

Hereditary Spastic Paraplegia (HSP) Testing

Panel Gene List:

Comprehensive HSP Panel Gene List: ABCD1, ALDH18A1, ALS2, AP4B1, AP4E1, AP4M1, AP4S1, AP5Z1, ATL1, ATP13A2, B4GALNT1, BSCL2, C12orf65, CYP2U1, CYP7B1, DDHD1, DDHD2, ERLIN2, FA2H, GBA2, GJC2, KIAA0196 (aka WASHC5), KIF1A, KIF1C, KIF5A, L1CAM, NIPA1, NT5C2, PLP1, PNPLA6, REEP1, SACS, SLC16A2, SPAST, SPG7 (aka PGN), SPG11, SPG20, SPG21, TECPR2, TFG, VPS37A, ZFYVE26*

* This panel does not include deletion/duplication analysis of the GJC2 gene.

Uncomplicated HSP Panel Gene List: ALS2, AP5Z1, ATL1, BSCL2, CYP7B1, DDHD1, KIAA0196 (aka WASHC5), KIF1A, KIF5A, NIPA1, PNPLA6, REEP1, SPAST, SPG7

HSP-Related Inborn Errors of Metabolism Gene List (not included in the comprehensive HSP panel except ABCD1): ABCD1, ARG1, ARSA, BTD, CYP27A1, GALC, GBE1, GCH1, MMACHC, MTHFR, OPA3, PTS, SLC19A3, SPR, TH

Clinical Features:

Hereditary spastic paraplegia (HSP) is a group of disorders characterized by axonal degeneration and lower extremity spasticity stiffness and weakness. These disorders are clinically classified as uncomplicated (“pure”) HSP, in which symptoms are confined to lower extremity spasticity, hypertonic bladder and lower limb sensory disturbances, or complicated HSP, which is characterized by additional neurological and non-neurological findings.^{1,2} These findings may include intellectual disability, epilepsy, ataxia, neuropathy, extrapyramidal disturbances, cataracts, vomiting, and dysmorphic features.³ The age of onset of clinical symptoms of HSP ranges from early childhood to late adulthood and some types of HSP exhibit both uncomplicated and complicated forms even within the same family. Symptoms that occur very early in childhood may be non-progressive while later-onset symptoms generally progress over many years.² The prevalence of spastic paraplegias is estimated to be between 1.3-9.6/100,000.²

Genetics:

HSP results from pathogenic variants in genes that encode proteins involved in the development or maintenance of corticospinal tract neurons.³ Spastic paraplegias are inherited in either an autosomal dominant, autosomal recessive, X-linked or mitochondrial (maternal) manner. Some types of HSP demonstrate both autosomal dominant and autosomal recessive inheritance and some genetic types of HSP are associated with both uncomplicated and complicated symptoms.^{4,5,6} Wide clinical variability occurs between and within different types of HSP, even within a family.⁷ A clinical diagnosis of HSP is based on medical and family history,

neurological and neuropsychological evaluations, neuropathological studies, other ancillary testing and exclusion of metabolic disorders with similar clinical presentations.^{2,3} However, clinical evaluation alone may not be sufficient to distinguish the various genetic causes of HSP given their phenotypic and genetic heterogeneity. The HSP panels at GeneDx can assist in confirming a clinical diagnosis, can define the sub-type of HSP and may aid in the development of a comprehensive medical plan including symptom management and recurrence risk assessment.

Test Methods:

Our HSP testing includes a comprehensive HSP panel and a smaller HSP subpanel that includes genes associated primarily with uncomplicated HSP. In addition, an HSP-related inborn errors of metabolism (HSP-IEM) panel is also available to order concurrently or separately if desired, as a number of infantile and childhood onset metabolic disorders present with spastic paraparesis or other similar symptoms. These disorders also have characteristic biochemical findings and/or other neurological, behavioral, eye and skin features, and some of these have specific treatments. The complete list of genes and associated disorders included in the comprehensive HSP panel and HSP-related inborn errors of metabolism panel are in the attached tables.

Using genomic DNA from the submitted specimen, the complete coding regions and splice site junctions of the genes on this panel are enriched using a proprietary targeted capture system developed by GeneDx for next-generation sequencing with CNV calling (NGS-CNV). The enriched targets are simultaneously sequenced with paired-end reads on an Illumina platform. Bi-directional sequence reads are assembled and aligned to reference sequences based on NCBI RefSeq transcripts and human genome build GRCh37/UCSC hg19. After gene specific filtering, data are analyzed to identify sequence variants and most deletions and duplications involving coding exons; however, technical limitations and inherent sequence properties effectively reduce this resolution for some genes. For the *GJC2* gene, sequencing but not deletion/duplication analysis, is performed. Alternative sequencing or copy number detection methods are used to analyze regions with inadequate sequence or copy number data by NGS. Reported clinically significant variants are confirmed by an appropriate orthogonal method. Reportable variants include pathogenic variants, likely pathogenic variants and variants of uncertain significance. Likely benign and benign variants, if present, are not routinely reported but are available upon request.

Clinical Sensitivity:

The technical sensitivity of sequencing is estimated to be > 99% at detecting single nucleotide events. It will not reliably detect deletions greater than 20 base pairs, insertions or rearrangements greater than 10 base pairs, or low-level mosaicism. The copy number assessment methods used with this test cannot reliably detect copy number variants of less

than 500 base pairs or mosaicism and cannot identify balanced chromosome aberrations. Assessment of exon-level copy number events is dependent on the inherent sequence properties of the targeted regions, including shared homology and exon size.

Genes on the Comprehensive HSP Panel:

Gene	Uncomplicated/Complicated	Inheritance	Disease Associations
<i>ABCD1*</i>	Complicated	XL	Adrenoleukodystrophy
<i>ALDH18A1</i> (<i>P5C5</i>)	Complicated	AD/AR	Spastic paraplegia 9A/Spastic paraplegia 9B
<i>ALS2</i>	Uncomplicated/Complicated	AR	Infantile onset hereditary spastic paraplegia (IAHSP)
<i>AP4B1</i>	Complicated	AR	Spastic paraplegia 47
<i>AP4E1</i>	Complicated	AR	Spastic paraplegia 51
<i>AP4M1</i>	Complicated	AR	Spastic paraplegia 50
<i>AP4S1</i>	Complicated	AR	Spastic paraplegia 52
<i>AP5Z1</i>	Uncomplicated/Complicated	AR	Spastic paraplegia 48
<i>ATL1</i>	Uncomplicated/Complicated	AD/AR	Spastic paraplegia 3A/ Hereditary sensory neuropathy type 1D
<i>ATP13A2</i> (<i>PARK9</i>)	Complicated	AR	Spastic paraplegia 78
<i>B4GALNT1</i>	Complicated	AR	Spastic paraplegia 26
<i>BSCL2</i>	Uncomplicated/Complicated	AD/AR	Spastic paraplegia 17/Silver syndrome/ Distal hereditary motor neuropathy, type V (dHMNV)/ Congenital generalized lipodystrophy, type 2/ Progressive encephalopathy with lipodystrophy (PELD)
<i>C12orf65</i>	Complicated	AR	Spastic paraplegia 55/ Combined oxidative phosphorylation deficiency 7 (COXPD7)
<i>CYP2U1</i>	Complicated	AR	Spastic paraplegia 56

Gene	Uncomplicated/Complicated	Inheritance	Disease Associations
<i>CYP7B1</i>	Uncomplicated/Complicated	AR	Spastic paraplegia 5A
<i>DDHD1</i>	Uncomplicated/Complicated	AR	Spastic paraplegia 28
<i>DDHD2</i>	Complicated	AR	Spastic paraplegia 54
<i>ERLIN2</i>	Complicated	AD/AR	Spastic paraplegia 18
<i>FA2H</i>	Complicated	AR	Spastic paraplegia 35
<i>GBA2</i>	Complicated	AR	Spastic paraplegia 46
<i>GJC2**</i>	Complicated	AD/AR	Spastic paraplegia 44/ Hypomyelinating leukodystrophy-2 (HLD2)/ Hereditary lymphedema type 1C (LMPH1C)
<i>KIAA0196</i> (<i>WASHC5</i>)	Uncomplicated	AD/AR	Spastic paraplegia 8/ Ritscher-Schinzel syndrome- developmental malformation syndrome (3C syndrome)
<i>KIF1A</i>	Uncomplicated/Complicated	AD/AR	Spastic paraplegia 30/Hereditary sensory neuropathy type IIC (HSN2C)
<i>KIF1C</i>	Complicated	AR	Spastic paraplegia 58/Spastic ataxia 2
<i>KIF5A</i>	Uncomplicated/Complicated	AD	Spastic paraplegia 10, Neonatal intractable myoclonus (NEIMY)
<i>L1CAM</i>	Complicated	XL	Spastic paraplegia 1 /MASA syndrome/ X-linked aqueductal stenosis
<i>NIPA1</i>	Uncomplicated/Complicated	AD	Spastic paraplegia 6
<i>NT5C2</i>	Complicated	AR	Spastic paraplegia 45
<i>PLP1</i>	Complicated	XL	Spastic paraplegia 2/Pelizaeus-Merzbacher disease (PMD)
<i>PNPLA6</i>	Uncomplicated/Complicated	AR	Spastic paraplegia 39/ Boucher-Neuhauser syndrome (BNHS)
<i>REEP1</i>	Uncomplicated/Complicated	AD	Spastic paraplegia 31/ Distal hereditary motor neuropathy,

Gene	Uncomplicated/Complicated	Inheritance	Disease Associations
			type VB (dHMN VB)
SACS	Complicated	AR	AR spastic ataxia of Charlevoix-Saguenay (ARSACS)
SLC16A2	Complicated	XL	Spastic paraplegia 22 (Allan-Herndon-Dudley syndrome)
SPAST	Uncomplicated/Complicated	AD	Spastic paraplegia 4
SPG7 (PGN)	Uncomplicated/Complicated	AR	Spastic paraplegia 7
SPG11 (KIAA1840)	Complicated	AR	Spastic paraplegia 11/ Juvenile amyotrophic lateral sclerosis type 5 (ALS5)
SPG20	Complicated	AR	Spastic paraplegia 20 (Troyer syndrome)
SPG21 (ACP33)	Complicated	AR	Spastic paraplegia 21 (Mast syndrome)
TECPR2	Complicated	AR	Spastic paraplegia 49
TFG	Complicated	AR	Spastic paraplegia 57
VPS37A	Complicated	AR	Spastic paraplegia 53
ZFYVE26	Complicated	AR	Spastic paraplegia 15

*For patients with previous biochemical testing indicative of X-linked adrenoleukodystrophy, single gene testing for the ABCD1 gene is available.

**Deletion/duplication testing of the GJC2 gene is not included

Genes on the HSP-IEM Panel:

Gene	Inheritance	Disease Associations
ABCD1*	XL	Adrenoleukodystrophy
ARG1	AR	Arginase deficiency
ARSA	AR	Metachromatic leukodystrophy
BTD	AR	Biotinidase Deficiency
CYP27A1	AR	Cerebrotendinous xanthomatosis
GALC	AR	Krabbe disease
GBE1	AR	Adult polyglucosan body neuropathy (APBN)/ Glycogen

Gene	Inheritance	Disease Associations
		storage disease IV
<i>GCH1</i>	AD/AR	GTPCH related DOPA-responsive dystonia (DRD)/ GTP cyclohydrolase deficiency
<i>MMACHC</i>	AR	Methylmalonic aciduria and homocystinuria cblC type
<i>MTHFR</i>	AR	Methylenetetrahydrofolate reductase
<i>OPA3</i>	AD/AR	Optic atrophy 3 with cataracts/ OPA3-related 3-Methylglutaconic aciduria
<i>PTS</i>	AR	6-Pyruvoyl-tetrahydrobiopterin synthase deficiency
<i>SLC19A3</i>	AR	Biotin-thiamine-responsive basal ganglia disease
<i>SPR</i>	AR	Dopa-responsive dystonia due to sepiapterin reductase deficiency
<i>TH</i>	AR	Tyrosine hydroxylase deficiency/Segawa syndrome

*For patients with previous biochemical testing indicative of X-linked adrenoleukodystrophy, single gene testing for the *ABCD1* gene is available.

References:

1. Lo Giudice et al. (2014) *Exp Neurol* 25: 518-39.
2. Fink JK (2014) *Semin Neurol* 34: 293-305.
3. Finsterer et al. (2012) *J Neurol Sci* 318 (1-2): 1-18.
4. Tesson et al. (2015) *Hum. Genet.* 134 (6):511-38.
5. de Souza et al. (2017) *Cerebellum* 16 (2):525-551.
6. Fink JK (2013) *Acta Neuropathol* 126(3): 307-328.
7. Fink JK. Hereditary Spastic Paraplegia Overview. 2000 Aug 15 [Updated 2014 Feb 6]. In: Pagon RA, Adam MP, Ardinger HH, et al., editors. *GeneReviews*® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2014. Available from: <http://www.ncbi.nlm.nih.gov/books/NBK1509/>