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Congenital Muscular Dystrophies

Congenital muscular dystrophies (CMD) are a heterogeneous group of diseases including Walker Warburg Syndrome (WWS), Muscle-Eye-Brain Disease (MEB), Fukuyama Congenital Muscular Dystrophy (FCMD) and Congenital Muscular Dystrophy Type 1C (MDC1C). They usually present at birth or within the first 6 months of life. Initial signs include hypotonia, muscle weakness and the variable appearance of contractures.

WWS, MEB, FCMD and MDC1C are caused by mutations affecting glycosylation enzymes, proteins that add sugars to other proteins. In these diseases, defects in the sugar-adding mechanism disrupt the properties of α-dystroglycan, a protein critical for normal muscle function.

Genetics

CMDs are autosomal recessively inherited neuromuscular disorders. An individual is affected if s/he receives two copies of a defective gene, one from each parent. Any person with one copy of the defective gene is a carrier; carriers do not have and will never develop the disease. Two carriers have a 25% chance that their child will be born with the condition.

Who Should be Tested?

- Individuals clinically suspected of being affected with WWS, MEB, FCMD, or MDC1C
- Individuals with a family history of WWS, MEB, FCMD or MDC1C, to determine carrier status
- Pregnancies at increased risk of being affected with WWS, MEB, FCMD or MDC1C

Test Methods

- Complete sequencing of the coding region and flanking exon/intron boundaries of the *POMT1*, *POMT2*, *POMGnT1*, *FCMD* and *FKRP* genes, to identify point mutations.

Walker Warburg Syndrome (WWS): WWS is the most severe form of CMD, and presents in the pre or neonatal period. Brain malformations and ocular abnormalities are characteristic of WWS, and life expectancy is less than three years. Mutations in the *POMT1*, *POMT2*, *POMGnT1* and *FKRP* genes have been found in ~25% of WWS patients.

Muscle-Eye-Brain Disease (MEB): Characteristics of MEB disease include neonatal hypotonia, developmental delay and ocular abnormalities. Mutations in the *POMGnT1* gene are found in ~80% of MEB patients, and mutations in the *FKRP* gene are found in ~10%. Although MEB has been reported in various ethnic backgrounds, it is most common in Finland.

Fukuyama Congenital Muscular Dystrophy (FCMD): FCMD presents during the neonatal period with hypotonia, weakness, and poor suck reflex. Most cases (~95%) are due to mutations in the *FCMD* gene, and 5% as a result of mutations in the *FKRP* gene. FCMD has been reported in various ethnic backgrounds, however it is most common in Japan.

Congenital Muscular Dystrophy Type 1C (MDC1C): MDC1C is a severe form of congenital muscular dystrophy with onset at birth. Characteristics include facial weakness, hypertrophy of the leg muscles, weakness of the shoulder girdle and elevated CK levels. The majority of cases (90%) are a result of mutations in the *FKRP* gene.

Potential Outcomes & Interpretation of Test Results

Reason for referral	Gene Mutations Allele 1 / allele 2	Explanation
Diagnosis	None detected / none detected	This result does not support a diagnosis
Diagnosis	Mutation detected / none detected	This result is unable to confirm a diagnosis
Diagnosis	Mutation detected / mutation detected	This result confirms a diagnosis
Carrier testing	None detected / none detected	This individual is unlikely to be a carrier
Carrier testing	Mutation detected / none detected	This individual is a carrier and may transmit a mutation to offspring

For More Information

Online Mendelian Inheritance in Man http://www.ncbi.nlm.nih.gov/omim/

- MEB #253280
- CMD1C #606612
- WWS #236670
- FCMD #253800

GeneReviews online clinical information resource http://www.ncbi.nlm.nih.gov/bookshelf/br.fcgi?book=gene&part=cmd-overview

To locate a genetics center near you, please visit the Canadian Association of Genetic Counsellors website at www.cagc-accg.ca or the National Society of Genetic Counsellors website at www.nsgc.org

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1. Current molecular testing may not detect all possible mutations for this disease. A negative test does not rule out the possibility that the individual carries a rare mutation not detected by this assay.

2. Additional testing such as muscle biopsy and serum creatine kinase analysis is strongly recommended, as it can be a useful complement to molecular testing.

3. The clinical course or severity of symptoms cannot be predicted by molecular analysis.

4. Test results should be interpreted in the context of clinical findings, family history, ethnic background and other laboratory data.

5. This test was developed and its performance characteristics validated by the Genome Diagnostics Laboratory at the Hospi-tal for Sick Children. It has not been cleared or approved by the U.S. Food and Drug Admini-stration. The FDA has deter-mined that such clearance or approval is not necessary. This test is used for clinical purposes.