



Neuromuscular Disorders Exome

Neuromuscular disorders (NMD) are a clinically and genetically diverse group of conditions affecting the peripheral nervous system and muscle, including muscular dystrophies, congenital myopathies, congenital myasthenic syndrome, and peripheral neuropathies [1]. Most NMDs have an underlying genetic basis, although there are also acquired forms NMD such as botulism and pharmaceutical induced myopathies [1]. Onset of symptoms is variable between different NMD, and can range from prenatal onset to childhood or adult onset conditions. It is becoming increasingly recognized that many genes associated with NMD can lead to multiple disease phenotypes in different families, and some can be associated with both autosomal dominant and recessive inheritance [1].

Clinical Utility of Genetic Testing for Neuromuscular Disorders

Genetic testing for neuromuscular disorders can present challenges, due to the wide clinical and genetic heterogeneity that exists. Certain types of neuromuscular disorders can be associated with multiple genes, and conversely some genes can be observed in association with multiple sub-types of neuromuscular disease [2]. Additionally, there may be significant phenotypic overlap between different categories of neuromuscular disorders, leading to challenges in clinical diagnosis. Despite this complexity, determining the molecular basis of disease using genetic testing can be useful in predicting prognosis and disease course. Utilizing exome sequencing technology for the Neuromuscular Disorders Exome test allows us to have a dynamic gene list that can be updated regularly as new genes are identified.

The Neuromuscular Disorders Exome includes analysis of 421 genes

The Neuromuscular Disorder Exome involves analysis of exome sequencing data in a predefined set of 421 genes associated with neuromuscular disorders. These include genes known to be associated with a neuromuscular phenotype as the only feature, as well as genes associated with certain syndromes for which a neuromuscular phenotype 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 421 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 421 genes that have been associated with neuromuscular disorders is generated. The list of 421 genes has been carefully compiled by review of the scientific literature on the genetics of neuromuscular disorders. For cases without a clearly pathogenic variant identified in the predefined list of 421 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 421 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 97-99% of exons in the genes of interest are targeted at a minimum depth of 10X in the diagnostic Neuromuscular Disorders Exome. Our analytical pipeline presents variants in only the preselected 421 genes implicated in neuromuscular disorders. In addition to sequence analysis of the coding regions and splice junctions of the preselected genes, analysis for the recurrent c.930+189C>T deep intronic variant in the *COL6A1* gene is also performed. 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 neuromuscular disorder-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 Neuromuscular Disorders 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 or encrypted email.

Neuromuscular Disorders Exome

Sample specifications:	3 to10 cc of blood in a purple top (EDTA) tube
Cost:	\$4,000
CPT codes:	81415
Turn-around time:	6 weeks

Note: We cannot bill insurance for the this test.

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.

For more information about our testing options, please visit our website at dnatesting.uchicago.edu or contact us at 773-834-0555.

References:

1. Laing, N.G., *Genetics of neuromuscular disorders*. Crit Rev Clin Lab Sci, 2012. **49**(2): p. 33-48.
2. Kitamura, Y., et al., *Target resequencing of neuromuscular disease-related genes using next-generation sequencing for patients with undiagnosed early-onset neuromuscular disorders*. J Hum Genet, 2016. **61**(11): p. 931-942.

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