmental delay, seizures, dystonia, and parkinsonism. Gait impairment is prominent with toe walking and a broad-based ataxic gait. Symptomatic treatment with levodopa therapy has demonstrated some early benefit, but the effect is usually short-lived.

27.6.3.5 Fatty acid hydroxylase-associated neurodegeneration

Fatty acid hydroxylase-associated neurodegeneration (FAHN) is caused by autosomal recessive mutations to the *FA2H* gene, which plays an essential role in myelin production and cell cycle regulation [41]. *FA2H* encodes a fatty acid 2-hydroxylase that localizes to the ER and requires iron as a cofactor. It is postulated that a reduction in 2-OH fatty acids leads to the abnormal white matter changes typically seen in FAHN [41]. Presentation is usually in the first decade of life with disorders of gait and frequent falls, progressing to spasticity, dystonia, and ataxia.

27.6.3.6 Coenzyme A synthetase protein-associated neurodegeneration

Coenzyme A synthetase (COASY) protein-associated neurodegeneration is caused by an inborn error of metabolism in coenzyme A metabolism. Inheritance is autosomal recessive and involves a missense mutation in the *COASY* (coenzyme A synthetase), which encodes for a bifunctional enzyme that catalyzes the final two steps of coenzyme A synthesis, the biosynthesis of which is essential to human cells [42]. Affected individuals present with cognitive difficulties and gait abnormalities in the first decade of life. Dystonia and dysarthria are common, with the "eye of the tiger" pattern seen on neuroimaging.

27.6.3.7 Neuroferritinopathy

Neuroferritinopathy is a rare monogenic autosomal-dominant disorder characterized by a mutation in the gene encoding the L chain of ferritin (*FtL*), with mutations resulting in a change to the C-terminal portion of the protein. This leads to a reduction in the physical stability of the protein and a wider, permeable quaternary channel, leading to a greater propensity of ferritin to precipitate and form toxic aggregates [43]. Neuroferritinopathy typically presents in the fourth to sixth decade of life with dystonia (action-induced and orofacial), parkinsonism, and chorea, with later-onset cognitive decline [44].

27.6.3.8 Aceruloplasminaemia

Aceruloplasminemia is an autosomal recessive disorder characterized by low or absent ceruloplasmin. The *CP* single copy gene encodes ceruloplasmin, a multicopper ferroxidase that facilitates iron export from cells and oxidizes Fe^{2+} to Fe^{3+}, enabling ferric iron to bind to transferrin [45]. The ceruloplasmin protein is expressed as a glycosylphosphatidylinositol (GPI)-linked form in astrocytes, with mutant forms resulting in ferrous iron being unable to become oxidized when it enters the CNS with subsequent astrocytic accumulation. Iron accumulation occurs in both the brain and viscera, with low serum levels of copper and iron and high serum ferritin levels [45]. Symptoms manifest during childhood with systemic features including diabetes, macrocytic anemia, cognitive decline, and facial dystonia, with the treatment of choice being iron chelation.

27.6.3.9 Kufor Rakeb

A variant of NBIA, Kufor Rakeb is an autosomal recessively inherited disorder caused by a mutation in the *ATP13A2* gene (PARK9) that encodes for a lysosomal type 5 P-type ATPase [46,47]. ATP13A2 protein consists of 10 transmembrane domains, with both termini oriented toward the cytosol, and likely involved in maintaining a pool of healthy, functioning mitochondria [48]. This disorder is characterized by early-onset extrapyramidal signs with a supranuclear gaze palsy, hypometric saccades and dystonia. Neuroimaging demonstrates atrophy affecting cerebral and subcortical tissue [37,49].

27.6.4 Niemann–Pick type C

Case report

A 12-year old boy was referred by his general practitioner following reports of clumsiness, and difficulties with coordination at school and home. He was also reported to have hearing problems and had been diagnosed with sensorineural hearing loss a few years earlier. In the months prior to the appointment his parents had also noticed some slurring of his speech, and coughing when drinking water. Systemic examination revealed hepatosplenomegaly, later confirmed with ultrasound examination. Neurological examination revealed impaired vertical eye movements, with particular difficulty initiating saccades. There was evidence of a cerebellar ataxia with dysmetria and intention tremor on finger–nose testing, and a broad based ataxic gait when mobilizing independently. There was no reported family history of similar symptoms.

An autosomal recessive disorder, Niemann–Pick type C is a lipid storage disorder resulting in accumulation of cholesterol and other lipids in the liver, spleen, and brain, leading to progressive neurodegeneration. Diagnostic testing includes genetic testing and Filipin staining of skin fibroblasts. Niemann–Pick type C is characterized by two mutations: *NPC1* (on chromosome 18q11.2), which accounts for 95% of cases, and *NPC2* (on chromosome 14q24.3) responsible for the remaining 5% of cases. Common presenting features include hepatosplenomegaly, while neurological symptoms include ataxia and impaired horizontal saccades. The rate of neurodegeneration in NPC varies with age at onset, with those with earlier onset disease progressing at a faster rate than those with later-onset symptoms. Miglustat (reversible inhibitor of glycosphingolipid synthesis) has been demonstrated to slow disease progression, with greatest benefit in those with later-onset symptoms.

27.6.5 Dentarubral–pallidoluysian atrophy

An autosomal dominantly inherited neurodegenerative disorder, dentarubral–pallidoluysian atrophy (DRPLA) involves a combination of neurological and psychological signs and symptoms. These include a progressive dementia, seizures, and disorders of movement including myoclonus, chorea, and ataxia [50]. Those with early-onset DRPLA tend to develop progressive myoclonic epilepsy with dementia, whereas those with later-onset forms develop cerebellar ataxia, choreoathetosis, and dementia. DRPLA is caused by a trinucleotide (CAG) repeat expansion (>48 repeats being pathogenic) in the atrophin-1 (*ATN-1*) gene. *ATN-1* mutations involve a pathogenic gain of function, resulting in toxic neuronal accumulation of ATN-1. Inheritance of DRPLA mutations demonstrates both anticipation and somatic mosaicism, whereby the same individual has two genetically distinct population of cells [50].

27.7 Conclusion

The large number of disease-causing genes identified in movement disorders to date reflects the broad and complex nature of these disorders. While several of these genes have provided a mechanism for improved understanding of the pathology and biochemical disturbance observed in these conditions, further work is still required. In the majority of cases, treatment remains supportive and symptomatic, rather than disease-modifying or curative. Improved cellular and systemic understanding of disorder pathology should aid in drug-screening processes and identification of novel therapeutic targets.

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