PREVENTION GENETICS
DISEASE PREVENTION THROUGH GENETIC TESTING

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Limb Girdle Muscular Dystrophy, Type 2L (LGMD2L) and Distal Miyoshi Myopathy (MMD3) *via ANO5/TMEM16E* Gene Sequencing (Test #469)

Brief Description of Clinical Features: Mutations in the *ANO5* gene (*TMEM16E*; OMIM #608662) cause limb girdle muscular dystrophy type 2L (LGMD2DL; OMIM #611307) and distal, non-dysferlin Miyoshi myopathy (MMD3; Bolduc et al. *Am J Hum Genet* 86:213-221, 2010). LGMD2L can be distinguished clinically from other forms of limb girdle muscular dystrophy by asymmetric atrophy of the quadriceps femoris and biceps brachii (Jarry et al. *Brain* 130:368-380, 2007; Bolduc et al. 2010). Onset of symptoms among eight patients from eight French Canadian families varied from 20 to 55 years of age, and marked intrafamilial variability in phenotypic severity was noted (Bolduc et al. 2010). Facial muscles were spared, and there were no instances of cardiomyopathy (Jarry et al. 2007). Muscle pathology revealed collagen disorganization and basal lamina duplication but no sign of inflammation (Jarry et al. 2007).
The Miyoshi myopathy phenotype associated with *ANO5* mutations (MMD3) has been reported in members of two families presenting clinically with distal weakness, particularly of the calf muscles, and calf hypertrophy (Bolduc et al. 2010). Patients are reported to have difficulty with toe-walking, and they develop asymmetric involvement of proximal muscles of the lower and upper limb girdles latter in the disease course. Quadriceps atrophy was observed in individual members of the two reported families but was not a universal finding (Bolduc et al. 2010). Serum CK levels were elevated in all patients with MMD3, but among the LGMD2L patients they varied from normal to elevated.

Genetics: LGMD2L and MMD3 are inherited as autosomal recessive disorders. Asymptomatic, mutation-positive adult members of LGMD2L families have been reported (Bolduc et al. 2010). The *ANO5* gene encodes anoctamin, a protein with unknown function but with a putative calcium activated chloride channel function (Bolduc et al. 2010). Evidence exists that anoctamin has a role in membrane repair (Bolduc et al. 2010). Reported pathogenic allelic variants include a splice site mutation, a single nucleotide duplication, and missense mutations.

Description of This Particular Test: Anoctamin 5 is coded by exons 1-22 of the *ANO5/TMEM16E* gene located on chromosome 11p13. Testing is accomplished by amplifying each coding exon and ~50 bp of adjacent noncoding sequence, then determining the nucleotide sequence using standard dideoxy sequencing methods and a capillary electrophoresis instrument.

Reference Sequences: **Genomic: NC_000011.8** **mRNA: NM_213599.2**
Protein: NP_998764.1 **mRNA and Protein: CCDS 31444.1**

Indication for Testing: Individuals with symptoms consistent with LGMDL and autosomal recessive inheritance. Individuals with a Miyoshi myopathy phenotype and normal dysferlin studies.

Sensitivity of test: *ANO5* mutations have thus far been described in only a few patients worldwide, therefore, clinical sensitivity cannot be estimated. LGMD2L may be more prevalent among French Canadians than the general population.

Turnaround Time: Maximum of 40 days, although many tests are completed in 2 – 3 weeks.

Specimen Requirements: See page 4 of Requisition Form.

Price:	**Sequencing of *ANO5***	**Exons 1-22**		**$ 1090**
CPT Codes:				
Sample Ascertainment	83890	$ 30	DNA Isolation	83891 $ 40
Amplification x21	83898	$ 320	Sequencing x21	83904 $ 490
Separation	83894	$ 90	Interpretation/Report	83912 $ 120

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