

HEREDITARY SPASTIC PARAPLEGIA

Hereditary spastic paraplegias (HSPs) comprise a genetically and clinically heterogeneous group of neurodegenerative disorders characterized by lower limb spasticity and weakness with hyperreflexia and extensor plantar responses. HSP is estimated to affect 1 in 20,000 individuals in the European population, and can also occur in individuals of other ethnic backgrounds. Clinically, HSPs can be divided into two main groups: uncomplicated (pure) and complicated (complex) forms. Pure HSPs are characterized by spasticity in the lower limbs; whereas complex HSPs are characterized by the presence of additional neurological or non-neurological features. The age of symptom onset, rate of symptom progression, and extent of disability are variable both within and between HSP families.

GENETICS

The genetics of HSP are complex and different modes of inheritance (autosomal dominant, autosomal recessive and X-linked recessive) have been described. The three targeted Next-Generation Sequencing (NGS) panels at our laboratory include genes associated with all modes of inheritance (see table below).

BEFORE MOLECULAR TESTING

For a patient where a clinical diagnosis of HSP is suspected, the following tests should be undertaken first, to exclude other causes:

1. An MRI of the brain and spinal cord to rule out structural causes of progressive spasticity
2. Biochemical testing of Vitamin B12, Vitamin E, very long chain fatty acids, lysosomal work-up, plasma amino acids and serum lipoprotein analysis

If the above tests are negative, proceed with molecular testing for HSP.

WHO SHOULD BE TESTED?

- Individuals clinically suspected of being affected with HSP
- The relatives of a proband with identified pathogenic variant(s) in an HSP-associated gene
- Pregnancies at increased risk due to a family history of HSP

TEST METHODS

- Complete sequencing of the coding region and flanking intron/exon boundaries of the genes listed below. This is done via NGS of the targeted gene panels. Testing can be requested for one, two or all three panels based on the suspected mode of inheritance. Please refer to our "A Guide to Next-Generation Sequencing" information sheet available on our website, for further details.
- Exon targeted dosage analysis is available using an oligonucleotide microarray platform.

INTERPRETATION OF TEST RESULTS

Genetic testing may reveal one or more variants in the HSP genes, which should be interpreted in the context of the suspected inheritance pattern, clinical findings, family history and other experimental data.

Please refer to our "A Guide to Interpreting Sequence Variations" information sheet available on our website, for further details.

For More Information

Spastic Paraplegia Foundation

<http://www.sp-foundation.org/>
1-877-773-4483

GeneReviews: HSP

<http://www.ncbi.nlm.nih.gov/books/NBK1509/>

SickKids Genomic Diagnostics Laboratory:

www.sickkids.ca/genome-diagnostics

To locate a genetics center near you:

Canadian Association of Genetic Counsellors (CAGC):
<http://www.cagc-accg.ca>

National Society of Genetic Counselors (NSGC):
<http://www.nsgc.org>



1. Current molecular testing may not detect all possible mutations for this disease. A negative test does not rule out the possibility of HSP.

2. The clinical course or severity of symptoms cannot be predicted by molecular analysis.

3. Test results should be interpreted in the context of clinical findings, family history and other laboratory data.

4. This test was developed and its performance characteristics validated by the Molecular Genetics Laboratory at the Hospital for Sick Children. It has not been cleared or approved by the U.S. Food and Drug Administration. The FDA has determined that such clearance or approval is not necessary. This test is used for clinical purposes.

Panel (version 2)	Genes
Autosomal Recessive (34 genes)	ALDH18A1, ALS2, AP4B1, AP4E1, AP4M1, AP4S1, AP5Z1, C10orf2, C12orf12, CYP2U1, CYP7B1, DDHD1, DDHD2, ENTPD1, ERLIN1, ERLIN2, FA2H, GBA2, GJC2, KIF1A, KIF1C, NT5C2, PGAP1, PNPLA6, POLG, SACS, SPG11, SPG20, SPG21, SPG7, TECPR2, VPS37A, ZFYVE26
Autosomal Dominant (15 genes)	ALDH18A1, ATL1, BSCL2, C10orf2, HSPD1, KIAA0196, KIF5A, NIPA1, POLG, POLG2, REEP1, SPAST, RTN2, SLC33A1, SETX
X-Linked Recessive (3 genes)	L1CAM, PLP1, SLC16A2