Hereditary Spastic Paraplegia (HSP) Panel

PANEL GENE LIST

Comprehensive HSP Panel Gene List: ABCD1, ACO2, ADCY5, ALDH18A1, ALDH3A2*, ALS2, AMPD2, AP4B1, AP4E1, AP4M1, AP4S1, AP5Z1, ARG1, ARL6IP1, ARSA, ATL1, ATP13A2, B4GALNT1, BSCL2, BTD, C12orf65, C19orf12, CYP27A1, CYP2U1, CYP7B1, DDHD1, DDHD2, ENTPD1*, ERLIN1, ERLIN2, EXOSC3*, FA2H, FAR1*, FARS2, GALC, GBA2, GBE1, GCH1, GJA1*, GJC2*, IBA57, IFIH1*, KIAA0196 (aka WASHC5), KIF1A, KIF1C, KIF5A, L1CAM, MMACHC, MTHFR, NFU1*, NIPA1, NT5C2, OPA3, PEX16*, PLA2G6, PLP1, PNPLA6, POLR3A, PTS, RAB3GAP2, REEP1, REEP2, RNASEH2B*, SACS, SERAC1*, SLC16A2, SLC19A3, SLC25A15*, SLC33A1, SPAST, SPG7 (aka PGN), SPG11, SPG20, SPG21, SPR, TECPR2, TFG, TH, TUBB4A, UCHL1, VPS37A, VPS53*, ZFYVE26*

**Sequence analysis only of the ACO2, ALDH3A2, ENTPD1, EXOSC3, FAR1, GJA1,GJC2, IFIH1, NFU1, PEX16, RNASEH2B, SERAC1, SLC25A15, and VPS53 genes*

CLINICAL FEATURES

Hereditary spastic paraplegia (HSP) comprises a diverse group of neurodegenerative disorders characterized by progressive lower limb spasticity 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 Comprehensive HSP panel 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

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. Alternative sequencing or copy number detection methods are used to analyze or confirm 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. 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. For the *ACO2, ALDH3A2, ENTPD1, EXOSC3, FAR1, GJA1, GJC2, IFIH1, NFU1, PEX16, RNASEH2B, SERAC1, SLC25A15,* and *VPS53* genes, sequencing but not deletion/duplication analysis, is performed.

CLINICAL SENSITIVITY

The comprehensive HSP panel includes genes associated with uncomplicated and complicated forms of HSP alongside HSP-related inborn errors of metabolism (HSP-IEM). These disorders also have characteristic biochemical findings and/or other neurological, behavioral, eye and skin features, and some of these have specific treatments. See table below for a complete list of genes and associated disorders included in the comprehensive HSP panel.

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Gene	Inheritance	Disease Associations	Diagnostic Yield in Selected Population(s)
*ABCD1**	XL	Adrenoleukodystrophy	Rare[1,2,3,4]
*ACO2***	AR	Optic atrophy 9/Infantile cerebellar-retinal degeneration	Rare[76,77,78,79]
ADCY5	AD/AR	ADCY5-related dyskinesia/ ADCY5_related disorders	Rare[80,81]
ALDH18A1 (P5C5)	AD/AR	Spastic paraplegia 9A/Spastic paraplegia 9B	Rare[5]
*ALDH3A2***	AR	Sjogren-Larsson syndrome	Rare; most common in people of Swedish ancestry[82]
ALS2	AR	Infantile onset hereditary spastic paraplegia (IAHSP)	Rare in IAHSP[6,7,8,9]
AMPD2	AR	Spastic paraplegia 63	Rare[83]
AP4B1	AR	Spastic paraplegia 47	Rare[10,11]
AP4E1	AR	Spastic paraplegia 51	Rare[12,13,14]
AP4M1	AR	Spastic paraplegia 50	Rare[14,15]
AP4S1	AR	Spastic paraplegia 52	Rare[13]
AP5Z1	AR	Spastic paraplegia 48	Rare[16,17,18,19]
ARG1	AR	Arginase deficiency	Rare[84,85]
ARL6IP1	AR	Spastic paraplegia 61	Rare[86,87]
ARSA	AR	Metachromatic leukodystrophy	Rare[88]

Gene	Inheritance	Disease Associations	Diagnostic Yield in Selected Population(s)
ATL1	AD/AR	Spastic paraplegia 3A/ HSN type ID;	Unknown in HSAN[24]; 10-15% of AD HSP and 80% of early onset AD HSP[82]
ATP13A2 (PARK9)	AR	Spastic paraplegia 78	Rare[26]
B4GALNT1	AR	Spastic paraplegia 26	Rare[27]
BSCL2	AD/AR	Spastic paraplegia 17/Silver syndrome/ Distal hereditary motor neuropathy, type V (dHMNV)/ Congenital generalized lipodystrophy, type 2/ Progressive encephalopathy with lipodystrophy (PELD)	Rare in HSP and dHMN[28] ; AR for CGL2[29] and PELD[30]
BTD	AR	Biotinidase deficiency	Rare[89]
C12orf65	AR	Spastic paraplegia 55/ Combined oxidative phosphorylation deficiency 7 (COXPD7)	Rare[31]; Rare for COXPD7[32]
C19orf12	AD/AR	Spastic paraplegia 43/Mitochondrial membrane protein-associated neurodegeneration (MPAN)	Rare in HSP[90,91] and MPAN[92]
CYP27A1	AR	Cerebrotendinous xanthomatosis	Rare[93]
CYP2U1	AR	Spastic paraplegia 56	Rare[33]
CYP7B1	AR	Spastic paraplegia 5A	Accounts for ~5% of familial and 8% of sporadic AR HSP[20]
DDHD1	AR	Spastic paraplegia 28	Rare[33]
DDHD2	AR	Spastic paraplegia 54	Rare[34,35]
*ENTPD1***	AR	Spastic paraplegia 64	Rare[94,54]
ERLIN1	AR	Spastic paraplegia 62	Rare[95]
ERLIN2	AD/AR	Spastic paraplegia 18	Rare[36,37]
*EXOSC3***	AR	Pontocerebellar hypoplasia type 1/spastic paraplegia with cerebellar features	Rare[96,97]
FA2H	AR	Spastic paraplegia 35	Rare[38,39]
*FAR1***	AD/AR	Peroxisomal fatty acyl-CoA reductase 1 disorder	Rare[98,99]
FARS2	AR	Spastic paraplegia 77	Rare[100, 101, 102]
GALC	AR	Krabbe disease	Founder mutations in Dutch and European population[103, 104]; ~45% from 30-kb deletion[105]; Italian founder mutation[106]
GBA2	AR	Spastic paraplegia 46	Rare[40,41]
GBE1	AR	Adult polyglucosan body neuropathy (APBN)/ Glycogen storage disease IV	Rare[107]
GCH1	AD/AR	GTPCH related DOPAresponsive dystonia (DRD)/ GTP cyclohydrolase deficiency	Rare[108]
*GJA1***	AD/AR	Spastic paraplegia with brain hypomyelination	Rare[109]
*GJC2***	AD/AR	Spastic paraplegia 44/ Hypomyelinating leukodystrophy-	Rare for HSP[42]

Gene	Inheritance	Disease Associations	Diagnostic Yield in Selected Population(s)
		2 (HLD2)/ Hereditary lymphedema type 1C (LMPH1C)	
IBA57	AR	Spastic paraplegia 74	Rare[110]
*IFIH1***	AD	Aicardi-Goutieres syndrome 7/Singleton-Merten syndrome 1	Rare[111,112]
KIAA0196 (*WASHC5*)	AD/AR	Spastic paraplegia 8/ RitscherSchinzel syndromedevelopmental malformation syndrome (3C syndrome)	Rare[43,44]; Founder mutations in First Nations population in northern Manitoba associate with AR Ritscher-Schinzel syndrome[45]
KIF1A	AD/AR	Spastic paraplegia 30/Hereditary sensory neuropathy type IIC (HSN2C)	Rare for HSP[46,47,48]; Rare for HSN2C[49]
KIF1C	AR	Spastic paraplegia 58/Spastic ataxia 2	Rare[50,51]
KIF5A	AD	Spastic paraplegia 10, Neonatal intractable myoclonus (NEIMY)	Accounts for ~ 3% of familial HSP[20]; Accounts for 10% of complicated HSP in French European population[52]
L1CAM	XL	Spastic paraplegia 1 /MASA syndrome/ X-linked aqueductal stenosis	Accounts for ~1% of familial HSP[20]
MMACHC	AR	Methylmalonic aciduria and homocystinuria cblC type	Rare[113,114]
MTHFR	AR	Methylenetetrahydrofolate reductase	Rare[115]
*NFU1***	AR	Multiple mitochondrial dysfunctions syndrome 1	Rare[116]
NIPA1	AD	Spastic paraplegia 6	Rare[53]
NT5C2	AR	Spastic paraplegia 45	Rare[54]
OPA3	AD/AR	Optic atrophy 3 with cataracts/ OPA3-related 3-Methylglutaconic aciduria	Rare[117, 118]
*PEX16***	AR	Zellweger spectrum disorder	~1% of ZSD attributed to variants in this gene[119]
PLA2G6	AR	PLA2G6-Associated Neurodegeneration	Rare[120]
GBA2	AR	Spastic paraplegia 46	Rare[40,41]
GBE1	AR	Adult polyglucosan body neuropathy (APBN)/ Glycogen storage disease IV	Rare[107]
GCH1	AD/AR	GTPCH related DOPAresponsive dystonia (DRD)/ GTP cyclohydrolase deficiency	Rare[108]
*GJA1***	AD/AR	Spastic paraplegia with brain hypomyelination	Rare[109]

Gene	Inheritance	Disease Associations	Diagnostic Yield in Selected Population(s)
*GJC2***	AD/AR	Spastic paraplegia 44/ Hypomyelinating leukodystrophy-2 (HLD2)/ Hereditary lymphedema type 1C (LMPH1C)	Rare for HSP[42]
IBA57	AR	Spastic paraplegia 74	Rare[110]
*IFIH1***	AD	Aicardi-Goutieres syndrome 7/Singleton-Merten syndrome 1	Rare[111,112]
KIAA0196 (*WASHC5*)	AD/AR	Spastic paraplegia 8/ RitscherSchinzel syndromedevelopmental malformation syndrome (3C syndrome)	Rare[43,44]; Founder mutations in First Nations population in northern Manitoba associate with AR Ritscher-Schinzel syndrome[45]
KIF1A	AD/AR	Spastic paraplegia 30/Hereditary sensory neuropathy type IIC (HSN2C)	Rare for HSP[46,47,48]; Rare for HSN2C[49]
KIF1C	AR	Spastic paraplegia 58/Spastic ataxia 2	Rare[50,51]
PLP1	XL	Spastic paraplegia 2/PelizaeusMerzbacher disease (PMD)	Rare[55]
PNPLA6	AR	Spastic paraplegia 39/ BoucherNeuhauser syndrome (BNHS)	Rare for HSP[56,57]; Rare for BNHS[57,58]
POLR3A	AR	Spastic ataxia	Rare[121, 122]
PTS	AR	6-Pyruvoyl-tetrahydrobiopterin synthase deficiency	Rare[123]
RAB3GAP2	AR	Spastic paraplegia 69/ Warburg micro syndrome/ Martsolf syndrome	Accounts for ~11% of RAB18 deficiency[124]
REEP1	AD	Spastic paraplegia 31/ Distal hereditary motor neuropathy, type VB (dHMN VB)	Accounts for ~5% of familial HSP[20]; Rare with dHMN[59]
REEP2	AD/AR	Spastic paraplegia 72	Rare[125,126]
*RNASEH2B***	AD	Aicardi-Goutieres syndrome/ Spastic paraplegia with leukodystrophy	Rare[111]
SACS	AR	AR spastic ataxia of Charlevoix-Saguenay (ARSACS)	Founder mutations in French Canadian[60], Dutch[61], and Belgian populations[62]. Only gene associated with AR spastic ataxia

Gene	Inheritance	Disease Associations	Diagnostic Yield in Selected Population(s)
			of Charlevoix-Saguenay (ARSACS)
*SERAC1***	AR	Methylglutaconic aciduria, deafness, encephalopathy Leighlike syndrome (MEGDEL)/ Oligosystemic juvenile-onset spastic paraplegia	Rare[127]
SLC16A2	XL	Spastic paraplegia 22 (AllanHerndon-Dudley syndrome)	Rare[63,64]
SLC19A3	AR	Biotin-thiamine-responsive basal ganglia disease	Rare[128]
*SLC25A15***	AR	Hyperornithinemiahyperammonemiahomocitrullinemia syndrome	Rare[129,84]
SLC33A1	AD/AR	Spastic paraplegia 42/ Congenital cataracts, hearing loss, and neurodegeneration	Rare[130, 131]
SPAST	AD	Spastic paraplegia 4	~40% of familial HSP; ~20% of sporadic HSP[20]
SPG7 (PGN)	AR/AD	Spastic paraplegia 7	Accounts for ~2% of familial and ~9% of sporadic HSP[20]
SPG11 (KIAA1840)	AR	Spastic paraplegia 11/ Juvenile amyotrophic lateral sclerosis type 5 (ALS5)	Accounts for ~6% of familial and ~7% of sporadic HSP[20]; ~20% of AR HSP[65]; Accounts for ~40% of AR juvenile ALS[66]
SPG20	AR	Spastic paraplegia 20 (Troyer syndrome)	Founder mutation in Amish population[67]
SPG21 (ACP33)	AR	Spastic paraplegia 21 (Mast syndrome)	High frequency in Old Order Amish[68]; otherwise rare[69]
SPR	AR	Dopa-responsive dystonia due to sepiapterin reductase deficiency	Rare[132]
TECPR2	AR	Spastic paraplegia 49	Rare[70]
TFG	AR/AD	Spastic paraplegia 57	Rare[71,72,73,74]
TH	AR	Tyrosine hydroxylase deficiency/Segawa syndrome	Rare[133, 134]
TUBB4A	AD	Torsion dystonia 4/ Hypomyelinating Leukodystrophy 6	Rare[135,136]
UCHL1	AR	Spastic paraplegia 79	Rare[137,138]
VPS37A	AR	Spastic paraplegia 53	Rare[75]
*VPS53***	AR	Progressive cerebello-cerebral atrophy	Rare[139]
ZFYVE26	AR	Spastic paraplegia 15	Accounts for ~1% of familial HSP[20]; ~4% of AR HSP[52]

*For patients with previous biochemical testing indicative of X-linked adrenoleukodystrophy, single gene testing for the ABCD1 gene is available.
**Deletion/duplication testing of these genes is not included

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