



## Hereditary Spastic Paraplegia Exome Panel

### Hereditary Spastic Paraplegia Overview

Hereditary spastic paraplegia (HSP) is a clinically and genetically heterogeneous group of neurodegenerative disorders, characterized by progressive spasticity and weakness of the lower extremities due to pyramidal tract dysfunction (1). HSP can be associated with brisk reflexes, extensor plantar reflexes, and urinary urgency (2). Clinically, HSP can be classified as “complicated” or “complex” if the patient presents with other neurological and systemic features in addition to HSP, such as ataxia, dystonia, intellectual disability, dementia, optic atrophy, retinitis pigmentosa, epilepsy, muscular atrophy, deafness, ichthyosis, and short stature (1, 3). HSP can be classified as pure or uncomplicated if no additional findings are present (2). Age of onset of HSP can range from early childhood to late adulthood. In early onset cases spasticity is typically more prominent than muscle weakness, and motor delays may be observed (3). For later onset cases, muscle weakness may be more marked, and symptoms may progress more rapidly compared to early onset cases (3). HSP has been estimated to have a prevalence of 1-10 individuals per 100,000 (4).

### Hereditary Spastic Paraplegia Etiology

HSP is a highly genetically heterogeneous group of disorders (4). A significant proportion of HSP is inherited in an autosomal dominant manner, and the majority of dominant HSP is classified as uncomplicated or pure HSP (2). There are also numerous genes associated with autosomal recessive HSP. X-linked and mitochondrial inheritance can also be observed in HSP.

### Clinical Utility of Genetic Testing for Hereditary Spastic Paraplegia

Genetic testing for HSP can present challenges, due to the wide clinical and genetic heterogeneity that exists. Determining the molecular basis of disease using genetic testing can be useful in predicting prognosis and disease course, and can aid in identification of at-risk family members. Utilizing whole exome sequencing technology for the Hereditary Spastic Paraplegia Exome Panel test allows us to have a dynamic gene list that can be updated regularly as new genes are identified.

## The Hereditary Spastic Paraplegia Exome Panel includes analysis of 60 genes

The Hereditary Spastic Paraplegia Exome Panel involves analysis of exome sequencing data in a predefined set of 60 genes associated with hereditary spastic paraplegia (HSP). This includes genes associated with uncomplicated HSP, as well as genes associated with syndromes for which spastic paraplegia is a commonly observed feature in affected individuals (complicated HSP). Age of onset of symptoms for the included genes ranges from early childhood to late adulthood.

*For a complete list of the 60 genes analyzed, please visit our website at [dnatesting.uchicago.edu](http://dnatesting.uchicago.edu)*

### Testing Analysis

Of the thousands of variants identified by whole exome sequencing, a list of variants that are located within in a predefined set of 60 genes that have been associated with HSP is generated. The list of 60 genes has been carefully compiled by review of the scientific literature on the genetics of HSP. For cases without a clearly pathogenic variant identified in the predefined list of HSP genes, an additional analysis of previously reported pathogenic variants and truncating variants in known disease genes (present in the HGMD database) will be performed. For variants outside of the predefined list of 60 genes, only those considered to be the likely cause of the patient’s phenotype will be reported. Most of the variants that are identified as part of whole exome sequencing will not undergo interpretation by a laboratory staff member. Only those variants considered to be potentially relevant to the patient’s condition are reviewed by a team of Board-Certified PhD geneticists, MD

geneticists, and genetic counselors who will determine the likelihood of the variant being related to the patient's disorder based on the phenotypic information provided by the ordered clinician.

### **Test methods:**

Whole exome sequencing is performed using the Agilent SureSelect Clinical Research Exome kit that is designed to target the exome with greater coverage of known disease-associated genes. Sequencing is performed using Illumina technology and reads are aligned to the reference sequence. Approximately 97-98% of exons in the genes of interest are targeted at a minimum depth of 10X in the diagnostic Dystonia Exome panel. Our analytical pipeline presents variants in only the preselected 60 genes implicated in dystonia. Variants are identified and evaluated using a custom collection of bioinformatic tools and comprehensively interpreted by our team of directors and genetic counselors. All pathogenic and likely pathogenic variants are confirmed by Sanger sequencing. Certain types of mutations will not be detected by this test, including trinucleotide repeat expansions. In some cases, exome sequencing data may be used to detect larger copy number variations (CNVs) such as whole or partial gene deletions/duplications. The sensitivity of exome sequencing to detect intragenic deletions/duplications >20bp in size is not currently known.

### **Reporting Results**

Typically only variants that occur in genes within the pre-defined set of HSP-associated genes will be reported. Mutations in genes unrelated to the individual's reported phenotype are considered secondary or incidental findings. Secondary or incidental findings will not be interrogated or reported in the Hereditary Spastic Paraplegia Exome Panel. Results, along with an interpretive report, will be faxed to the referring physician. Additional reports will be provided as requested. All abnormal results will be reported by telephone.

### **Required Forms:**

- Movement Disorder Exome Panel Test Requisition Form
- Completed Clinical Checklist
- Completed Consent Form

### **Hereditary Spastic Paraplegia Exome Panel**

Sample specifications:	3 to 10 cc of blood in a purple top (EDTA) tube
Cost:	\$3000
CPT codes:	81415
Turn-around time:	6 weeks

**Note: We do not bill insurance directly for this specific test**

***For more information about our testing options, please visit our website at [dnatesting.uchicago.edu](http://dnatesting.uchicago.edu) or contact us at 773-834-0555.***

### **Re-analysis**

As new gene discoveries and associations are reported in the literature, we can review past cases for findings in these genes. Re-analysis of exome sequencing data is available upon request.

### **References:**

1. Faber I, Servelhere KR, Martinez AR et al. Clinical features and management of hereditary spastic paraplegia. Arq Neuropsiquiatr 2014; 72: 219-226.
2. Depienne C, Stevanin G, Brice A et al. Hereditary spastic paraplegias: an update. Curr Opin Neurol 2007; 20: 674-680.
3. Harding AE. Classification of the hereditary ataxias and paraplegias. Lancet 1983; 1: 1151-1155.
4. Fink JK. Hereditary spastic paraplegia: clinico-pathologic features and emerging molecular mechanisms. Acta Neuropathol 2013; 126: 307-328.

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