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

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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 *ABCD1* gene, deletion/duplication analysis is performed by multiplex ligation-dependent probe amplification (MLPA). 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. 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.

Test 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
*ABCD1**	Complicated	XL	Adrenoleukodystrophy
ALDH18A1 (P5C5)	Complicated	AD/AR	Spastic paraplegia 9A/Spastic paraplegia 9B
ALS2	Uncomplicated/Complicated	AR	Infantile onset hereditary spastic paraplegia (IAHSP)
AP4B1	Complicated	AR	Spastic paraplegia 47
AP4E1	Complicated	AR	Spastic paraplegia 51
AP4M1	Complicated	AR	Spastic paraplegia 50
AP4S1	Complicated	AR	Spastic paraplegia 52
AP5Z1	Uncomplicated/Complicated	AR	Spastic paraplegia 48
ATL1	Uncomplicated/Complicated	AD/AR	Spastic paraplegia 3A/ Hereditary sensory neuropathy type 1D
ATP13A2 (PARK9)	Complicated	AR	Spastic paraplegia 78
B4GALNT1	Complicated	AR	Spastic paraplegia 26
BSCL2	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)
C12orf65	Complicated	AR	Spastic paraplegia 55/ Combined oxidative phosphorylation deficiency 7 (COXPD7)
CYP2U1	Complicated	AR	Spastic paraplegia 56

Gene	Uncomplicated/Complicated	Inheritance	Disease Associations
CYP7B1	Uncomplicated/Complicated	AR	Spastic paraplegia 5A
DDHD1	Uncomplicated/Complicated	AR	Spastic paraplegia 28
DDHD2	Complicated	AR	Spastic paraplegia 54
ERLIN2	Complicated	AR	Spastic paraplegia 18
FA2H	Complicated	AR	Spastic paraplegia 35
GBA2	Complicated	AR	Spastic paraplegia 46
*GJC2***	Complicated	AD/AR	Spastic paraplegia 44/ Hypomyelinating leukodystrophy-2 (HLD2)/ Hereditary lymphedema type 1C (LMPH1C)
KIAA0196 (*WASHC5*)	Uncomplicated	AD/AR	Spastic paraplegia 8/ Ritscher-Schinzel syndrome-developmental malformation syndrome (3C syndrome)
KIF1A	Uncomplicated/Complicated	AD/AR	Spastic paraplegia 30/Hereditary sensory neuropathy type IIC (HSN2C)
KIF1C	Complicated	AR	Spastic paraplegia 58/Spastic ataxia 2
KIF5A	Uncomplicated/Complicated	AD	Spastic paraplegia 10, Neonatal intractable myoclonus (NEIMY)
L1CAM	Complicated	XL	Spastic paraplegia 1 /MASA syndrome/ X-linked aqueductal stenosis
NIPA1	Uncomplicated/Complicated	AD	Spastic paraplegia 6
NT5C2	Complicated	AR	Spastic paraplegia 45
PLP1	Complicated	XL	Spastic paraplegia 2/Pelizaeus-Merzbacher disease (PMD)
PNPLA6	Uncomplicated/Complicated	AR	Spastic paraplegia 39/ Boucher-Neuhauser syndrome (BNHS)
REEP1	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
GCH1	AD/AR	GTPCH related DOPA-responsive dystonia (DRD)/ GTP cyclohydrolase deficiency
MMACHC	AR	Methylmalonic aciduria and homocystinuria cblC type
MTHFR	AR	Methylenetetrahydrofolate reductase
OPA3	AD/AR	Optic atrophy 3 with cataracts/ OPA3-related 3-Methylglutaconic aciduria
PTS	AR	6-Pyruvoyl-tetrahydrobiopterin synthase deficiency
SLC19A3	AR	Biotin-thiamine-responsive basal ganglia disease
SPR	AR	Dopa-responsive dystonia due to sepiapterin reductase deficiency
TH	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:

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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/