THE UNIVERSITY OF CHICAGO | Genetic Services Laboratories

Dystonia Exome

Dystonia Overview

Dystonia is a rare movement disorder associated with abnormal movements and/or postures, caused by sustained or intermittent involuntary muscle contractions (1). Age of onset can vary from infancy to late-adulthood. Dystonic movements are typically patterned or twisting, and may be tremulous (1). In some patients, dystonia symptoms may be paroxysmal or have a temporal pattern (1). Dystonia may be generalized, or limited to specific regions of the body (focal, segmental, multifocal, or hemidystonia); cervical dystonia and eye-lid dystonia (blepharospasm) are two of the most common forms of adult-onset focal dystonia (2). Compared to individuals with adult-onset dystonia, childhood-onset dystonia is more often generalized (3). Dystonia can be classified as "isolated" if dystonia is the only motor feature other than tremor, "combined" if other movement disorders such as myoclonus or parkinsonism are also present, or "complex" if dystonia is one of a number of disease manifestations (1, 2).

Dystonia Etiology

Dystonia can be associated with a wide range of inherited or acquired etiologies. Acquired causes of dystonia can include brain injury, infections, teratogenic exposures, neoplasms, and vascular abnormalities such as arteriovenous malformations (1). Some individuals with dystonia have an associated structural brain abnormality, particularly those with hemidystonia (4). Inherited forms of dystonia show a high degree of genetic and clinical heterogeneity (3). An estimated 20% of patients with adult-onset dystonia have a positive family history for the disorder, indicating a likely genetic etiology (2). However, as pathogenic variants can arise *de novo*, a lack of a family history does not exclude a genetic etiology. Hereditary forms of isolated or combined dystonia are most commonly inherited in an autosomal dominant manner, however autosomal recessive, X-linked and mitochondrial inheritance patterns are also observed, particularly for complex dystonia.

Clinical Utility of Genetic Testing for Dystonia

Genetic testing for dystonia 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. In some cases, determining the underlying genetic defect can also inform treatment decisions (5, 6). Utilizing whole exome sequencing technology for the Dystonia Exome test allows us to have a dynamic gene list that can be updated regularly as new genes are identified.

The Dystonia Exome includes analysis of 173 genes

The Dystonia Exome involves analysis of exome sequencing data in a predefined set of 173 genes associated with dystonia. These include genes known to be associated with dystonia as the only feature, as well as genes associated with certain syndromes for which dystonia is a commonly observed feature in affected individuals. Age of onset of symptoms for the included genes ranges from infancy to adulthood.

For a complete list of the 173 genes analyzed, please visit our website at 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 173 genes that have been associated with dystonia is generated. The list of 173 genes has been carefully compiled by review of the scientific literature on the genetics of dystonia. For cases without a clearly pathogenic variant identified in the predefined list of 173 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 173 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. Our analytical pipeline presents variants in only the preselected 173 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 dystonia-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 Dystonia Exome. 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 Test Requisition Form
- Completed Clinical Checklist
- Completed Consent Form

Dystonia Exome

Sample specifications:	3 to 10 cc of blood in a purple top (EDTA) tube
Cost:	$3500
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 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. Balint B, Bhatia KP. Dystonia: an update on phenomenology, classification, pathogenesis and treatment. Curr Opin Neurol 2014: 27: 468-476.
2. Lohmann K, Klein C. Update on the Genetics of Dystonia. Curr Neurol Neurosci Rep 2017: 17: 26.
3. van Egmond ME, Kuiper A, Eggink H et al. Dystonia in children and adolescents: a systematic review and a new diagnostic algorithm. J Neurol Neurosurg Psychiatry 2015: 86: 774-781.
4. Stoessl AJ, Mckeown MJ. Movement disorders. Handb Clin Neurol 2016: 136: 957-969.
5. Friedman J, Roze E, Abdenur JE et al. Sepiapterin reductase deficiency: a treatable mimic of cerebral palsy. Ann Neurol 2012: 71: 520-530.
6. Furukawa Y, Kish SJ. Dopa-responsive dystonia: recent advances and remaining issues to be addressed. Mov Disord 1999: 14: 709-715.

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