

Genetic Testing for Neurodegenerative Disorders

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I. Policy Description

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.¹

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

For guidance on preconception screening for neurodegenerative disorders such as spinal muscular atrophies, please refer to AHS-M2179-Prenatal Screening (Genetic).

II. Related Policies

Policy Number	Policy Title
AHS-M2028	Genetic Testing for <i>FMR1</i> Mutations
AHS-M2038	Genetic Testing for Familial Alzheimer Disease
AHS-M2072	Genetic Testing for Diagnosis of Inherited Peripheral Neuropathies
AHS-M2085	Genetic Testing of Mitochondrial Disorders
AHS-M2145	General Genetic Testing, Germline Disorders
AHS-M2179	Prenatal Screening (Genetic)

III. Indications and/or Limitations of Coverage

Application of coverage criteria is dependent upon an individual’s benefit coverage at the time of the request. Specifications pertaining to Medicare and Medicaid can be found in the “Applicable State and Federal Regulations” section of this policy document.

- 1) Genetic counseling **IS REQUIRED** for individuals prior to and after undergoing genetic testing for diagnostic, carrier, and/or risk assessment purposes.

Amyotrophic Lateral Sclerosis (ALS)

- 2) For diagnosis in individuals with suspected ALS **and** a first-degree **or** second-degree relative (see Note 1) with ALS or frontotemporal dementia, genetic testing for ALS, including the genes *C9ORF72*, *SOD1*, *TARDBP*, and *FUS*, **MEETS COVERAGE CRITERIA**.

Ataxias, including Friedreich ataxia

1. For individuals with sporadic ataxia (no prior family history of ataxia) **or** a family history compatible with an inherited cerebellar ataxia, single gene testing (when a familial variant is known or when a specific ataxia is suspected) or multi-gene panel testing (when a specific ataxia is not suspected) **MEETS COVERAGE CRITERIA**.
- 3) To confirm a diagnosis in individuals with suspected ataxia-telangiectasia, genetic testing for *ATM* **MEETS COVERAGE CRITERIA**.

Dystonias

- 4) Genetic testing of *TOR1A* (formerly *DYT1*) **MEETS COVERAGE CRITERIA** 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.
- 5) Genetic testing of *THAP1* (formerly *DYT6*) **MEETS COVERAGE CRITERIA** 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.
- 6) To aid in the diagnosis of symptomatic individuals with familial paroxysmal nonkinesigenic dyskinesia (PNKD), genetic testing of *PNKD* **MEETS COVERAGE CRITERIA**.
- 7) In individuals with paroxysmal exercise-induced dyskinesia, genetic testing of *SLC2A1* (formerly *GLUT1*) **MEETS COVERAGE CRITERIA** 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.
- 8) In asymptomatic individuals, genetic testing of *TOR1A* **DOES NOT MEET COVERAGE CRITERIA**.

Hereditary Spastic Paraplegia (HSP)

- 9) To confirm clinical diagnosis and to determine the genetic type of Hereditary Spastic Paraplegia (HSP), genetic testing for HSP **MEETS COVERAGE CRITERIA**.

Huntington disease (HD)

10) Genetic testing for Huntington disease **MEETS COVERAGE CRITERIA** in the following situations:

- a) When an adult patient presents with an 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:
 - (a) Declining school performance
 - (b) Seizures
 - (c) Oral motor dysfunction
 - (d) Rigidity
 - (e) Gait disturbance

Parkinsonism, including Parkinson disease

11) Genetic testing of *SNCA* **MEETS COVERAGE CRITERIA** for an individual only if there is a family history with multiple affected members in more than one generation suggestive of dominant inheritance.

12) Genetic testing of *LRRK2* **MEETS COVERAGE CRITERIA** 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).

13) Genetic testing of the *PRKN* (formerly *PARK2* or *parkin*) *PINK1*, and *PARK7* (formerly *DJ-1*) genes **MEETS COVERAGE CRITERIA** 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.

14) Genetic testing of the *ATP13A2*, *PLA2G6*, and *FBXO7* genes **MEETS COVERAGE CRITERIA** only 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)

15) To diagnose individuals suspected of having SMA, genetic testing for SMA (*SMN1* deletion/mutation and *SMN2* copy number) **MEETS COVERAGE CRITERIA**.

Wilson disease (WD)

16) Genetic testing of *ATP7B* MEETS COVERAGE CRITERIA in the following situations:

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

NOTES:

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 two or more gene tests being run on the same platform, please refer to AHS-R2162 Reimbursement Policy.

IV. Table of Terminology

Term	Definition
ACOG	American College of Obstetricians and Gynecologists
<i>ACP33</i>	<i>SPG21 abhydrolase domain containing, maspardin</i>
<i>ADAR</i>	<i>Adenosine deaminase RNA specific</i>
<i>ADCK3</i>	AARF domain containing kinase 3
<i>ADCY5</i>	Adenylate cyclase 5
<i>ADHSP</i>	Autosomal dominant hereditary spastic paraplegia
<i>AFG3L2</i>	<i>AFG3 like matrix AAA peptidase subunit 2</i>
<i>ALDH18A1</i>	<i>Aldehyde dehydrogenase 18 family member A1</i>
<i>ALDH3A2</i>	<i>Aldehyde dehydrogenase 3 family member A2</i>
ALS	Amyotrophic lateral sclerosis
ALSA	Amyotrophic Lateral Sclerosis Association
<i>AMPD2</i>	<i>Adenosine monophosphate deaminase 2</i>
<i>ANO3</i>	<i>Anoctamin 3</i>
<i>AP4B1</i>	<i>Adaptor related protein complex 4 subunit beta 1</i>
<i>AP4M1</i>	<i>Adaptor related protein complex 4 subunit mu 1</i>
<i>AP4S1</i>	<i>Adaptor related protein complex 4 subunit sigma 1</i>
<i>AP5Z1</i>	<i>Adaptor related protein complex 5 subunit zeta 1</i>
APTX	Ataxia with oculomotor apraxia
<i>ARHSP</i>	Autosomal recessive hereditary spastic paraplegia
AT	Ataxia-telangiectasia
<i>ATAD3A</i>	<i>ATPase family AAA domain containing 3A</i>
<i>ATL1</i>	<i>Atlastin GTPase 1</i>
ATLD	Ataxia telangiectasia-like disorder
ATM	Ataxia-telangiectasia mutated
<i>ATN1</i>	<i>Atrophin 1</i>
ATP	Adenosine triphosphate

ATP13A2	<i>ATPase cation-transporting 13A2</i>
ATP2B4	<i>ATPase plasma membrane Ca²⁺ transporting 4</i>
ATP7B	<i>ATPase copper transporting beta</i>
ATXN1/2/3/7/8/10	<i>Ataxin 1/2/3/7/8/10</i>
ATXN8OS	<i>Ataxin 8 opposite strand lncRNA</i>
B4GALNT1	<i>Beta-1,4-N-acetyl-galactosaminyltransferase 1</i>
BEAN1	<i>Brain expressed associated with NEDD4 1</i>
BICD2	<i>BICD cargo adaptor 2</i>
BSCL2	<i>BSCL2 lipid droplet biogenesis associated, seipin</i>
C12orf65	<i>Mitochondrial translation release factor in rescue</i>
C19orf12	<i>Chromosome 19 open reading frame 12</i>
C9ORF72	<i>Chromosome 9 Open Reading Frame 72</i>
CACNA1A	<i>Calcium Voltage – Gated Channel Subunit Alpha 1 A</i>
CCDC88C	<i>Coiled-coil domain containing 88C</i>
CLIA	Clinical Laboratory Improvement Amendments
CMS	Centres for Medicare and Medicaid Services
CMT	Charcot Marie-Tooth Neuropathy
CPT1C	<i>Carnitine palmitoyltransferase 1C</i>
CSF	Cerebrospinal fluid
CYP2U1	<i>Cytochrome P450 family 2 subfamily U member 1</i>
CYP7B1	<i>Cytochrome P450 family 7 subfamily B member 1</i>
DD	Developmental delay
DDHD1/2	<i>DDHD domain containing ½</i>
DI-CMT	Dominant intermediate Charcot Marie-Tooth neuropathy
DJ-1	<i>Parkinsonism associated deglycase</i>
DNA	Deoxyribonucleic acid
DNM2	<i>Dynamamin 2</i>
DRPLA	Dentatorubral-pallidoluysian atrophy
DYT1	<i>Dystonia 1/6/8/11</i>
EEF2	<i>Eukaryotic translation elongation factor 2</i>
EFNS	European Federation of Neurological Societies
EHDN	Working Group on Genetic Counselling and Testing of the European Huntington's Disease Network
ELOVL5	<i>Elongation of very long chain fatty acid elongase 5</i>
ENMC	European Neuromuscular Center
ENS	European Neurological Society
ENTPD1	<i>Ectonucleoside triphosphate diphosphohydrolase 1</i>
ERLIN1/2	<i>ER lipid raft associated ½</i>
ESPGHAN	Hepatology Committee of the European Society for Paediatric Gastroenterology, Hepatology and Nutrition
FA	Friedreich's ataxia
FA2H	<i>Fatty acid 2-hydroxylase</i>

FALSA	Familial amyotrophic lateral sclerosis
FARA	Friedreich's Ataxia Research Alliance
<i>FGF14</i>	<i>Fibroblast growth factor 14</i>
<i>FMR1</i>	<i>Fragile X mental retardation 1</i>
FRDA	<i>Frataxin</i>
<i>FUS</i>	<i>FUS RNA binding protein</i>
FXN	<i>Frataxin</i>
FXTAS	Fragile X Associated Tremor and Ataxia Syndrome
GAA	<i>Alpha glucosidase</i>
GAD1	<i>Glutamate decarboxylase 1</i>
<i>GAK- DGKQ</i>	<i>Cyclin G associated kinase-diacylglycerol kinase theta</i>
GBA	<i>Glucocerebrosidase</i>
GBA2	<i>Glucocerebrosidase beta 2</i>
GCH1	<i>GTP cyclohydrolase 1</i>
GJC2	<i>Gap junction protein gamma 2</i>
GLUT1	<i>Glucose transporter protein type 1</i>
GRID2	<i>Glutamate ionotropic receptor delta type subunit 2</i>
H2O2	Hydrogen peroxide
HD	Huntington disease/Huntington's disease
HDL4	Huntington disease like 4
HLA	<i>Human leukocyte antigen</i>
HMN	Hereditary motor neuropathy
HSP	Hereditary spastic paraplegia
<i>HSPD1</i>	<i>Heat shock protein family D (Hsp60) member 1</i>
HTT	<i>Huntingtin</i>
ICARS	International cooperative ataxia rating scale
ID	Intellectual disability
ITALSGEN	Italian Amyotrophic Lateral Sclerosis Genetic consortium
<i>ITPR1</i>	<i>Inositol 1,4,5-trisphosphate receptor type 1</i>
<i>KCND3</i>	<i>Potassium voltage-gated channel subfamily D member 3</i>
<i>KIAA1096</i>	<i>Proline-rich coiled-coil 2C</i>
<i>KIF1A/1C/5A</i>	<i>Kinesin family member 1A/1C/5A</i>
<i>KLC2/4</i>	<i>Kinesin light chain 2/4</i>
<i>L1CAM</i>	<i>L1 cell adhesion molecule</i>
LDT	Laboratory developed test
LRRK2	Leucine rich repeat kinase-2
<i>MARS1</i>	<i>Methionyl-tRNA synthetase 1</i>
MDS	International Parkinson and Movement Disorder Society
MDS-ES	Movement Disorder Society – European Section
MELAS	Mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes
MERRF	Myoclonus epilepsy, ragged-red-fibers
MHC	<i>Major histocompatibility complex</i>

MR1	<i>Major histocompatibility complex, class I-related</i>
MRE11A	<i>MRE11 homolog, double strand break repair nuclease</i>
mRNA	Messenger ribonucleic acid
MT-ATP6	<i>Mitochondrially encoded ATP synthase membrane subunit 6</i>
NAF	National Ataxia Foundation
NARP	Neuropathy, ataxia, and retinitis pigmentosa
NIPA1	<i>NIPA magnesium transporter 1</i>
NOP56	<i>NOP56 ribonucleoprotein</i>
NORD	National Organization for Rare Disorders
NT5C2	<i>5'-nucleotidase, cytosolic II</i>
O2	Oxygen
PARK1/2/4/7/8	<i>Parkinson disease ½/4/7/8</i>
PD	Parkinson disease
PDYN	<i>Prodynorphin</i>
PGAP1	<i>Post-GPI attachment to proteins inositol deacylase 1</i>
PINK1	<i>PTEN induced kinase 1</i>
PKND	Paroxysmal dyskinesia with dystonia
PLA2G6	<i>Phospholipase A2 group VI</i>
PLP1	<i>Proteolipid protein 1</i>
PNKD	Paroxysmal nonkinesigenic dyskinesia
PNPLA6	<i>Patatin like phospholipase domain containing 6</i>
POLG	<i>DNA polymerase gamma, catalytic subunit</i>
PPP2R2B	<i>Protein phosphatase 2 regulatory subunit B beta</i>
PRKCG	<i>Protein kinase C gamma</i>
REEP1/2	<i>Receptor accessory protein ½</i>
RTN2	<i>Reticulon 2</i>
SACS	<i>Sacsin molecular chaperone</i>
SARA	Scale for the assessment and rating of ataxia
SCA	Spinocerebellar ataxia
SCAR9	Spinocerebellar ataxia 9
SGCE	<i>Sarcoglycan epsilon</i>
SLC2A1	<i>Solute carrier family 2, member 1</i>
SLC16A2	<i>Solute carrier family 16, member 2</i>
SLC33A1	<i>Solute carrier family 33, member 1</i>
SMA	Spinal muscular atrophies
SMN1/2	<i>Survival of motor neuron ½</i>
SNCA	<i>Alpha-synuclein</i>
SNP	Single nucleotide variant
SOD1	<i>Superoxide dismutase 1</i>
SPAST	Spastin
SPG1 – 74	<i>Spastic paraplegia 1 – 74</i>
SPTBN2	<i>Spectrin beta, non-erythrocytic 2</i>

STR	Short tandem repeat
TARDBP	TAR DNA binding protein
TBP	TATA-binding protein
TECPR2	Tectonin beta-propeller repeat containing 2
TFG	Trafficking from ER to golgi regulator
TGM6	Transglutaminase 6
THAP1	THAP domain containing 1
TOR1A	Torsin family 1 member A
TRPC3	Transient receptor potential cation channel subfamily C member 3
TTBK2	Tau tubulin kinase 2
TTPA	Alpha tocopherol transfer protein
TUBB4A	Tubulin beta 4A class Iva
UBQLN2	Ubiquilin 2
UPDRS	Unified Parkinson's Disease Rating Scale
USP8	Ubiquitin specific peptidase 8
WASHC5	WASH complex subunit 5
WD	Wilson Disease/Wilson's Disease
WDR48	WD repeat domain 48
ZFYVE26/27	Zinc finger FYVE-type containing 26/27

V. Scientific Background

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.¹

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.”² 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.³

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 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.”⁴

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.⁵

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, 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 HDL4) ¹	Gait ataxia, dementia	<i>TBP</i>
SCA18	Pyramidal signs, weakness, sensory axonal neuropathy	<i>7q22-q32</i>
SCA19/22	Predominantly cerebellar syndrome, sometimes with cognitive impairment or myoclonus	<i>KCND3</i> gene
SCA20	Palatal tremor and dysphonia	<i>11q12</i>

Disorder	Distinguishing features	Gene
SCA21	Mild to severe cognitive impairment	<i>TMEM240</i>
SCA23	Distal sensory deficits	<i>PDYN</i>
SCA24	Recessive inheritance; redesignated as SCAR4	<i>1p36</i>
SCA25	Sensory neuropathy, facial tics, gastrointestinal symptoms	<i>2p21-p13</i>
SCA26	Pure cerebellar ataxia	<i>EEF2</i>
SCA27	Cognitive impairment	<i>FGF14</i>
SCA28	Ophthalmoparesis and ptosis	<i>AFG3L2</i>
SCA29	Early onset, nonprogressive ataxia; may be an allelic variant of SCA15	<i>3p26</i>
SCA30	Slowly progressive, relatively pure ataxia	<i>4q34.3-q35.1</i>
SCA31	Decreased muscle tone	<i>BEAN</i>
SCA32	Cognitive impairment; affected individuals with azoospermia and testicular atrophy	<i>7q32-q33</i>
SCA33	Not assigned	
SCA34	Skin lesions consisting of papulosquamous erythematous ichthyosiform plaques	<i>ELOVL4</i>
SCA35	Late onset, slowly progressive gait and limb ataxia	<i>TGM6</i>
SCA36	Late onset, truncal ataxia, dysarthria, variable motor neuron disease and sensorineural hearing loss	<i>NOP56</i>
SCA37	Late onset, falls, dysarthria, clumsiness, abnormal vertical eye movements	<i>1p32</i>
SCA38	Slowly progressive pure cerebellar phenotype	<i>ELOVL5</i>
SCA39	Not assigned	
SCA40	Hyperreflexia and spasticity	<i>CCDC88</i>
DRPLA	Chorea, seizures, myoclonus, dementia	<i>ATN1</i>

¹SCA17 is synonymous with HDL4 (Huntington disease-like 4).⁶

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 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).⁷

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 (≤ 14 and 15-24 years, respectively), compared to 0.56 points per year for late-onset patients (≥ 25 years).⁸

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.⁹

Schuermans, et al. (2024) 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).¹⁰

Dystonias

Dystonias are a class of movement disorders characterized by “sustained or intermittent muscle contractions causing abnormal, often repetitive movements, postures, or both.”¹¹ 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.¹¹

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.¹¹ Even though DYT-TOR1A dystonia is inherited in an autosomal dominant pattern, the penetrance is only 30%.¹¹⁻¹³ 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 *MR1*, 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.¹¹

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 *GCH1*, *THAP1*, *TOR1A*, *ANO3*, and *ADCY5*. The authors noted *GCH1*, *THAP1*, and *TOR1A* as

associated with isolated, generalized dystonia and *ANO3* and *ADCY5* associated with a combined myoclonus-dystonia phenotype.¹⁴

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.¹⁵ 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.¹⁶ 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.¹⁷

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*.¹⁶

GBA- (glucocerebrosidase) associated PD is coupled with the lysosomal storage condition known as Gaucher disease, which is commonly seen in Ashkenazi Jews.¹⁶ 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.¹⁸

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 one 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.¹⁶

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.¹⁶

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.¹⁶

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.¹⁶

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 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.”¹⁹

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.”²⁰

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%).²¹

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 O₂ and H₂O₂. 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.²²

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.²²

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 3.5.²³

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.²⁴

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.”²⁵

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 this gene cause impaired binding of copper to the protein, causing copper accumulation in the hepatocyte and eventually the bloodstream.²⁶

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.²⁷

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.²⁸

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 ≥ 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.²⁹

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 12.3×10^{-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.³⁰

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.³¹

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 8.³¹

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.³²

Schroth, et al. (2024) completed a systematic literature review on SMA newborn screening and proposed guideline recommendations for diagnostic testing that includes newborn screening. Their first recommendation states “SMA infants identified by NBS and before treatment initiation should be characterized by *SMN2* copy number, current motor function, age at symptom onset, and severity of symptoms.” The authors state that “this initial essential characterization of the infant before treatment guides care and management discussions with parents and caregivers and guides discussion with payers regarding access to treatments.”³³

Efimova, et al. (2024) studied newborn screening results for 5q-SMA. The study included results from 202,908 screenings from across Russia in 2022. “It was found that 38.46% had two *SMN2* copies, 42.31% had three copies, 15.38% had four copies, and 3.85% had five copies of *SMN2*.” Screening results led to further investigation, treatment, and management for patients with more than two *SMN2* copies. The authors concluded that “the study emphasizes the need for a standardized algorithm for early diagnosis and management through NBS to benefit affected families.”³⁴

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.³⁵ 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.^{36,37} 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.³⁷ 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.³⁷

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%).”³⁸

In 2018, GeneReview published an updated overview of HSP. This overview was last updated in 2025. This document states the following regarding genetic testing:

- “A multigene panel that includes some or all the genes listed in Tables 1 and 2 is most likely to identify the genetic cause of the condition while limiting identification of pathogenic variants and variants of uncertain significance in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this GeneReview. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.”
- “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.”³⁹
- 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: Autosomal Dominant Uncomplicated Hereditary Spastic Paraplegia: Genes and Selected Clinical Features³⁹

Gene ¹	SPG Designation	HSP Phenotype(s)	Onset	Other
ADAR	Not assigned	Uncomplicated HSP ²	Early childhood	Reported in a single Hispanic person
ALDH18A1	SPG9A	Uncomplicated HSP ³ Cataracts Gastroesophageal reflux Motor neuronopathy Variably present: dysarthria, ataxia, cognitive impairment	Adolescence to adulthood (1 subject w/infantile onset)	Rare Also assoc w/AR complicated HSP (SPG9B)
ATL1	SPG3A	Uncomplicated HSP characterized by minimal progression	Infantile to childhood (rarely adult onset)	Uncomplicated HSP characterized by minimal progression w/status

Gene ¹	SPG Designation	HSP Phenotype(s)	Onset	Other
		w/status course; may present as spastic diplegic cerebral palsy Complicated HSP w/axonal motor neuropathy &/or distal amyotrophy w/lower motor neuron involvement (Silver syndrome phenotype)		course; may present as spastic diplegic cerebral palsy Complicated HSP w/axonal motor neuropathy &/or distal amyotrophy w/lower motor neuron involvement (Silver syndrome phenotype)
ATP2B4	Not assigned	Uncomplicated HSP ²	Adulthood	Single family
BSCL2	SPG17	Uncomplicated HSP (foot deformity may be present) Complicated HSP w/amyotrophy of leg muscles &/or pathologic nerve conduction velocities; can be indistinguishable from ALS	Adulthood	Rare
CPT1C	SPG73 (OMIM 616282)	Uncomplicated HSP (foot deformity may be present)	Early adulthood	Single family
DNM2	Not assigned	Predominantly uncomplicated HSP w/variable axonal polyneuropathy & mild distal amyotrophy in feet	Before age 20 years	Single family
ERLIN2	SPG18	Uncomplicated HSP Amyotrophy w/ALS-like phenotype can develop in later stages of disease	Juvenile to adulthood	Most pathogenic variants are assoc w/AR HSP
HSPD1	SPG13 (OMIM 605280)	Predominantly uncomplicated HSP w/mild distal amyotrophy	Adulthood	Rare
KIF5A	SPG30	Uncomplicated HSP	Juvenile to adulthood	5%-6% of all AD HSP

Gene ¹	SPG Designation	HSP Phenotype(s)	Onset	Other
		Complicated HSP ± mild ID, optic nerve atrophy, & rarely epilepsy ⁷		Also, assoc w/AR hereditary sensory & motor neuropathy type 2 8
KIF5A	SPG10 (OMIM 604187)	Uncomplicated HSP or predominantly uncomplicated HSP Complicated HSP w/polyneuropathy, pes cavus, &/or ataxia	Juvenile or adulthood	Uncomplicated HSP or predominantly uncomplicated HSP Complicated HSP w/polyneuropathy, pes cavus, &/or ataxia
NIPA1	SPG6	Uncomplicated HSP characterized by severe weakness & spasticity; rapidly progressive Complicated HSP w/epilepsy or variable peripheral neuropathy	Adulthood (infantile onset rare)	Rare (~1% of AD HSP)
REEP1	SPG31 (OMIM 610250)	Uncomplicated HSP or predominantly uncomplicated HSP w/mild amyotrophy	2nd to 7th decades	Common; 4%-6% of all AD HSP
REEP2	SPG72 (OMIM 615625)	Predominantly uncomplicated HSP w/musculoskeletal problems & mild postural tremor	Very early, average age 4 years	Rare Inheritance can be AD or AR.
RTN2	SPG12 (OMIM 604805)	Uncomplicated HSP	Before age 20 years	5% of early-onset AD HSP, but overall rare
SLC33A1	SPG42 (OMIM 612539)	Uncomplicated HSP w/mild pes cavus; slowly progressive Complicated HSP	Early adulthood	
SPAST	SPG4	Uncomplicated HSP. Subtle cognitive impairment has been documented but its relation to the disease remains undetermined	Infancy to 7th decade	40% of AD HSP

Gene ¹	SPG Designation	HSP Phenotype(s)	Onset	Other
		(deficits appear late in disease course & are not present in all affected members of a given family). Complicated HSP w/variable distal amyotrophy &/or ataxia		
SPG7	SPG7	Uncomplicated HSP Complicated HSP w/dysarthria, ataxia, optic atrophy, &/or supranuclear palsy	Juvenile or adulthood	AD inheritance suggested for some pathogenic variants, but rare
WASHC5	SPG8	Uncomplicated HSP w/severe motor deficit in some persons	Adulthood (rare infantile onset reported)	Rare (~1% of AD HSP)

AD = autosomal dominant; AR = autosomal recessive; ALS = amyotrophic lateral sclerosis; HSP = hereditary spastic paraplegia; ID = intellectual disability; **Table 2:** Autosomal Recessive Uncomplicated Hereditary Spastic Paraplegia: Genes and Selected Clinical Features³⁹

Gene ¹	SPG Designation	HSP Phenotype(s)	Onset	Other
AP5Z1	SPG48 (OMIM 613647)	Uncomplicated HSP w/urinary incontinence Complicated HSP w/parkinsonism, dystonia, thin corpus callosum, & leukodystrophy; severe DD in infantile onset	Childhood	Rare, first described in Old Order Amish population (later identified in various ethnic groups) Also known as Mast syndrome

Gene ¹	SPG Designation	HSP Phenotype(s)	Onset	Other
ATL1	SPG3A	Uncomplicated HSP w/minimal progression & static course ; may present as spastic diplegic cerebral palsy Complicated HSP w/peripheral neuropathy; autonomic failure reported	Infantile to childhood (rarely adult onset)	AR inheritance is very rare; almost exclusively inherited in an AD manner
CYP7B1	SPG5A (OMIM 270800)	Uncomplicated HSP Complicated HSP w/ataxia, polyneuropathy, extrapyramidal signs, & MRI signs of leukodystrophy	Juvenile to early adulthood	SPG5A was diagnosed in 9/172 families w/histories consistent w/AR inheritance
DDHD1	SPG28 (OMIM 609340)	Uncomplicated HSP Complicated HSP w/scoliosis, axonal neuropathy, & cerebellar ataxia	Childhood	Rare

Gene ¹	SPG Designation	HSP Phenotype(s)	Onset	Other
ERLIN2	SPG18	Uncomplicated HSP Complicated HSP w/DD, seizures, & contractures; juvenile primary lateral sclerosis phenotype reported	Childhood	Rare Typically associated w/complicated HSP (uncomplicated AR HSP reported rarely) Also associated w/AD uncomplicated HSP
REEP2	SPG72 (OMIM 620606)	Predominantly uncomplicated HSP w/musculoskeletal problems & mild postural tremor	Early childhood	Rare Inheritance can be AD or AR.
SPG7	SPG7	Uncomplicated HSP Complicated HSP including optic neuropathy, progressive external ophthalmoplegia/ptosis, slowed speech, swallowing difficulties, palatal tremor, & subtle cognitive impairment	Juvenile or adulthood	5%-12% of AR HSP AD inheritance suggested for some pathogenic variants; this remains controversial

Gene ¹	SPG Designation	HSP Phenotype(s)	Onset	Other
SPG11	SPG11	Uncomplicated HSP Complicated HSP w/ID, polyneuropathy, & ataxia; can also present as juvenile ALS.	Infancy to early adolescence	Typically associated w/complicated HSP (uncomplicated AR HSP reported rarely)
USP8	SPG59	Uncomplicated HSP	Childhood	Rare

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

VI. 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 four 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.⁴⁰

ALS Association

The ALS Association published information on genetic testing on their website. They state that “With the approval of the first genetically targeted therapy for ALS and the advancement of prevention research, knowing whether you have an ALS-linked gene mutation has become more important.” The guidelines go on to state that “If genetic testing identifies a disease-linked 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.⁴¹

Ataxias (including Friedreich ataxia)

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).”⁴²

Friedreich’s Ataxia Research Alliance (FARA)

The FARA notes genetic diagnostic information on their website.

They state that in “It is important to note that many genetic tests for FA are repeat expansion analyses of the first intron of the *FXN* gene, and thus can only detect abnormal GAA repeat expansions, not the less common point mutations, insertions, or deletions found in about 4% of affected individuals. If genetic testing for a patient with suspected FA returns with a repeat expansion detected on only one allele, further testing that sequences the whole *FXN* gene may be warranted.” “Carrier testing is recommended for anyone with a positive family history of Friedreich ataxia and for partners of known

carriers. Pre-symptomatic testing for at-risk siblings or relatives is available, however, genetic counseling is strongly recommended to assist individuals/families in considering the risks versus benefits of testing a genetic condition with one recently approved treatment that is not available yet globally.”⁴³

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.”⁴⁴

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

“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.”⁴⁴

In 2022, FARA published clinical management guidelines for FA. The guidelines state that “The goal of carrier testing for adult siblings of a person with FRDA is to allow for reproductive planning. The decision to undergo carrier testing should be voluntary and made after appropriate genetic counseling, which should include a review of the autosomal recessive inheritance pattern and natural history of FRDA. Carrier status for FRDA does not in itself confer any medical risk. It should be emphasized to the person undergoing testing that while a carrier for FRDA is healthy, they are at risk of transmitting the *FXN* pathogenic variant to offspring.” Therefore, the guidelines recommend: “Requests for carrier testing by at-risk adult siblings are best managed on a case-by-case basis; there is no evidence to support the routine provision or refusal of carrier testing for Friedreich ataxia.” For immature minors, the guidelines state: “We cannot recommend the routine offer of pre-symptomatic genetic testing over refusal to offer testing for immature minors at risk of Friedreich ataxia. Each situation is unique and should be managed on a case-by-case basis with referral to a team with expertise in pre-symptomatic genetic testing and the related issues.” For mature minors, the guidelines state: “We conditionally recommend testing over refusal of testing for an asymptomatic mature at-risk minor who requests genetic testing for Friedreich ataxia. When a mature minor requests testing, a referral should be made to a team with expertise in pre-

symptomatic genetic testing for Friedreich ataxia and the related issues.” For relatives of a person with FA other than siblings, the guidelines state “Carrier testing should be first undertaken on the closest relative as a negative result means that genetic testing of more distant relatives may not be necessary.”⁴⁵

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.⁴⁶ The guidelines list genes associated with types of ataxia.⁴⁷

Spinocerebellar ataxias:

Type ⁴⁸	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>
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.”⁴⁷

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), *APTX*, *SETX*, *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."⁴⁷

National Ataxia Foundation

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.⁴⁹

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)."

"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)."⁵⁰

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."⁵¹

Hereditary Spastic Paraplegia (HSP)

National Organization for Rare Disorders (NORD)

The 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."⁵²

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."⁵²

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:
 - "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”⁵³

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.⁴⁸ MacLeod et al. (2013) was affirmed by the American Association of Neurology on January 14, 2014.⁵⁴

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.⁵⁵

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.⁵⁶

Spinal Muscular Atrophies (SMA)

218th 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 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.”⁵⁷

“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.”⁵⁷

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. “In patients with a family history of spinal muscular atrophy, molecular testing reports of the affected individual and carrier testing of the related parent should be reviewed, if possible, before testing. If the reports are not available, *SMN1* deletion testing should be recommended for the low-risk partner.” These guidelines were reaffirmed in 2025.⁵⁸

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.”⁵⁹

VII. Applicable State and Federal Regulations

DISCLAIMER: If there is a conflict between this Policy and any relevant, applicable government policy for a particular member [e.g., Local Coverage Determinations (LCDs) or National Coverage Determinations (NCDs) for Medicare and/or state coverage for Medicaid], then the government policy will be used to make the determination. For the most up-to-date Medicare policies and coverage, please visit the Medicare search website: <https://www.cms.gov/medicare-coverage-database/search.aspx>. For the most up-to-date Medicaid policies and coverage, visit the applicable state Medicaid website.

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.

VIII. Applicable CPT/HCPCS Procedure Codes

CPT	CPT Description
81177	ATN1 (atrophin 1) (e.g., dentatorubral-pallidoluysian atrophy) gene analysis, evaluation to detect abnormal (e.g., expanded) alleles
81178	ATXN1 (ataxin 1) (e.g., spinocerebellar ataxia) gene analysis, evaluation to detect abnormal (e.g., expanded) alleles
81179	ATXN2 (ataxin 2) (e.g., spinocerebellar ataxia) gene analysis, evaluation to detect abnormal (e.g., expanded) alleles
81180	ATXN3 (ataxin 3) (e.g., spinocerebellar ataxia, Machado-Joseph disease) gene analysis, evaluation to detect abnormal (e.g., expanded) alleles
81181	ATXN7 (ataxin 7) (e.g., spinocerebellar ataxia) gene analysis, evaluation to detect abnormal (e.g., expanded) alleles
81182	ATXN8OS (ATXN8 opposite strand [non-protein coding]) (e.g., spinocerebellar ataxia) gene analysis, evaluation to detect abnormal (e.g., expanded) alleles
81183	ATXN10 (ataxin 10) (e.g., spinocerebellar ataxia) gene analysis, evaluation to detect abnormal (e.g., expanded) alleles
81184	CACNA1A (calcium voltage-gated channel subunit alpha1 A) (e.g., spinocerebellar ataxia) gene analysis; evaluation to detect abnormal (e.g., expanded) alleles
81185	CACNA1A (calcium voltage-gated channel subunit alpha1 A) (e.g., spinocerebellar ataxia) gene analysis; full gene sequence
81186	CACNA1A (calcium voltage-gated channel subunit alpha1 A) (e.g., spinocerebellar ataxia) gene analysis; known familial variant
81243	FMR1 (fragile X messenger ribonucleoprotein 1) (e.g., fragile X syndrome, X-linked intellectual disability [XLID]) gene analysis; evaluation to detect abnormal (e.g., expanded) alleles
81244	FMR1 (fragile X messenger ribonucleoprotein 1) (e.g., fragile X syndrome, X-linked intellectual disability [XLID]) gene analysis; characterization of alleles (e.g., expanded size and promoter methylation status)

CPT	CPT Description
81271	HTT (huntingtin) (e.g., Huntington disease) gene analysis; evaluation to detect abnormal (e.g., expanded) alleles
81274	HTT (huntingtin) (e.g., Huntington disease) gene analysis; characterization of alleles (e.g., expanded size)
81284	FXN (frataxin) (e.g., Friedreich ataxia) gene analysis; evaluation to detect abnormal (expanded) alleles
81285	FXN (frataxin) (e.g., Friedreich ataxia) gene analysis; characterization of alleles (e.g., expanded size)
81286	FXN (frataxin) (e.g., Friedreich ataxia) gene analysis; full gene sequence
81289	FXN (frataxin) (e.g., Friedreich ataxia) gene analysis; known familial variant(s)
81329	SMN1 (survival of motor neuron 1, telomeric) (e.g., spinal muscular atrophy) gene analysis; dosage/deletion analysis (e.g., carrier testing), includes SMN2 (survival of motor neuron 2, centromeric) analysis, if performed
81343	PPP2R2B (protein phosphatase 2 regulatory subunit Bbeta) (e.g., spinocerebellar ataxia) gene analysis, evaluation to detect abnormal (e.g., expanded) alleles
81344	TBP (TATA box binding protein) (e.g., spinocerebellar ataxia) gene analysis, evaluation to detect abnormal (e.g., expanded) alleles
81400	Molecular pathology procedure, Level 1 (e.g., identification of single germline variant [e.g., SNP] by techniques such as restriction enzyme digestion or melt curve analysis)
81401	Molecular pathology procedure, Level 2 (e.g., 2-10 SNPs, 1 methylated variant, or 1 somatic variant [typically using nonsequencing target variant analysis], or detection of a dynamic mutation disorder/triplet repeat)
81403	Molecular pathology procedure, Level 4 (e.g., analysis of single exon by DNA sequence analysis, analysis of >10 amplicons using multiplex PCR in 2 or more independent reactions, mutation scanning or duplication/deletion variants of 2-5 exons)
81404	Molecular pathology procedure, Level 5 (e.g., analysis of 2-5 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 6-10 exons, or characterization of a dynamic mutation disorder/triplet repeat by Southern blot analysis)
81405	Molecular pathology procedure, Level 6 (e.g., analysis of 6-10 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 11-25 exons, regionally targeted cytogenomic array analysis)
81406	Molecular pathology procedure, Level 7 (e.g., analysis of 11-25 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 26-50 exons)
81407	Molecular pathology procedure, Level 8 (e.g., analysis of 26-50 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of >50 exons, sequence analysis of multiple genes on one platform)
81408	Molecular pathology procedure, Level 9 (e.g., analysis of >50 exons in a single gene by DNA sequence analysis)
81479	Unlisted molecular pathology procedure
0136U	ATM (ataxia telangiectasia mutated) (e.g., ataxia telangiectasia) mRNA sequence analysis (List separately in addition to code for primary procedure) (Use 0136U in conjunction with 81408) Proprietary test: +RNAinsight™ for ATM Lab/Manufacturer: Ambry Genetics

CPT	CPT Description
0231U	CACNA1A (calcium voltage-gated channel subunit alpha 1A) (e.g., spinocerebellar ataxia), full gene analysis, including small sequence changes in exonic and intronic regions, deletions, duplications, short tandem repeat (STR) gene expansions, mobile element insertions, and variants in non-uniquely mappable regions Proprietary test: Genomic Unity® CACNA1A Analysis Lab/Manufacturer: Variantyx Inc
0233U	FXN (frataxin) (e.g., Friedreich ataxia), gene analysis, including small sequence changes in exonic and intronic regions, deletions, duplications, short tandem repeat (STR) expansions, mobile element insertions, and variants in non-uniquely mappable regions Proprietary test: Genomic Unity® FXN Analysis Lab/Manufacturer: Variantyx Inc
0236U	SMN1 (survival of motor neuron 1, telomeric) and SMN2 (survival of motor neuron 2, centromeric) (e.g., spinal muscular atrophy) full gene analysis, including small sequence changes in exonic and intronic regions, duplications and deletions, and mobile element insertions Proprietary test: Genomic Unity® SMN1/2 Analysis Lab/Manufacturer: Variantyx Inc

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Procedure codes appearing in Medical Policy documents are included only as a general reference tool for each policy. They may not be all-inclusive.

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X. Review/Revision History

Effective Date	Summary
02/01/2026	Reviewed and Updated: Updated background, guidelines, and evidence-based scientific references. Literature review did not necessitate any modification to the coverage criteria. The following changes were made for clarity: CC3 and CC17 edited for clarity Note 2 edited to change “2” to “two”: “Note 2: For two or more gene tests being run on the same platform, please refer to AHS-R2162-Reimbursement Policy.”
01/01/2025	Reviewed and Updated: Updated background, guidelines, and evidence-based scientific references. Literature review did not necessitate any modification to

	<p>the coverage criteria. The following changes were made for clarity: Following discussion with our clinical advisory board, Avalon is changing from “genetic counseling is recommended” (only required GC was for Huntington Disease) to requiring genetic counseling for all genetic testing related to neurodegenerative disorders. Results in a new CC1 that is not specific to a neurodegenerative disorder, reads: “1) Genetic counseling IS REQUIRED for individuals prior to and after undergoing genetic testing for diagnostic, carrier, and/or risk assessment purposes.” Results in the removal of former CC10, as GC requirements are now encompassed in CC1: “10) For individuals with a family history of Huntington Disease who are pursuing genetic testing, genetic counseling is REQUIRED.” Reference to M2179 moved from a coverage criterion to the policy description. Results in the deletion of CC17: “17) Preconception carrier screening for SMA is covered in accordance with Avalon Policy AHSM2179-Prenatal Screening (Genetic).” Note 2 was updated to reflect changes to Avalon’s definition of a genetic panel within R2162. Now reads: “Note 2: For 2 or more gene tests being run on the same platform, please refer to AHS-R2162-Reimbursement Policy.” Updated CPT code description for CPT code 81243, 81244, 81406 (annual CPT updates, effective 1/1/2024)</p>
12/01/2024	Initial Policy Implementation