

## Corporate Medical Policy

### Genetic Testing for Neurodegenerative Disorders AHS – M2167

**File Name:** Genetic\_testing\_for\_neurodegenerative\_disorders  
**Origination:** 11/2020  
**Last Review:** 11/2023

#### Description of Procedure or Service

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Neurodegenerative diseases are characterized by progressive loss of neurons along with deposition of misfolded proteins throughout the body, leading to clinical symptoms such as cognitive decline and movement problems. Conditions that fall within this classification include Parkinson Disease, dystonia, ataxia, and more (Kovacs, 2016).

Genetic counseling is strongly recommended for individuals pursuing genetic testing for neurodegenerative disorders.

This policy does not address Alzheimer's Disease or ataxia due to mitochondrial disorders. For information on these conditions, please see AHS-M2038 Genetic Testing for Familial Alzheimer Disease or AHS-M2085 Genetic Testing of Mitochondrial Disorders.

#### Related Policies

Prenatal Screening (Genetic) AHS – M2179  
Genetic Testing for FMR1 Mutations AHS – M2028  
Genetic Testing for Familial Alzheimer's Disease AHS – M2038  
Preimplantation Genetic Testing AHS – M2039  
Genetic Testing for Diagnosis of Inherited Peripheral Neuropathies AHS – M2072  
Genetic Testing of Mitochondrial Disorders AHS – M2085  
General Genetic Testing, Germline Disorders AHS – M2145

***\*\*\*Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.***

#### Policy

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**BCBSNC will provide coverage for Genetic Testing for Neurodegenerative Disorders when it is determined to be medically necessary because the medical criteria and guidelines shown below are met.**

#### Benefits Application

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This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit design; therefore member benefit language should be reviewed before applying the terms of this medical policy.

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## When Genetic Testing for Neurodegenerative Disorders is covered

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### *Amyotrophic Lateral Sclerosis (ALS)*

Genetic testing for ALS, including the genes *C9ORF72*, *SOD1*, *TARDBP*, and *FUS* is considered medically necessary for diagnosis in individuals with suspected ALS **and** a first-degree **or** second-degree relative (see Note 1) with ALS or frontotemporal dementia.

### *Ataxias, including Friedreich ataxia*

For individuals with sporadic ataxia **or** a family history compatible with an inherited cerebellar ataxia with no known deleterious familial mutation, single gene testing (when a specific ataxia is suspected) or multi-gene panel testing (when a specific ataxia is not suspected) is considered medically necessary.

Genetic testing for *ATM* to confirm a diagnosis in individuals with suspected ataxia-telangiectasia is considered medically necessary.

### *Dystonias*

Genetic testing of *TOR1A* (formerly *DYT1*) is considered medically necessary in the following situations:

- a) In individuals with limb-onset, primary dystonia before the age of 30 years.
- b) In individuals with limb-onset, primary dystonia with onset after age 30 when there is a family history compatible with early-onset dystonia.

Genetic testing of *THAP1* (formerly *DYT6*) is considered medically necessary in the following situations:

- a) In individuals with an early-onset dystonia or familial dystonia with cranio-cervical predominance.
- b) In individuals with early-onset dystonia after exclusion of *TOR1A*-associated dystonia.

Genetic testing of paroxysmal nonkinesigenic dyskinesia (*PNKD*) to aid in the diagnosis of symptomatic individuals with familial *PNKD* is considered medically necessary.

Genetic testing of *SLC2A1* (formerly *GLUT1*) in individuals with paroxysmal exercise-induced dyskinesia is considered medically necessary if the individual has at least one of the following:

- a) A history of epileptic seizures.
- b) Hemolytic anemia.
- c) A low CSF/serum glucose ratio.

### *Hereditary Spastic Paraplegia (HSP)*

Genetic testing for Hereditary Spastic Paraplegia (HSP) to confirm clinical diagnosis and to determine the genetic type of HSP is considered medically necessary.

### *Huntington disease (HD)*

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For individuals with a family history of Huntington Disease who are pursuing genetic testing, genetic counseling is **required**.

Genetic testing for Huntington disease is considered medically necessary in the following situations:

- a) When an adult patient presents with otherwise unexplained clinical syndrome of a progressive choreatic movement disorder and neuropsychiatric disturbances.
- b) In an adult patient with a positive family history of the disease.
- c) In a juvenile patient with the following:
  - i) A known familial history of HD.
  - ii) Presenting with two or more of the following:
    1. Declining school performance
    2. Seizures
    3. Oral motor dysfunction
    4. Rigidity
    5. Gait disturbance

## ***Parkinsonism, including Parkinson disease***

Genetic testing of *SNCA* is considered medically necessary for an individual only if there is a family history with multiple affected members in more than one generation suggestive of dominant inheritance.

Genetic testing of *LRRK2* is considered medically necessary in the following situations:

- a) In symptomatic individuals with a positive family history suggestive of dominant inheritance.
- b) In symptomatic individuals belonging to a population with known high mutation frequencies of the *LRRK2* gene (i.e. Ashkenazi Jews, Imazighen, and Euskaldunak).

Genetic testing of the *PRKN* (formerly *PARK2* or *parkin*), *PINK1*, and *PARK7* (formerly *DJ-1*) genes is considered medically necessary in the following situations:

- a) In individuals with an onset of disease by the age of 50 years with a positive family history suggestive of recessive inheritance.
- b) In individuals with an onset of disease by the age of 40 years regardless of family history.

Genetic testing of the *ATP13A2*, *PLA2G6*, and *FBXO7* genes only is considered medically necessary when **all** of the following conditions are met:

- a) With onset of disease by the age of 40 years.
- b) Prior testing of *PRKN*, *PINK1*, and *PARK7* genes was negative for known pathogenic variants.

## ***Spinal Muscular Atrophies (SMA)***

Genetic testing for SMA (*SMN1* deletion/mutation and *SMN2* copy number) to diagnose individuals suspected of having SMA is considered medically necessary.

Preconception carrier screening for SMA is considered medically necessary in accordance with Avalon Policy AHS-M2179-Prenatal Screening (Genetic).

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## *Wilson disease (WD)*

Genetic testing of *ATP7B* is considered medically necessary in the following situations:

- a) To confirm a diagnosis of Wilson disease in a symptomatic individual.
- b) In a first-degree relative (see Note 1) of an individual with known *ATP7B* mutation to guide potential therapy.

**Note 1:** First-degree relatives include parents, full siblings, and children of the individual. Second-degree relatives include grandparents, aunts, uncles, nieces, nephews, grandchildren, and half-siblings of the individual.

**Note 2:** For 5 or more gene tests being run on the same platform, please refer to Laboratory Procedures Reimbursement Policy AHS- R2162.

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## **When Genetic Testing for Neurodegenerative Disorders is not covered**

Genetic testing of *TOR1A* in asymptomatic individuals is considered not medically necessary.

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## **Policy Guidelines**

Neurodegenerative diseases are characterized by progressive loss of neurons along with deposition of misfolded proteins throughout the body. These misfolded proteins have altered biochemical properties, causing dysfunction. Clinical symptoms may include cognitive decline (primarily dementia) and movement problems (cerebellar dysfunction, hyper- or hypo-kinesia, etc.). The molecular spectrum of these disorders may vary, but typically involve oxidative or neuroinflammatory damage (Kovacs, 2016).

### *Ataxias (including Friedreich ataxia)*

Ataxias encompass the set of conditions that are characterized by “motor incoordination Resulting from dysfunction of the cerebellum and its connections” (P. Opal & H.Y. Zoghbi, 2023). This policy focuses on progressive and degenerative ataxias, which are further subdivided into autosomal dominant, autosomal recessive, and X-linked forms.

Friedreich ataxia is the most common hereditary ataxia and is inherited in an autosomal recessive manner. Most cases are caused by mutations in the frataxin gene (*FXN*), which is responsible for transport and management of iron. The frataxin mutation is typically an expanded trinucleotide (GAA) repeat in the first intron of the frataxin gene, which reduces expression of frataxin. Severity of phenotype varies with the number of repeats; larger repeats are generally more severe. Impaired iron management leads to a variety of clinical symptoms, such as neurological problems (progressive ataxia, dysphagia, motor weakness, loss of tendon reflexes, etc.), cardiomyopathy, diabetes mellitus, and skeletal deformities. Clinical findings may suggest Friedreich ataxia, but diagnosis is generally confirmed through genetic testing (P Opal & H.Y Zoghbi, 2023b).

Another autosomal recessive ataxia is ataxia-telangiectasia (AT). AT is caused by a defective gene on chromosome 11q22.3, leading to faulty DNA repair mechanisms. This gene (designated AT “M” for mutated) primarily regulates the cell cycle and prevents the cell cycle from progressing if there is DNA damage. When this gene fails, somatic mutations may accumulate. Symptoms such as immune deficiency, cerebellar ataxia, unusual eye movements, and other neurologic abnormalities are characteristic of ataxia telangiectasia. Ataxia is one of the first clinical symptoms of patients with AT, but other

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organ systems are usually affected, such as the skin and circulatory system. Similarly, ataxia-telangiectasia-like disorder (ATLD) can affect individuals similarly to AT; however, ATLD is due to mutations within the *MRE11A* gene involved in double-strand DNA break recognition and repair. The rate of neurodegeneration in ATLD is typically slower than AT. ATLD is more rare than AT; however, “it is estimated that as many as 5 percent of AT cases may be incorrectly diagnosed and actually have ATLD, given the similarity in clinical manifestations and coding sizes of the two affected genes” (Opal, 2022).

Spinocerebellar ataxias (SCAs) are the most common autosomal dominant ataxias. At least 30 types of SCAs with varying phenotypes occur, although, cerebellar ataxia is a primary feature of each type. For example, SCA1 is characterized by dysarthria and bulbar dysfunction whereas SCA2 is characterized by “slow saccadic eye movements.” Several SCA types have a signature CAG repeat beyond what is present in the wildtype; this expansion is pathogenic. As with Friedreich ataxia, larger number of repeats usually lead to more severe symptoms. The four most common SCAs are SCA1, 2, 3, and 6, and each type is caused by a different pathogenic mutation. Below is a table displaying each SCA, its distinguishing features, and its primary associated gene (P Opal & H.Y. Zoghbi, 2023a).

Disorder	Distinguishing features	Gene
SCA1	Pyramidal signs, peripheral neuropathy	<i>ATXN1</i>
SCA2	Slow saccades; less often myoclonus, areflexia	<i>ATXN2</i>
SCA3 (MJD)	Slow saccades, persistent stare, extrapyramidal signs, peripheral neuropathy	<i>ATXN3</i>
SCA4	Sensory neuropathy	<i>16q22.1</i>
SCA5	Early onset but slow progression	<i>SPTBN2</i>
SCA6	May have very late onset, mild, may lack family history, nystagmus	<i>CACNA1A</i>
SCA7	Macular degeneration	<i>ATXN7</i>
SCA8	Mild disease	<i>ATXN8,</i> <i>ATXN8OS</i>
SCA9	Not assigned	
SCA10	Generalized or complex partial seizures	<i>ATXN10</i>
SCA11	Mild disease	<i>TTBK2</i>
SCA12	Tremor, dementia	<i>PPP2R2B</i>
SCA13	Mental retardation	<i>KCNC3</i>
SCA14	Intermittent myoclonus with early onset disease	<i>PRKCG</i>
SCA15/16	Slowly progressive	<i>ITPR1</i>
SCA17 (or 4HDL4) <sup>1</sup>	Gait ataxia, dementia	<i>TBP</i>
SCA18	Pyramidal signs, weakness, sensory axonal neuropathy	<i>7q22-q32</i>

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<b>SCA19/22</b>	Predominantly cerebellar syndrome, sometimes with cognitive impairment or myoclonus	<i>KCND3</i> gene
<b>SCA20</b>	Palatal tremor and dysphonia	<i>11q12</i>
<b>SCA21</b>	Mild to severe cognitive impairment	<i>TMEM240</i>
<b>SCA23</b>	Distal sensory deficits	<i>PDYN</i>
<b>SCA24</b>	Recessive inheritance; redesignated as SCAR4	<i>1p36</i>
<b>SCA25</b>	Sensory neuropathy, facial tics, gastrointestinal symptoms	<i>2p21-p13</i>
<b>SCA26</b>	Pure cerebellar ataxia	<i>EEF2</i>
<b>SCA27</b>	Cognitive impairment	<i>FGF14</i>
<b>SCA28</b>	Ophthalmoparesis and ptosis	<i>AFG3L2</i>
<b>SCA29</b>	Early onset, nonprogressive ataxia; may be an allelic variant of SCA15	<i>3p26</i>
<b>SCA30</b>	Slowly progressive, relatively pure ataxia	<i>4q34.3-q35.1</i>
<b>SCA31</b>	Decreased muscle tone	<i>BEAN</i>
<b>SCA32</b>	Cognitive impairment; affected individuals with azoospermia and testicular atrophy	<i>7q32-q33</i>
<b>SCA33</b>	Not assigned	
<b>SCA34</b>	Skin lesions consisting of papulosquamous erythematous ichthyosiform plaques	<i>ELOVL4</i>
<b>SCA35</b>	Late onset, slowly progressive gait and limb ataxia	<i>TGM6</i>
<b>SCA36</b>	Late onset, truncal ataxia, dysarthria, variable motor neuron disease and sensorineural hearing loss	<i>NOP56</i>
<b>SCA37</b>	Late onset, falls, dysarthria, clumsiness, abnormal vertical eye movements	<i>1p32</i>
<b>SCA38</b>	Slowly progressive pure cerebellar phenotype	<i>ELOVL5</i>
<b>SCA39</b>	Not assigned	
<b>SCA40</b>	Hyperreflexia and spasticity	<i>CCDC88</i>
<b>DRPLA</b>	Chorea, seizures, myoclonus, dementia	<i>ATNI</i>
<b><sup>1</sup>SCA17 is synonymous with HDL4 (Huntington disease-like 4) (Toyoshima et al., 2012).</b>		

Jacobi et al. (2015) described the disease progression of SCAs 1, 2, 3, and 6. A total of 462 patients were evaluated on the Scale for the Assessment and Rating of Ataxia (SARA). Annual SARA score increase was 2.11 for SCA1 patients, 1.49 for SCA2, 1.56 for SCA3, and 0.80 for SCA6. The increase of non-ataxia signs plateaued in types 1, 2, and 3. SCA6 symptoms were found to increase more slowly than the other three types. Factors

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associated with a faster increase of SARA score across all types were short duration of follow-up, older age at inclusion (per additional year), and longer repeat expansions (per additional repeat unit) (Jacobi et al., 2015).

Reetz et al. (2015) examined the effect of the number of GAA repeats in the FXN gene on clinical symptoms of Friedreich's Ataxia (FA). A total of 592 patients with FA were sequenced and evaluated. The authors found that with every 100 GAA repeats, the age of onset was 2-3 years earlier. Disease progression was also found to be faster in patients with more repeats; the annual worsening of the Scale for the Assessment and Rating of Ataxia (SARA) score was 1.04 points per year and 1.37 points per year for early and intermediate onset ( $\leq 14$  and 15-24 years, respectively), compared to 0.56 points per year for late-onset patients ( $\geq 25$  years) (Reetz et al., 2015).

Leotti et al. (2021) examined the contribution that the expanded CAG repeat length has on the rate of disease progression in spinocerebellar ataxia type 3/Machado-Joseph disease (SCA3/MJD). Expanded CAG repeat in ATXN3 is the mutation that causes SCA3/MJD, and the length of CAG repeat can determine the age of onset of clinical symptoms. The authors studied 82 patients with SCA3/MJD over 15 years using the International Cooperative Ataxia Rating Scale (ICARS) and found that "The length of the CAG repeat was positively correlated with a more rapid ICARS progression, explaining 30% of the differences between patients." The authors concluded that the length of CAG repeat in ATXN3 has major influence over clinical symptoms (Leotti et al., 2021).

Schuermans et al. (2023) performed an observational study to assess the diagnostic value of exome sequencing and multigene panel analysis for adult-onset neurologic disorders, including ataxias. In 2019, 6 diagnostic gene panels were introduced at the center for Medical Genetics of the Ghent University Hospital to diagnose patients with neurologic disorders. One of these panels was for ataxia and spasticity and included 390 genes. While the most common ataxia genes were not included in this panel, only 33% of the diagnosed patients had first been tested for SCAs, Friedrich ataxia, or fragile X tremor/ataxia syndrome. The panels included single nucleotide variants, small indels, and copy number variants. Of the panels and targeted patient populations examined by the authors, the multi-gene panel for ataxia and spasticity had the highest diagnostic yield, identifying the causal pathogenic variant (s) in 19% of the assessed patients (70 of 365) (Schuermans et al., 2023).

## Dystonias

Dystonias are a class of movement disorders characterized by "sustained or intermittent muscle contractions causing abnormal, often repetitive, movements, postures, or both" (Deik & Comelia, 2023). Movements are typically twisting or patterned and are often worsened by voluntary action. The basic neurochemistry of dystonia is unknown (and without consistent findings), and cell degeneration is typically not seen. However, some types of dystonia (particularly early-onset versions) have clear associations with certain genes. For example, *TOR1A* and *THAP1* both carry pathogenic mutations for early-onset dystonia. *TOR1A* (*DYT1*) encodes a protein that binds to ATP (torsin A) while *THAP1* (*DYT6*) encodes a transcription regulator for torsin A (Deik & Comelia, 2023).

Dystonias are divided into classes or types. They can be focal (involving a single site), multifocal segmental (involving region(s) of the body), generalized (involving the trunk and at least two additional sites), or hemidystonia (affecting only one side of the body). The etiology of the disorder can be either idiopathic or of known causation. Dystonias can be due to trauma or may be inherited. Those forms of proven genetic origin can be inherited in different inheritance patterns, including autosomal dominant, autosomal recessive, X-linked recessive, or even mitochondrial inheritance. The most common inherited form of dystonia is DYT-TOR1A (or DYT1) dystonia. DYT-TOR1A accounts for approximately 40-65% of early-onset generalized dystonia in populations other than the Ashkenazi Jewish population. Within the latter population, DYT-TOR1A is estimated to account for 90% of these cases (Deik & Comelia, 2023). Even though DYT-TOR1A dystonia is inherited in an autosomal dominant pattern, the penetrance is only 30% (Bressman, 2004; Deik & Comelia, 2023; Ozelius & Lubarr, 2016). Paroxysmal dyskinesia with dystonia (PKND) is a special class of dystonia that involves spontaneous episodes of dystonia. Several environmental factors have been proposed to precipitate these episodes, such as stress, caffeine, and fatigue. The primary gene associated with PKND is *MRI*, or *DYT8*. Another special class of dystonia is myoclonus-dystonia, which is characterized by short, involuntary movements of the neck or arms in addition to normal dystonia symptoms. The main established type of myoclonus-dystonia is caused by mutations in the *SGCE* (*DYT11*) gene (Deik & Comelia, 2023).

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Zech et al. (2017) performed whole exome sequencing on 16 patients with “genetically undefined early-onset generalized dystonia.” Six patients had mutations of known dystonia-related genes. The mutated genes were *GCHI*, *THAPI*, *TORIA*, *ANO3*, and *ADCY5*. The authors noted *GCHI*, *THAPI*, and *TORIA* as associated with isolated, generalized dystonia and *ANO3* and *ADCY5* associated with a combined myoclonus-dystonia phenotype (Zech et al., 2017).

## *Parkinsonism (Parkinson Disease, PD)*

Parkinsonism is a constellation of symptoms with “any combination of bradykinesia, rest tremor, rigidity, and postural instability.” The most common form of parkinsonism is Parkinson disease (PD), a progressive neurodegenerative disorder characterized by degeneration of dopaminergic neurons in the brain (Chou, 2023b). The pathogenesis of PD is driven by loss of dopamine from the basal ganglia in the brain; though a number of compensatory mechanisms may mitigate this loss of dopamine, the progression of disease eventually leads to clinical symptoms (Jankovic, 2023). The “cardinal” features of PD are “tremor, bradykinesia, and rigidity”; postural instability is commonly considered a defining feature, yet it typically manifests late in the course of disease. Other motor symptoms such as dysphagia, blurred vision, shuffling, are common; these secondary motor symptoms are commonly derived from the cardinal features. Nonmotor symptoms include cognitive deterioration, dementia, and other mood disorders (Chou, 2023a).

The exact cause of PD is unknown, but several genetic factors have been identified. These genes do not imply a particular phenotype, and each mutation vary in severity of symptomology. Genes associated with PD are *SNCA* (*PARK1/4*), *LRRK2* (*PARK8*), *PINK1*, *PARK2*, *DJ-1* (*PARK7*), and *GBA* (Jankovic, 2023).

*GBA*- (glucocerebrosidase) associated PD is coupled with the lysosomal storage condition known as Gaucher disease, which is commonly seen in Ashkenazi Jews (Jankovic, 2023). Sidransky et al. (2009) compared PD patients with a *GBA* mutation to those with PD but without a *GBA* mutation, and they found that the patients with a *GBA* mutation had an earlier age of onset and greater chance of cognitive impairment, albeit with less pronounced cardinal features (Sidransky et al., 2009).

*SNCA* encodes alpha-synuclein. Although its exact role is not well understood, it is thought to function in synaptic plasticity and makes up as much as 1 percent of total central nervous system protein. Observations suggest a role for mutated alpha-synuclein in the pathogenesis of PD; for example, Lewy bodies, the primary pathologic hallmark of PD, have insoluble, aggregated alpha-synuclein as a major component. It may also be possible for misfolded alpha-synuclein to be transmitted from diseased neurons to healthy ones. *PARK1* refers to a missense mutation in *SNCA* whereas *PARK4* refers to a multiplication (Jankovic, 2023).

*LRRK2* (*leucine-rich repeat kinase-2*) encodes a protein called dardarin. Dardarin is thought to function as a kinase for phosphorylation of certain proteins, such as alpha-synuclein and microtubule-associated protein tau. Dardarin may also be implicated in membrane and protein transport. The phenotype of *LRRK2* mutations is noted to be less severe than other genotypes of PD; patients have been observed to respond to levodopa, have a later age of onset, and less severe cognitive deterioration (Jankovic, 2023).

*PARK2* encodes a protein called parkin. This protein is associated with degradation of certain proteins in wild-type genes; the mutated version of parkin cannot clear proteins, allowing them to aggregate in the neuron. This mutation typically leads to an early-age onset of PD and clinical symptoms, although the severity of these early symptoms does not appear to be significantly worse than other genotypes (Jankovic, 2023).

*DJ-1* and *PINK1* are both associated with autosomal recessive inheritance and early age of onset (under 50 for *PINK1* mutations, under 40 for *DJ-1* mutations). *PINK1* mutations are possibly associated with mitochondrial dysfunction whereas *DJ-1* mutations may lead to increased neuro-oxidative stress (Jankovic, 2023).

Nalls et al. (2014) performed a meta-analysis of genome-wide association studies on PD. A common set of 7893274 variants with 13708 cases and 95282 controls were evaluated. Thirty-two loci were identified as having genome-wide significant association. These 32 loci were re-tested in an independent set of 5353 cases and 5551



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controls, and 24 of these loci replicated their significance. Four loci (*GBA*, *GAK-DGKQ*, *SNCA*, *HLA* region) were considered to have a “secondary independent risk variant.” The authors noted that the effect of each individual loci was small, but cumulative risk was “substantial” (Nalls et al., 2014).

Maple-Grødem et al. (2021) studied the significance of *glucocerebrosidase* gene (*GBA*) carrier status on motor impairment in patients with incident PD. The authors studied 528 patients with PD, using genomic DNA assessment and the Unified Parkinson's Disease Rating Scale (UPDRS). *GBA* carriers had a faster annual increase in UPDRS score than non-carriers. The authors conclude that “*GBA* variants are linked to a more aggressive motor disease course over 7 years from diagnosis in patients with PD” (Maple-Grødem et al., 2021).

## *Amyotrophic Lateral Sclerosis (ALS)*

Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disorder that causes significant motor neuron degeneration all over the body. This causes a variety of neuromuscular problems, such as spasticity, weakness, atrophy, hyperreflexia, cognitive impairment, and eventual death. ALS is divided into two categories: sporadic (90% of cases) and familial (10%) (Elman et al., 2023).

The primary genes tested in ALS cases are superoxide dismutase (*SOD1*) and chromosome 9 open reading frame 72 (*C9ORF72*), both of which lead to familial ALS. The enzyme *SOD1* catalyzes toxic superoxide radicals to O<sub>2</sub> and H<sub>2</sub>O<sub>2</sub>. The mutation thought to be the primary cause of *SOD1*-mediated toxicity is a gain-of-function mutation, creating many reactive oxygen species. Other hypotheses of *SOD1*-mediated toxicity include misfolded proteins caused by *SOD1* mutations and production of protein aggregates that damage motor neurons (Maragakis, 2023).

*C9ORF72* expansions are another common cause of familial ALS. This mutation is a hexanucleotide repeat (GGGGCC) that forms a structure called the G-quadruplex. The exact pathogenic mechanism is unknown, but some hypotheses include creation of defective RNA transcripts and creation of toxic dipeptide proteins that cause RNA processing to falter (Maragakis, 2023).

Chiò et al. (2012) evaluated the genetic landscape of ALS in an Italian cohort. A total of 475 patients were examined, and 51 were noted to carry a mutation associated with ALS. Familial ALS was found in 46 of these patients, and 31 of these 46 were found to have a genetic mutation (leaving 20 mutations in the remaining 429 sporadic cases). After performing a logistic regression, the authors found that “the chance to carry a genetic mutation was related to the presence of comorbid frontotemporal dementia by an odds ratio of 3.5” (Chiò et al., 2012).

Vajda et al. (2017) evaluated clinician opinion on genetic testing in ALS. Responses from 167 clinicians in 21 countries were analyzed. Approximately 90.2% of respondents were found to have offered genetic testing to patients they defined as having familial ALS and 49.4% to patients with sporadic ALS. The four main genes tested were *SOD1*, *C9ORF72*, *TARDBP*, and *FUS*. Further, 42% of respondents did not offer genetic testing to asymptomatic family members of patients with familial ALS (Vajda et al., 2017).

Bandres-Ciga et al. (2019) used publicly available genome-wide association studies to identify shared polygenic risk genetic factors and casual associations in 20,806 ALS cases and 59,804 controls. Positive associations were found with smoking and moderate physical activity levels, and negative associations were found with higher education, cognitive performance, and light physical activity levels. Further, the authors report that “hyperlipidemia is a causal risk factor for ALS and localized putative functional signals within loci of interest” (Bandres-Ciga et al., 2019).

## *Wilson Disease (WD)*

Wilson disease (WD) is a condition caused by defective copper transport. This leads to accumulation of copper in several organs, such as the brain, eyes, and liver. Eventually, the liver becomes cirrhotic, while other neurological conditions may develop. The primary gene handling hepatocyte copper transport is *ATP7B*. Normally, this gene mediates the transport of copper into apoceruloplasmin, which is then secreted into the bloodstream. Mutations in

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this gene cause impaired binding of copper to the protein, causing copper accumulation in the hepatocyte and eventually the bloodstream (Schilsky, 2022).

Dong et al. (2016) evaluated the genetic spectrum of WD in Chinese patients. A total of 632 patients with WD were compared against 503 controls. Further, 161 variants were found in the WD patents, and 142 were considered pathogenic or “likely pathogenic.” The authors concluded that 569 of the 632 patients (90%) could be diagnosed with two or more “likely pathogenic” or worse variants. Finally, the 14 most common variants were found at least once in 537 of the 569 (94%) genetically diagnosed patients (Dong et al., 2016).

## *Huntington Disease (HD)*

Huntington disease (HD) is a progressive, neurodegenerative disorder characterized by choreiform (brief, abrupt, and involuntary) movements, psychiatric disorders, and eventual dementia. During the early stages of the disease, patients may be able to function day-to-day and perform typical tasks; however, as the disease progresses, patients lose their ability to function independently and require assistance. In the late stages of the disease, patients often become bedridden as cognitive and motor ability continues to decline, with death occurring 10 to 40 years after onset. Currently there is no cure, and the disorder is inherited in an autosomal dominant fashion (Suchowersky, 2023).

Huntington disease is primarily caused by a trinucleotide repeat expansion. A cytosine-adenine-guanine “repeat” encodes for polyglutamine tracts in the *huntingtin (HTT)* gene, and the “expansion” refers to additional repeats of this trinucleotide side. Approximately 6-26 CAG repeats is considered wild-type, 27-35 repeats is considered intermediate (i.e. typically do not cause disease but may expand in future generations), and  $\geq 36$  repeats is considered diagnostic of HD. CAG repeat length is considered to correlate with both rate of disease progression and severity of neurological changes. The CAG repeat expansion leads to a toxic “gain-of-function” of the *HTT* protein, and although the exact function of this huntingtin protein is unknown, it interacts with several different proteins, implying that it has a function in several cellular events. Mutant huntingtin is seen to disrupt transcription, activation of proteases, synaptic transmission, and more (Zoghbi & Orr, 2022).

Baig et al. (2016) reviewed 22 years of predictive testing performed by the UK’s Huntington Consortium. A total of 9407 predictive tests were performed over 23 testing centers, with 8441 tests on individuals considered at 50% predictive risk. Of these 8441, 4629 were mutation negative and 3790 were mutation positive (with 22 tests as “uninterpretable”). A prevalence figure of  $12.3 \times 10^{-5}$  was used to evaluate the “cumulative uptake” of predictive testing at the 50% risk level; this amount was calculated to be 17.4% (the number of individuals at 50% risk that had undergone predictive testing). The authors concluded that the majority of individuals at risk for HD had not undergone predictive testing (Baig et al., 2016).

## *Spinal Muscular Atrophies (SMA)*

Spinal muscular atrophy (SMA) disorders encompass the set of disorders that are characterized by the degeneration of anterior “horn” cells in the spinal cord and motor nuclei in the lower brainstem. This leads to muscle weakness and atrophy, although cognition is unaffected. There are currently five main types of SMA, types 0 to 4. These types are organized by age of onset and clinical presentation, with types 0 and 1 presenting earliest and with the most severe symptoms and type 4 as the least severe phenotype. For example, type 0 presents prenatally and death occurs by six months, whereas type 4 patients usually remain ambulatory and have a normal lifespan (Bodamer, 2023).

The primary gene mutation occurs in the survival motor neuron 1 (*SMN1*) gene. This gene encodes a protein that appears to play a role in mRNA synthesis. The most common mutation in *SMN1* is a deletion of exon 7, representing up to 94% of SMA patients. Another gene, *SMN2*, may cause phenotypic changes in *SMN1* due to its effect as a gene modifier. *SMN2* encodes an extremely similar protein to *SMN1* (only one nucleotide difference), and it may compensate for *SMN1* loss. Severity of SMA correlates inversely with amount of *SMN2* gene copy numbers, which varies from 0 to 8 (Bodamer, 2023).

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Zarkov et al. (2015) evaluated the association between clinical symptoms and *SMN2* gene copy numbers. Forty-three patients with SMA were examined, and 37 of them had homozygous deletions of *SMN1* exon 7. The genetic characterization of these 37 patients were as follows: “One had SMA type I with 3 *SMN2* copies, 11 had SMA type II with 3.1 +/- 0.7 copies, 17 had SMA type III with 3.7 +/- 0.9 copies, while 8 had SMA type IV with 4.2 +/- 0.9 copies.” The authors concluded that “a higher *SMN2* gene copy number correlated with less severe disease phenotype,” but they noted that potential other phenotype modifiers could not be ignored (Zarkov et al., 2015).

## *Hereditary Spastic Paraplegia (HSP)*

Hereditary spastic paraplegia (HSP) represents a group of genetic neurodegenerative diseases characterized by increased spasticity of the lower limbs over time (Shribman et al., 2019). Spastic gait is often the only, or main, feature of the syndrome; bladder dysfunction is a common clinical finding as well. More than 70 types of HSP have been identified, and are often due to axon degeneration, leading to progressive degeneration of the corticospinal tracts (Fink, 2014; Opal & Ajroud-Driss, 2022). The classification of HSP may be based on age of onset, rate of progression, degree of spasticity, and genetics with more than 55 loci related to the disease (Opal & Ajroud-Driss, 2022). Some of the more common autosomal dominant forms of HSP may be caused by mutations in the *ATL1*, *SPAST*, *KIAA1096*, *KIF5A*, and *REEP1* genes; additional genes are associated with autosomal recessive forms, x-linked forms, and mitochondrial forms of HSP (Opal & Ajroud-Driss, 2022).

Dong et al. (2018) performed next-generation sequencing on 149 genes associated with HSP in a cohort of 99 individuals. A retrospective study on other patients with HSP was also completed. Different genetic mutations cause different subtypes of HSP such as SPG4, SPG3A, and SPG6. The researchers note that “In ADHSP [autosomal dominant HSP], we found that SPG4 (79%) was the most prevalent [subtype], followed by SPG3A (11%), SPG6 (4%) and SPG33 (2%)... In ARHSP [autosomal recessive HSP], the most common subtype was SPG11 (53%), followed by SPG5 (32%), SPG35 (6%) and SPG46 (3%)” (Dong et al., 2018).

In 2018, GeneReview published an updated overview of HSP. This overview was last updated in 2021. This document states the following regarding genetic testing:

- “Concurrent or serial single-gene testing can be considered if clinical findings and/or family history indicate that involvement of a particular gene or small subset of genes is most likely (see Tables 1, 2, 3, and 4)”
- “A multigene panel that includes some or all of the genes listed in Table 1 is most likely to identify the genetic cause of the condition at the most reasonable cost while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype”
- “Comprehensive genomic testing (which does not require the clinician to determine which gene[s] are likely involved) may be considered. Exome sequencing is most commonly used; genome sequencing is also possible. Exome array (when clinically available) may be considered if exome sequencing is not diagnostic”
- “Recommendations for the evaluation of parents of a proband with an apparent *de novo* pathogenic variant include molecular genetic testing of both parents for the pathogenic variant identified in the proband (Hedera, 2021)”

GeneReviews has published four tables (below) which show the genes associated with autosomal dominant HSP, autosomal recessive HSP, X-linked HSP, and maternal (mitochondrial) HSP.

**Table 1:** Hereditary Spastic Paraplegia: Genes and Distinguishing Clinical Features – Autosomal Dominant Inheritance (Hedera, 2021)

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Gene <sup>1</sup>	HSP Designation	Type of HSP	Onset	Distinguishing Clinical Features
<i>ADAR</i>	Not assigned	Uncomplicated	Early childhood	Abnormal pattern of interferon expression determined by reverse transcription PCR assay
<i>ALDH18A1</i>	SPG9A	Complicated	Adolescence to adulthood (1 subject w/infantile onset)	Cataracts Gastroesophageal reflux Motor neuronopathy  Variably present: Dysarthria Ataxia Cognitive impairment
<i>ATAD3A</i>	Not assigned	Complicated	Early onset	Amyotrophy Hyperkinetic movements May be confused w/hyperkinetic cerebral palsy
<i>ATL1</i>	SPG3A	Uncomplicated	Infantile to childhood (rarely adult onset)	Progression may be minimal w/static course. May present as spastic diplegic cerebral palsy Complicated phenotype w/peripheral neuropathy or autonomic failure reported
<i>BICD2</i>	Not assigned	Complicated	Childhood or adult	Infantile onset associated w/SMA w/variable upper motor signs & contractures Adult onset associated w/mild amyotrophy
<i>BSCL2</i> <sup>2</sup>	SPG17	Complicated	Adulthood	Distal amyotrophy affecting hands & feet Motor neuropathy Can be indistinguishable from ALS

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<i>CPT1C</i>	SPG73	Uncomplicated	Early adulthood	Foot deformity may be present.
<i>DNM2</i> <sup>3</sup>	Not assigned	Complicated	Before age 20 years	Axonal polyneuropathy may be present. Mild distal amyotrophy in feet
<i>ERLIN2</i>	SPG18 <sup>4</sup>	Uncomplicated	Juvenile to adulthood	None
<i>HSPD1</i>	SPG13	Uncomplicated	Adulthood	Mild distal amyotrophy
<i>KIF5A</i>	SPG30	Uncomplicated (for AD inheritance)	Juvenile to adulthood	Some individuals have mild ID. Optic nerve atrophy, epilepsy can be rarely seen in AD SPG30.
<i>KIF5A</i> <sup>4</sup>	SPG10	Complicated	Juvenile or adulthood	Polyneuropathy Pes cavus
<i>NIPA1</i>	SPG6	Uncomplicated	Adulthood (infantile onset rare)	Severe weakness & spasticity Rapidly progressive Rarely, complicated by epilepsy or variable peripheral neuropathy
<i>ATP2B4 (PMCA4)</i>	Not assigned	Uncomplicated	Adulthood	None
<i>REEP1</i>	SPG31	Uncomplicated	Variable from 2nd to 7th decades	Mild amyotrophy variably present.
<i>REEP2</i>	SPG72	Uncomplicated	Very early, average age 4 years	Musculoskeletal problems Mild postural tremor
<i>RTN2</i>	SPG12	Uncomplicated	Before age 20 years	None
<i>SLC33A1</i>	SPG42	Uncomplicated	Early adulthood	Slowly progressive Mild <i>pes cavus</i>
<i>SPAST</i>	SPG4	Uncomplicated	Variable from infancy to 7th decade	Cognitive decline & dementia common Distal amyotrophy variably present

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				Complicated phenotype w/ataxia variably present
<i>SPG7</i>	SPG7	Uncomplicated or complicated	Juvenile or adulthood	Dysarthria Ataxia Optic atrophy Supranuclear palsy Mitochondrial abnormalities on skeletal muscle biopsy
<i>WASHC5</i>	SPG8	Uncomplicated	Adulthood (rare infantile onset reported)	Severe motor deficit in some individuals
<i>TUBB4A</i> <sup>5</sup>	Not assigned	Complicated	Juvenile	Cerebellar ataxia MRI evidence of hypomyelination
<i>ZFYVE27</i>	SPG33	Uncomplicated	Adulthood	Mild pes cavus

AD = autosomal dominant; AR = autosomal recessive; ALS = amyotrophic lateral sclerosis; CMT = Charcot-Marie-Tooth neuropathy; DI-CMT = dominant intermediate Charcot-Marie-Tooth neuropathy; HMN = hereditary motor neuropathy; HSP = hereditary spastic paraplegia; SMA = spinal muscular atrophy

**Table 2:** Hereditary Spastic Paraplegia: Genes and Distinguishing Clinical Features – Autosomal Recessive Inheritance (Hedera, 2021)

Gene <sup>1</sup>	HSP Designation	Type of HSP	Onset	Distinguishing Clinical Features	Other
<i>SPG21</i> ( <i>ACP33</i> )	SPG21	Complicated	Childhood	Ataxia Adult-onset dementia & parkinsonism Polyneuropathy Akinetic mutism seen in advanced cases	Rare, first described in Old Order Amish population (later identified in various ethnic groups) Also known as Mast syndrome
<i>ALDH18A1</i>	SPG9B	Complicated	Adolescence to adulthood (one subject)	Cataracts Gastroesophageal reflux Motor neuronopathy	Rare Allelic w/AD HSP (SPG9A)

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			w/infantile onset)	Variably present: Dysarthria Ataxia Cognitive impairment	
<i>ALDH3A2</i>	Not assigned	Complicated	Childhood	Congenital ichthyosis Macular dystrophy Leukodystrophy Seizures in ~40% of patients	Rare Most common in people of Swedish ancestry Known as Sjögren-Larsson syndrome
<i>AMPD2</i> <sup>2</sup>	SPG63	Complicated	Infancy	Short stature Thin corpus callosum White matter changes	Rare
<i>AP4B1</i>	SPG47	Complicated	Infancy	Severe ID Facial dysmorphism Seizures Stereotypic laughter w/tongue protrusion	Rare
<i>AP4E1</i>	SPG51	Complicated	Infancy	Severe ID Facial dysmorphism Seizures Stereotypic laughter w/tongue protrusion	Rare
<i>AP4M1</i>	SPG50	Complicated	Infancy	Severe ID Facial dysmorphism Seizures Stereotypic laughter w/tongue protrusion	Rare
<i>AP4S1</i>	SPG52	Complicated	Infancy	Severe ID Facial dysmorphism Seizures Stereotypic laughter w/tongue protrusion	Rare
<i>AP5Z1</i>	SPG48	Uncomplicated	Typically adulthood; rarely infancy	Urinary incontinence Parkinsonism Dystonia Thin corpus callosum Leukodystrophy	Single family

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				Severe DD in infantile onset	
<i>ATL1</i>	SPG3A	Uncomplicated	Infantile to childhood (rarely adult onset)	Progression may be minimal w/static course May present as spastic diplegic cerebral palsy Complicated phenotype w/peripheral neuropathy or autonomic failure reported	AR inheritance is very rare.
<i>B4GALNT1</i>	SPG26	Complicated	Juvenile	Amyotrophy Dysarthria Ataxia DD Dystonia	Rare
<i>BICD2</i>	Not assigned	Complicated	Childhood	Amyotrophy Contractures	Rare
<i>C12orf65</i>	SPG55	Complicated	Childhood	DD Visual loss Polyneuropathy Arthrogryposis Signs of mitochondrial encephalomyopathy, some classified as Leigh syndrome	Rare
<i>C19orf12</i>	SPG43	Complicated	Childhood	Amyotrophy Dysarthria Multiple contractures Neurodegeneration w/brain iron accumulation in some	Rare
<i>CYP2U1</i>	SPG56	Complicated	Infancy	Severe DD Dystonia Polyneuropathy Calcification of basal ganglia	Rare
<i>CYP7B1</i>	SPG5A	Uncomplicated or complicated	Juvenile to early adulthood	Ataxia Polyneuropathy Extrapyramidal signs	SPG5A was diagnosed in 9 of 172 families w/histories



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				MRI signs of leukodystrophy	consistent w/AR inheritance of HSP. <sup>3</sup>
<i>DDHD1</i>	SPG28	Uncomplicated	Childhood	Scoliosis	Rare
<i>DDHD2</i>	SPG54	Complicated	Infancy	Severe DD Optic atrophy Thin corpus callosum Leukodystrophy	Rare
<i>ENTPD1</i>	SPG64	Complicated	Infancy	Mild cognitive disability Behavioral disturbances White matter changes	Rare
<i>ERLIN1</i>	SPG62	Complicated	Childhood	Amyotrophy Ataxia Phenotype consistent w/juvenile onset of ALS reported	Rare
<i>ERLIN2</i>	SPG18	Complicated (rarely pure AR HSP reported)	Childhood	DD Seizures Contractures Juvenile primary lateral sclerosis phenotype reported Allelic w/AD pure HSP	Rare
<i>FA2H</i> <sup>4</sup>	SPG35	Complicated	Childhood	Seizures Dystonia Parkinsonism w/iron accumulation in basal ganglia	Rare
<i>GAD1</i>	Not assigned	Complicated	Childhood	Moderate to severe ID Single reported family was described as having AR cerebral palsy	Rare (single family reported)
<i>GBA2</i>	SPG46	Complicated	Childhood	DD Ataxia Hearing loss Polyneuropathy	Rare
<i>GJC2</i> <sup>5</sup>	SPG44	Complicated	Childhood	Febrile seizures Deafness	Rare

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				Episodic spasms Variable degree of leukodystrophy	
<i>GRID2</i> <sup>6</sup>	Not assigned	Complicated	Childhood	Amyotrophy Ataxia	Rare
<i>IBA57</i> <sup>7</sup>	SPG74	Complicated	Childhood	Optic atrophy Peripheral neuropathy	Rare
<i>KIF1A</i> <sup>8</sup>	SPG30	Complicated	Childhood	Spastic ataxia Polyneuropathy	Rare
<i>KIF1C</i>	SPG58	Complicated	Childhood	Spastic ataxia Dystonia	Rare
<i>KLC2</i>	Not assigned	Complicated	Childhood	Optic atrophy Neuropathy Contractures in later stages Cognition remains intact	Rare Also known as spastic paraplegia optic atrophy, & neuropathy (SPOAN)
<i>KLC4</i>	Not assigned	Complicated	Childhood	Ataxia Multiple contractures Variable degree of leukodystrophy	Rare
<i>MARS1</i> <sup>9</sup>	SPG70	Complicated	Infancy	Nephrotic syndrome, polyneuropathy Mild ID Late onset of CMT2 (axonal) type also reported	Rare
<i>NT5C2</i>	SPG45	Complicated	Childhood	Optic atrophy Nystagmus Strabismus ID Hypoplastic corpus callosum	Rare
<i>PGAP1</i> <sup>10</sup>	SPG67	Complicated	Infancy	Severe DD Tremor Agenesis of corpus callosum	Rare

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				Hypomyelination	
<i>PNPLA6</i> <sup>11</sup>	SPG39	Complicated	Childhood	Amyotrophy Endocrine abnormalities w/short stature or hypogonadotropic hypogonadism Chorioretinal dystrophy	Rare
<i>REEP2</i>	SPG72	Uncomplicated	Early childhood	Musculoskeletal problems Mild postural tremor	Rare Inheritance can be dominant or recessive.
<i>SPART</i>	SPG20	Complicated	Juvenile	Distal amyotrophy Short stature Kyphoscoliosis Multiple limb contractures	Rare Mostly seen among Old Order Amish
<i>SPG7</i>	SPG7	Uncomplicated or complicated	Juvenile or adulthood	Dysarthria Ataxia Optic atrophy Supranuclear palsy Mitochondrial abnormalities on skeletal muscle biopsy	5%-12% of AR HSP AD inheritance suggested for some pathogenic variants; this remains controversial
<i>SPG11</i>	SPG11	Complicated	Childhood or early adulthood	DD Optic atrophy Ataxia Pseudobulbar signs Polyneuropathy Levodopa-responsive parkinsonism Hypoplastic or absent corpus callosum	5% of AR HSP 75% of HSP w/DD & hypoplasia of corpus callosum
<i>TECPR2</i>	SPG49	Complicated	Childhood	Central apnea Severe DD Microcephaly Dysmorphic features	Rare
<i>TFG</i>	SPG57	Complicated	Childhood	Optic atrophy Severe polyneuropathy	Rare

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<i>USP8</i>	SPG59	Uncomplicated	Childhood	None	Rare
<i>WDR48</i>	SPG60	Complicated	Infancy	Polyneuropathy DD	Rare
<i>ZFYVE26</i>	SPG15	Complicated	Childhood or early adulthood	DD Optic atrophy Ataxia Central retinal degeneration Polyneuropathy	1%-2% of AR HSP

AD = autosomal dominant; AR = autosomal recessive; ALS = amyotrophic lateral sclerosis; DD = developmental delay; HSP = hereditary spastic paraplegia; ID = intellectual disability

**Table 3:** Hereditary Spastic Paraplegia: Genes and Distinguishing Clinical Features – X-Linked Inheritance (Hedera, 2021)

Gene <sup>1</sup>	HSP Designation	Type of HSP	Onset	Distinguishing Clinical Features	Other
<i>LICAM</i> <sup>2</sup>	SPG1	Complicated	Infancy	ID Adducted thumbs Corpus callosum hypoplasia Aphasia Obstructive hydrocephalus	Rare
<i>PLP1</i> <sup>3</sup>	SPG2	Complicated	Early-childhood to juvenile onset (in manifesting XX heterozygotes: onset in 4th-7th decade)	Pure HSP phenotype present in early stages; later, other signs emerge Nystagmus Optic atrophy Dysarthria ID Variable degree of leukodystrophy on MRI	Rare In heterozygous XX individuals: variable phenotype w/relatively late onset & mild clinical manifestations
<i>SLC16A2</i>	SPG22	Complicated	Early childhood	Severe ID Infantile hypotonia Progressive spasticity Ataxia Dystonia	Rare SPG22 is a proposed designation. <sup>4</sup>

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				↑ T3 & normal to mildly ↑ TSH ↓ T4 hypomyelination on neuroimaging	Also referred to as Allan-Herndon-Dudley syndrome <sup>5</sup>
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AD = autosomal dominant; AR = autosomal recessive; DD = developmental delay; HSP = hereditary spastic paraplegia; ID = intellectual disability

**Table 4:** Hereditary Spastic Paraplegia: Gene and Distinguishing Clinical Features – Maternal (Mitochondrial) Inheritance (Hedera, 2021)

Gene	HSP Designation	Type of HSP	Onset	Distinguishing Clinical Features
<i>MT-ATP6</i>	Not assigned	Complicated	Adult	Cardiomyopathy, diabetes mellitus, sensory polyneuropathy

## Guidelines and Recommendations

### *Amyotrophic Lateral Sclerosis (ALS)*

#### Italian Amyotrophic Lateral Sclerosis Genetic (ITALSGEN) Consortium

The following guidelines were created as a result from a workshop on ALS genetic testing.

- “All ALS patients who have a first-degree or second-degree relative with ALS, frontotemporal dementia or both, should be offered genetic testing. At present, however, we do not recommend offering genetic testing to sporadic ALS patients, outside research protocols.”
- “Genetic testing at present is not indicated in asymptomatic at-risk subjects and, therefore, should not be proposed.”
- The guidelines also note that “two-thirds of mutations are found in four genes, C9ORF72, SOD1, TARDBP and FUS.” Therefore, they state that these genes should be “considered” for routine diagnostic protocol. Furthermore, they note that C9ORF72 testing is “worthwhile” in sporadic patients. If these 4 genes are negative, other ALS-related genes may be tested. Finally, UBQLN2 is a gene that should be tested if there is suspicion of an X-linked dominant inheritance (Chio et al., 2014).

#### ALS Association

The ALS Association published information on genetic testing on their website. They state that “Knowing whether your ALS is connected to a specific gene mutation could make you eligible for ongoing clinical trials testing treatments targeted at specific genes.” The guidelines go on to state that “if genetic testing identifies a disease-causing genetic mutation in a person with ALS, their family members generally have the option to pursue testing themselves” but note that this is a personal decision with significant costs and benefits (ALSA, 2023).

### *Ataxias (including Friedreich ataxia)*

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European Federation of Neurological Societies (EFNS) and European Neurological Society (ENS)

The EFNS-ENS released joint guidelines on diagnosis and management of chronic ataxias in adulthood. Their genetic testing guidelines are listed below:

“In the case of a family history that is compatible with an autosomal dominant cerebellar ataxia, screening for SCA1, 2, 3, 6, 7 and 17 is recommended (level B). In Asian patients, DRPLA should also be tested for.”  
“If mutation analysis is negative, we recommend contact with or a referral to a specialized clinic for reviewing the clinical phenotype and further genetic testing (good practice point).”

In the case of a family history compatible with an autosomal recessive cerebellar ataxia, they recommend a three-step diagnostic approach.

Step 1 includes mutation analysis of the *FRDA* gene for Friedreich's ataxia (although one can refrain from this in the case of severe cerebellar atrophy).

Step 2 includes mutation analysis of the *SACS*, *POLG*, Aprataxin (*APTX*) and *SPG7* genes (taking into account specific phenotypes).

Step 3 includes “referral to a specialized centre, e.g. for skin or muscle biopsy targeted at diagnoses such as Niemann–Pick type C, recessive ataxia with coenzyme Q deficiency [aarF domain containing kinase 3 (*ADCK3*)/autosomal recessive spinocerebellar ataxia 9 (*SCAR9*)] and mitochondrial disorders, or for extended genetic screening using gene panel diagnostics.”

“In the case of sporadic ataxia and independent from onset age, we recommend routine testing for SCA1, SCA2, SCA3, SCA6 and DRPLA (in Asian patients) (level B)” (van de Warrenburg et al., 2014).

## Friedreich's Ataxia Research Alliance (FARA)

The FARA notes genetic diagnostic information on their website.

They state that in “more than 95% of abnormal alleles, the mutation is expansion of naturally occurring GAA repeat in first intron (non-coding region) of the frataxin or *FRDA* gene.” “Genetic testing results in ~98% detection in symptomatic individuals. In rare cases, analysis of frataxin protein levels can be helpful to confirming or ruling out a diagnosis...Carrier testing is recommended for anyone with a positive family history of Friedreich ataxia and for partners of known carriers. Presymptomatic testing for at-risk siblings/relatives is available, however genetic counseling is strongly recommended to assist individuals/families in considering the risks vs benefits for testing an untreatable genetic condition” (FARA, 2022).

An expert working group was convened to review and provide guidelines for FA. This working group reviewed guidelines from a variety of different societies, and drafted their own guidelines based off their review. Their genetic testing items are as follows:

“Any individual in whom the diagnosis of *FRDA* is considered should undergo genetic testing for *FRDA*.”

“Referral to a clinical geneticist or genetic counselor should be considered on diagnosis of *FRDA*.”

“Requests for pre-symptomatic genetic testing are best managed on a case-by-case basis; there is no evidence to support the routine provision or refusal of pre-symptomatic genetic testing for *FRDA*.”

“The committee did not reach consensus on the issue of whether it is appropriate to conduct presymptomatic testing in a minor. Where a request for presymptomatic testing in a minor occurs, the individual/family should be referred to a team with expertise in this field for discussion about pre-symptomatic genetic testing in which the risks and benefits of pre-symptomatic genetic diagnosis are put forward. The risks and benefits from both the child's and parents' perspectives should be carefully reviewed during the pre-test assessment.”

“All patients identified pre-symptomatically and their families would benefit from immediate post-test counseling and psychosocial support and referral for appropriate neurological and cardiac surveillance.”

“Carrier testing should be first undertaken on the closest relative” (Corben et al., 2014).

For Friedreich Ataxia due to compound heterozygosity for a *FXN* Intron 1 GAA expansion and point mutation/insertion/deletion:

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“If a person compound heterozygous for a *FXN* GAA expansion and a point mutation/insertion/deletion has a similar phenotype to those with FRDA due to homozygosity for GAA expansions, they should be managed as per the guidelines in this document.”

“If spastic ataxia is the predominant phenotype, then the main management issue is that of spasticity and the guidelines for management of spasticity should be followed” (Corben et al., 2014).

## Ataxia UK

Genetic tests are recommended as part of the secondary care regimen for ataxia. The secondary care is divided into “first line” and “second line” for adults.

The first line genetic tests are for: FRDA, SCA1, 2, 3, 6, 7 (12, 17), and FXTAS. The second line genetic tests are for any remaining genes (de Silva et al., 2019). The guidelines list genes associated with types of ataxia (Bonney et al., 2016).

Spinocerebellar ataxias:

Type (SCA)	Gene
1	<i>ATXN1</i>
2	<i>ATXN2</i>
3	<i>ATXN3</i>
5	<i>SPTBN2</i>
6	<i>CACNA1A</i>
7	<i>ATXN7</i>
8	<i>ATXN8OS</i>
10	<i>ATXN10</i>
11	<i>TTBK2</i>
12	<i>PPP2R2B</i>
13	<i>KCNC3</i>
14	<i>PRKCG</i>
15/16	<i>ITPR1</i>
17	<i>TBP</i>
19/22	<i>KDND3</i>
23	<i>PDYN</i>
27	<i>FGF14</i>

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28	<i>AFG3L2</i>
31	<i>BEAN1</i>
35	<i>TGM6</i>
36	<i>NOP56</i>
38	<i>ELOVL5</i>
40	<i>CCDC88C</i>
41	<i>TRPC3</i>

The guidelines note that the clinical validity of genetic testing for SCA8 by CAG repeat sizing has not been determined. Therefore, SCA8 should not be offered as a routine test if family history is unknown. However, testing may be appropriate in “large pedigrees where the expansion has been proven to be segregating with the disease” (Bonney et al., 2016).

SCAs are considered autosomal dominant ataxias. Autosomal dominant ataxias also include GSS, DRPLA, POLG1, and EA types 1 and 2.

Autosomal recessive ataxia genes include *FXN* (Frederich’s Ataxia), *APT*X, *SET*X, *SACS*, *SPG7*, *ATM*, and *TTPA* (Ataxia with Vitamin E deficiency).

Mitochondrial Ataxias include NARP, MELAS, and MERRF.

X-Linked Ataxias include FXTAS (Fragile X associated Tremor and Ataxia Syndrome).

For children, second-line diagnostic tests for chronic ataxias include DNA testing for the *FXN* gene is recommended for suspected Frederich’s Ataxia, *ATM* testing is recommended for suspected ataxia-telangiectasia, and general DNA testing is recommended for “other conditions.” Finally, “genetic testing of asymptomatic ‘at-risk’ minors is not generally recommended, but should be considered on a case-by-case basis” (Bonney et al., 2016).

## National Ataxia Foundation (NAF)

The National Ataxia Foundation published a “Frequently Asked Questions” document regarding genetic testing for hereditary ataxias. For diagnostic testing, they noted that in sporadic ataxia cases (no prior family history of ataxia), genetic testing should only be done after non-genetic causes of ataxia have been excluded. For predictive testing, a patient “must” know what type of ataxia is present in their family to be eligible (NAF, 2015).

## Dystonias

### European Federation of Neurological Societies (EFNS)

The EFNS has released guidelines on the genetic testing of dystonias, which are listed below:

“Genetic testing should be performed after establishing the clinical diagnosis. Genetic testing is not sufficient to make a diagnosis of dystonia without clinical features of dystonia (level B). Genetic counselling is recommended.”

“DYT1 testing is recommended for patients with limb-onset, primary dystonia with onset before age 30 (level B), as well as in those with onset after age 30 if they have an affected relative with early-onset dystonia (level B).”



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“In dystonia families, DYT1 testing is not recommended in asymptomatic individuals (good practice point).”

“DYT6 testing is recommended in early-onset dystonia or familial dystonia with cranio-cervical predominance or after exclusion of DYT1 (good practice point).”

“Individuals with early-onset myoclonus affecting the arms or neck, particularly if positive for autosomal-dominant inheritance and if triggered by action, should be tested for the DYT11 gene (good practice point). If direct sequencing of the SGCE gene is negative, gene dosage studies increase the proportion of mutation-positives (level C).”

“Diagnostic testing for the PNKD gene (DYT8) is recommended in symptomatic individuals with PNKD (good practice point).”

“Gene testing for mutation in GLUT1 is recommended in patients with paroxysmal exercise-induced dyskinesias, especially if involvement of GLUT1 is suggested by low CSF/serum glucose ratio, epileptic seizures or haemolytic anaemia (good practice point)” (Albanese et al., 2011).

The EFNS also released guidelines on the diagnosis of Huntington’s Disease. In it, they recommend that “diagnostic testing for HD is recommended (Level B) when a patient presents with an otherwise unexplained clinical syndrome of a progressive choreatic movement disorder and neuropsychiatric disturbances with or without a positive family history of the disease” (Harbo et al., 2009).

## *Hereditary Spastic Paraplegia (HSP)*

### **National Organization for Rare Disorders (NORD)**

NORD has published a webpage on HSP. This page states that “Individuals seeking genetic counseling for HSP are recommended to consult a genetic counselor or medical geneticist for specific information”; further, “Genetic testing is often helpful in confirming the clinical diagnosis of HSP and in determining the genetic type of HSP. Results of genetic testing can be used, together with clinical information, to provide genetic counseling” (NORD, 2017).

Regarding genetic testing for a HSP diagnosis, NORD states that “Testing for HSP genes is available and performed for individual HSP genes, for panels containing dozens of HSP genes, and by analysis of all genes (whole exome and whole genome analysis). Genetic testing is often helpful to confirm the clinical diagnosis of HSP. Genetic testing is most often able to find causative gene mutations for subjects with HSP who have a family history of a similarly affected first-degree relative. Despite discovery of more than 60 genes in which mutations cause various types of HSP, many individuals with HSP do not have an identified gene mutation... at present, genetic testing results very rarely influence treatment which is largely directed toward reducing symptoms” (NORD, 2017).

## *Huntington Disease (HD)*

### **Working Group on Genetic Counselling and Testing of the European Huntington’s Disease Network (EHDN)**

This Working Group was convened to provide guidelines for diagnostic genetic testing for HD. The guidelines list four groups that “should be considered” for genetic testing.

- The first group is “the patient with a positive family history and specific motor symptoms.” The authors note that diagnosis of this group is “not difficult” and that the test may be “little more than a formality.”
- The second group is “the patient with no family history, but specific symptoms likely to be HD.” The authors consider diagnostic testing of this group to be “most clinically useful.”
- The third group is “the patient with a positive family history and prodromal symptoms, which suggest the impending onset of HD.” The authors state that the motor abnormalities are part of the diagnostic criteria, but other symptoms such as behavioral changes or other mental conditions may present in HD.
- The fourth group is “the child with a family history of HD and features of juvenile HD.” The authors note this group as challenging to diagnose, and alludes to diagnostic criteria set forth by Nance, which are as follows:

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- “a known family history of HD (often, but not exclusively, the father)
- and two or more of
  - declining school performance
  - Seizures
  - oral motor dysfunction
  - Rigidity
  - gait disturbance” (Craufurd et al., 2015)

Another Working Group was convened to evaluate the predictive testing guidelines for HD in 2013. In those guidelines, they noted that HD testing should not be part of routine blood work and that patients under 18 should not be tested. However, they state that genetic counseling should be offered to those desiring to take the test (MacLeod et al., 2013). MacLeod et al. (2013) was affirmed by the American Association of Neurology on January 14, 2014 (AAN, 2014).

The EDHN performed a literature review of scientific and consensual guidelines in 2019. The only major change had to do with deutetrabenazine (Grade A) as a treatment. Other studies were in agreement with previously noted guidelines and recommendations (Bachoud-Lévi et al., 2019).

## *Parkinsonism (Parkinson Disease, PD)*

### **European Federation of Neurological Societies (EFNS) and Movement Disorder Society–European Section (MDS-ES)**

These guidelines were created by a Task Force comprised of members from both societies. Their genetic testing recommendations for Parkinson disease are listed below:

- “Testing for SNCA point mutations and gene multiplications is recommended only in families with multiple affected members in more than one generation suggestive of dominant inheritance, with early- or late-onset PD.”
- “LRRK2 genetic testing for counselling purposes, specifically directed at known pathogenic variants is recommended in patients with a clinical picture of typical PD and a positive family history suggestive of dominant inheritance.”
- “In sporadic patients, genetic testing should be limited to the search for known LRRK2 founder mutations in the appropriate populations (i.e. with known high mutation frequencies).”
- “Genetic testing for GBA gene mutations is recommended in patients with typical PD with or without a positive family history, limited to the known founder mutations of established pathogenic role in the appropriate populations.”
- “Genetic testing of the parkin, PINK1 and DJ-1 genes for counselling purposes is recommended in patients with typical PD and positive family history compatible with recessive inheritance, particularly when the disease onset is before the age of 50 years. For sporadic cases, parkin, PINK1 and DJ-1 genetic testing is recommended when onset is very early, particularly before the age of 40.”
- “Testing of the ATP13A2, PLA2G6 and FBXO7 genes might be considered in cases with very-early-onset PD, if no mutation in parkin, PINK1 and DJ-1 gene has been found.”

For recommendation III, the guideline lists Ashkenazi Jews, North African Arabs, and Basques as examples of high mutation frequency populations (Berardelli et al., 2013).

## *Spinal Muscular Atrophies (SMA)*

### **218<sup>th</sup> European Neuromuscular Centre (ENMC) International Workshop**

Researchers, industry representatives, and other representatives from SMA Europe convened to review the current knowledge on the standards of care for SMA. Regarding genetic testing, they noted that “there was consensus that genetic testing is the first line investigation when this condition is suspected in a typical case and that muscle biopsy or electromyography should not be performed in a typical presentation. There was also

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consensus that, at variance with previous recommendations, the current gold standard is SMN1 deletion/mutation and SMN2 copy number testing, with a minimal standard of SMN1 deletion testing. Other areas concerning the value of SMN2 copy number were more controversial and a further Delphi round was planned to complete the task” (Finkel et al., 2017).

“Diagnostic testing for HD is recommended (Level B) when a patient presents with an otherwise unexplained clinical syndrome of a progressive choreatic movement disorder and neuropsychiatric disturbances with or without a positive family history of the disease” (Finkel et al., 2017).

## **American College of Obstetricians and Gynecologists (ACOG)**

ACOG recommended SMA screening for all individuals “considering pregnancy or are currently pregnant.” ACOG also noted that if one parent had a family history of SMA, the other parent should be tested for SMN1 deletion if molecular reports for the first parent were not available. These guidelines were reaffirmed in 2021 (ACOG, 2017).

## *Wilson Disease (WD)*

## **Hepatology Committee of the European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN)**

ESPGHAN has published a position paper regarding Wilson disease in children. The genetic testing-relevant items are listed below:

The paper stated that the scoring system used for diagnosis of Wilson’s Disease included identification of a pathogenic mutation, which was considered one point (the scoring system is as follows: 0-1: unlikely, 2-3: probable, 4+, highly likely). The paper also notes that if biochemical and clinical symptoms are present, only one mutation needs to be identified to diagnose Wilson disease. If the patient is asymptomatic, two mutations must be identified to diagnose “with certainty.” The diagnostic protocol calls for biochemical (copper metabolism testing), liver (ALT/AST, bilirubin, et al), and clinical evaluation before proceeding to molecular testing, and ATP7B is the primary gene mutation mentioned in evaluation of Wilson disease.

“Genetic counseling is essential for families of patients with WD, and screening first-degree relatives is recommended by both European and American guidelines.”

“It is essential to screen siblings of any patient newly diagnosed with WD because the chance of being a homozygote and developing clinical disease is 25%. Assessment should include physical examination, serum ceruloplasmin, liver function tests, and molecular testing for ATP7B mutations or haplotype studies if not available. Newborn screening is not warranted and screening may be delayed until 1 to 2 years of age” (Socha et al., 2018).

## **State and Federal Regulations, as applicable**

### **Food and Drug Administration (FDA)**

Many labs have developed specific tests that they must validate and perform in house. These laboratory-developed tests (LDTs) are regulated by the Centers for Medicare and Medicaid (CMS) as high-complexity tests under the Clinical Laboratory Improvement Amendments of 1988 (CLIA '88). LDTs are not approved or cleared by the U. S. Food and Drug Administration; however, FDA clearance or approval is not currently required for clinical use.

### **Billing/Coding/Physician Documentation Information**

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This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at [www.bcbsnc.com](http://www.bcbsnc.com). They are listed in the Category Search on the Medical Policy search page.

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*Applicable service codes: 81177, 81178, 81179, 81180, 81181, 81182, 81183, 81184, 81185, 81186, 81243, 81244, 81271, 81274, 81284, 81285, 81286, 81289, 81329, 81343, 81344, 81400, 81401, 81403, 81404, 81405, 81406, 81407, 81408, 81479, 0136U, 0231U, 0233U, 0236U*

BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.

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## Policy Implementation/Update Information

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- 11/10/20 New policy developed. Genetic testing for neurodegenerative disorders is covered when coverage criteria are met. Notification given 11/10/2020 for policy effective date 01/12/2021. (sk)
- 12/13/22 Reviewed by Avalon 3rd Quarter 2022 CAB. When Covered section updated. Table of Terminology added. Codes 81177, 81186, 96040, 0231U, 0233U, 0236U, and S0265 added to Billing/Coding section. Policy Guidelines updated. References updated. (sk)
- 10/24/23 Wording in Policy Statement, When Covered, and/or Not Covered section(s) changed from Reimbursement to Medical Necessity. (ldh)
- 12/05/23 Reviewed by Avalon 3rd Quarter 2023 CAB. Policy Guidelines and References updated. When Covered section edited for clarity. Added Note 1. Removed Table of Terminology. No change to policy statement. Removed CPT code 96040 and HCPCS code S0265 from the Billing/Coding section. Medical Director review 11/2023. (ldh)



# Genetic Testing for Neurodegenerative Disorders AHS – M2167

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