Expanded Neuromuscular Disorders Panel: Sequencing and CNV Analysis

**Condition Description**

Neuromuscular disorders (NMDs) collectively refer to the many disorders that affect the peripheral nervous system either by impairing the proper development or functioning of muscles, or by damaging the associated nerves or neuromuscular junctions. NMDs comprise over 200 Mendelian disorders, all of which are rare individually, but have an approximate disease prevalence of 1 in 3,000 altogether. Of the inherited NMDs, muscular dystrophies are the most common. Muscular dystrophies are highly heterogeneous muscle disorders that share clinical, genetic, and pathological characteristics; their major clinical characteristics include muscle degeneration and wasting, progressive muscle weakness, hypotonia, and elevated serum creatine kinase levels.

The expanded neuromuscular panel includes a wide range of clinical presentation and heterogeneity. They include muscular dystrophies, congenital myopathies, and congenital myasthenic syndrome. Over the past few years a number of genes with overlapping clinical phenotypes have been identified in neuromuscular disorders.

Note: This test does not detect the retrotransposon insertion in the 3' UTR of the FKTN gene common in some Asian populations. For patients with suspected Fukuyama congenital muscular dystrophy, testing for the FKTN insertion is recommended. Analysis for the FKTN insertion is available as a separate assay.

References:


**Genes**

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<th>Genes</th>
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<tr>
<td>ACTA1, AMPD1, ANOS1, BAG3, BIN1, BSL2, CAPN3, CAV3, CAVIN1, CFL2, CHAT, CHRNB1, CHRNA1, CHRND, CHRNE, CHRNG, COL6A1, COL6A2, COL6A3, COLQ, CRPPA, CRYAB, DAG1, DES, DMD, DNM2, DOK7, DYSF, EMD, FHL1, FKRP, FKN1, FLNC, GAA, GLE1, GNE, IGHMBP2, ITGA7, LAMA2, LARGE1, LDB3, LMNA, MTM1, MTMR14, MUSK, MYH2, MYH7, MYOT, NEB, PABPN1, PLEC, PLEKHD1, PLEKHS1, PMP2, POMGNT1, POMT1, POMT2, PYGM, RAPSN, RYR1, RYR2, SCN4A, SELENOM, SGCA, SGCB, SGCD, SGCE, SGC, SIL1, SYNE1, TCAP, TNNI2, TNNIT1, TPM2, TPM3, TRIM32, TTN, VCP, VRK1</td>
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**Indications**

This test is indicated for:

- Confirmation of a clinical diagnosis of neuromuscular disorders.

**Methodology**

**Next Generation Sequencing:** In-solution hybridization of all coding exons is performed on the patient's genomic DNA. Although some deep intronic regions may also be analyzed, this assay is not meant to interrogate most promoter regions, deep intronic regions, or other regulatory elements, and does not detect single or multi-exon deletions or duplications. Direct sequencing of the captured regions is performed using next generation sequencing. The patient's gene sequences are then compared to a standard reference sequence. Potentially causative variants and areas of low coverage are Sanger-sequenced. Sequence variations are classified as pathogenic, likely pathogenic, benign, likely benign, or variants of unknown significant. Variants of unknown significance may require further studies of the patient and/or family members.

**Copy Number Analysis:** Comparative analysis of the NGS read depth (coverage) of the targeted regions of genes on this panel was performed to detect copy number variants (CNV). The accuracy of the detected variants is highly dependent on the size of the event, the sequence context and the coverage obtained for the targeted region. Due to these variables and limitations a minimum validated CNV size cannot be determined; however, single exon deletions and duplications are expected to be below the detection limit of this analysis.

**Detection**

**Next Generation Sequencing:** Clinical Sensitivity: Unknown. Mutations in the promoter region, some mutations in the introns and other regulatory element mutations cannot be detected by this analysis. Results of molecular analysis should be interpreted in the context of the patient's clinical/biochemical phenotype.

Analytical sensitivity for sequence variant detection is ~99%.

**Copy Number Analysis:** The sensitivity and specificity of this method for CNV detection is highly dependent on the size of the event, sequence context and depth of coverage for the region involved. The assay is highly sensitive for CNVs of 500 base pairs or larger and those containing at least 3 exons. Smaller (< 500 base pairs) CNVs and those that involving only 1 or 2 exons may or may not be detected depending on the sequence context, size of exon(s) involved and depth of coverage.

**Specimen Requirements**
Submit only 1 of the following specimen types

**Type: Whole Blood (EDTA)**

**Specimen Requirements:**
- EDTA (Purple Top)
- Infants and Young Children (2 years of age to 10 years old): 3-5 ml
- Older Children & Adults: 5-10 ml
- Autopsy: 2-3 ml unclotted cord or cardiac blood

**Specimen Collection and Shipping:**
Ship sample at room temperature for receipt at EGL within 72 hours of collection. Do not freeze.

**Type: Saliva**

**Specimen Requirements:**
- Oragene™ Saliva Collection Kit
- Orangene™ Saliva Collection Kit used according to manufacturer instructions. Please contact EGL for a Saliva Collection Kit for patients that cannot provide a blood sample.

**Specimen Collection and Shipping:**
Please do not refrigerate or freeze saliva sample. Please store and ship at room temperature.

**Type: DNA, Isolated**

**Specimen Requirements:**
- Microtainer
- 8µg

Isolation using the Perkin Elmer™Chemagen™ Automated Extraction method or Qiagen™ Puregene kit for DNA extraction is recommended.

**Specimen Collection and Shipping:**
Refrigerate until time of shipment in 100 ng/µL in TE buffer. Ship sample at room temperature with overnight delivery.

**Related Tests**

- Neuromuscular Disorders Panel.
- Limb-girdle Muscular Dystrophy Panel.
- Congenital Muscular Dystrophy Panel.
- Expanded Neuromuscular Disorders: Deletion/Duplication Panel.