



Ataxia Exome Panel

Ataxias are a heterogeneous group of neurological disorders affecting individuals of all age groups and are characterized by the incoordination of voluntary movements. Features can include cerebellar dysfunction involving disturbance of stance, gait, eye movements, muscle tone, skilled movements and speech (1).

Genetic testing for ataxias can present challenges in daily clinical practice as the etiology and presenting symptoms can vary. Hereditary forms of ataxias include metabolic ataxias, autosomal recessive degenerative ataxias, progressive autosomal dominant spinocerebellar ataxias, X-linked, and mitochondrially-inherited ataxias. Metabolic ataxias are generally represented by autosomal recessive multisystem disease of infancy, typically with poor prognosis. In general, recessive ataxias often present as multisystem disorders, while autosomal dominant ataxias are typically restricted to the central nervous system (1). Spinocerebellar ataxias (SCA) are primarily caused by trinucleotide repeat expansions and worldwide SCA1, 2, 3, 6, and 7 explain 50-60% of all cases of autosomal dominant ataxia, while other known SCA subtypes are rare (<1%) (2). Being able to provide a genetic diagnosis allows for the opportunity for genetic counseling, long-term investigations and development of therapeutic strategies, and implications for patient management and prognosis (3).

The Ataxia Exome Panel includes analysis of 484 genes*		
The Ataxia Exome Panel involves analysis of exome sequencing data in a predefined set of 484 genes associated with ataxia and assembled by research and clinical experts in the field. These include genes known to be associated with ataxia as the predominant feature, genes associated with ataxia as part of the phenotype, and genes speculated to be involved in an ataxia phenotype based on expert opinion.		
<p>Autosomal Recessive Genes</p> <p>Over 230 ataxia genes including:</p> <ul style="list-style-type: none"> Freidreich's ataxia Spastic paraplegia Joubert syndrome Ceroid lipofuscinosis Mitochondrial disorders Inborn errors of metabolism Muscular dystrophy-dystroglycanopathies Mendelian Genetic syndromes And Many More 	<p>Autosomal Dominant Genes</p> <p>Over 70 genes including:</p> <ul style="list-style-type: none"> Spinocerebellar ataxias Mendelian genetic syndromes And Many More 	<p>X-linked Genes</p> <p>Including:</p> <ul style="list-style-type: none"> Epileptic encephalopathy Intellectual disability Mendelian genetic syndromes And Many More

For a list of the 484 genes analyzed, please visit our website.

*Note: This test does not screen for trinucleotide repeat expansions that are the known cause of the majority of SCAs, autosomal recessive Friedreich's ataxia and a variety of other hereditary forms of ataxia. Testing for trinucleotide repeat expansions is not currently offered by this laboratory and it is recommended that testing for SCA 1-3, 6, 7 and Friedreich's ataxia be considered prior to ordering the Ataxia Exome Panel.

Testing Analysis

Of the thousands of variants identified by exome sequencing, a list of variants that are located within in a predefined set of 484 genes that have been associated with ataxia is generated. The list of 484 genes has been carefully compiled by research and clinical experts in the field of ataxia. For cases without a clearly pathogenic variant identified in the predefined list of 484 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 484 genes, only those considered to be the likely cause of the patient's phenotype will be reported. Most variants identified as part of 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:

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 the Illumina technology and reads are aligned to the reference sequence. Approximately 90-95% of exons in the genes of interest are targeted at a minimum depth of 30X in the diagnostic Ataxia Exome panel. Our analytical pipeline presents variants on only the preselected 484 genes implicated in ataxia. 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.

Reporting Results

Only variants that occur in genes within the pre-defined set of ataxia-associated genes will be reported. As genes outside of this pre-defined gene set will not be interrogated, variants in the additional genes in the exome will not 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 nor reported in the Ataxia 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:

- Ataxia Exome Panel Test Requisition Form
- Completed Ataxia Clinical Checklist
- Completed Ataxia Exome Consent Form

Ataxia Exome Panel

Sample specifications:	3 to 10 cc of blood in a purple top (EDTA) tube
Cost:	\$4000
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.

Additional Resources:

Research studies on the genetics of ataxia are available in the laboratory of Dr. Margit Burmeister at the University of Michigan. For more information please visit <http://www.hg.med.umich.edu/faculty/margit-burmeister-phd> or contact Study Coordinator, Erin Sandford, Ph.D. esandfor@umich.edu.

References:

1. Mariotti C, Fancellu R, Di Donato S. An overview of the patient with ataxia. J Neurol 2005; 252: 511-518.
2. Brusse E, Maat-Kievit JA, van Swieten JC. Diagnosis and management of early- and late-onset cerebellar ataxia. Clin Genet 2007; 71: 12-24.
3. Németh AH, Kwasniewska AC, Lise S et al. Next generation sequencing for molecular diagnosis of neurological disorders using ataxias as a model. Brain 2013.

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