Merosin-Deficient CMD Type 1A (MDC1A): LAMA2 Gene Sequencing

**Condition Description**

The congenital muscular dystrophies are a group of genetically and clinically heterogeneous hereditary myopathies characterized by congenital hypotonia and muscle weakness, contractures, and delayed motor development. Muscle biopsy usually reveals a nonspecific dystrophic pattern. The clinical course is broadly variable and can involve the brain and eyes. Initial testing often includes clinical evaluation, muscle imaging, electromyography, and muscle biopsy, followed by targeted genetic testing.

Merosin-deficient congenital muscular dystrophy type 1A (MDC1A) usually presents in the neonatal period with marked muscle weakness and severe hypotonia, and ventilatory assistance may be required. Most infants stabilize and do not require further mechanical ventilation, although noninvasive night-time ventilation may be necessary. Feeding difficulties due to decreased suck and swallow can result in recurrent aspiration and poor nutrition. Joint contractures in the elbows, hips, knees, and ankles and scoliosis are common, and typically affected individuals are not able to ambulate or stand unsupported.

Affected individuals generally show normal cognitive development. By six months of age all affected individuals show characteristic white matter changes on MRI, including hypomyelination and hypodensity of white matter; these changes are not, however, unique to CMD. Occasionally structural brain abnormalities may be seen including occipital agyria and pontocerebellar hypoplasia. Individuals with more extensive brain abnormalities may have lower IQ. Approximately 30% of affected individuals have epilepsy.

Individuals affected with MDC1A usually show markedly elevated serum creatine kinase from birth. Muscle biopsies in the neonatal period may show significant inflammation which usually resolves into a typically more dystrophic pattern. Immunohistochemistry staining of a muscle or skin biopsy usually shows complete merosin (also called laminin alpha 2) protein deficiency and can be performed for diagnostic purposes. In some instances, merosin deficiency is not complete; these individuals may have a milder phenotype and later onset than individuals with complete deficiency, resembling limb-girdle muscular dystrophy.

MDC1A is an autosomal recessive disorder caused by mutations in the laminin alpha 2 gene LAMA2 (6q22-q23). Common mutations have not been observed.

For patients with suspected MDC1A, sequence analysis is recommended as the first step in mutation identification. For patients in whom mutations are not identified by full gene sequencing, deletion/duplication analysis is appropriate.

**References**


**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 significance. Variants of unknown significance may require further studies of the patient and/or family members.

**Detection**

Clinical Sensitivity: Unknown. Mutations in the promoter region, some mutations in the introns and other regulatory element mutations cannot be detected by this analysis. Large deletions will not be detected by this analysis. Results of molecular analysis should be interpreted in the context of the patient's biochemical phenotype.

Analytical Sensitivity: ~99%
Specimen Requirements

Submit only 1 of the following specimen types

* Preferred specimen type: Whole Blood

**Type: Whole Blood**

Specimen Requirements:

In EDTA (purple top) tube:
- Infants (2 years): 3-5 ml
- Older Children & Adults: 5-10 ml

Specimen Collection and Shipping: Refrigerate until time of shipment. Ship sample within 5 days of collection at room temperature with overnight delivery.

**Type: Saliva**

Specimen Requirements:

Oragene<sup>TM</sup> Saliva Collection kit (available through EGL) used according to manufacturer instructions.

Specimen Collection and Shipping: Store sample at room temperature. Ship sample within 5 days of collection at room temperature with overnight delivery.

**Special Instructions**

Submit copies of diagnostic biochemical test results with the sample, if appropriate. Contact the laboratory if further information is needed.

Sequence analysis is required before deletion/duplication analysis by targeted CGH array. If sequencing is performed outside of EGL Genetics, please submit a copy of the sequencing report with the test requisition.

**Related Tests**

- Deletion/duplication analysis of the *LAMA2* gene by CGH array is available for those individuals in whom sequence analysis is negative.
- **Familial mutation testing** is available to family members if mutations are identified by targeted mutation testing or sequencing analysis.
- Prenatal testing is available to couples who are confirmed carriers of mutations. Please contact the laboratory genetic counselor to discuss appropriate testing prior to collecting a prenatal specimen.