PYGM Gene Analysis in Glycogen Storage Disease type V (GSD V)

DISORDER ALSO KNOWN AS
McArdle disease, Myophosphorylase deficiency

CLINICAL FEATURES
Glycogen storage disease type V (GSD V) is an inherited disorder of glycogen metabolism that affects the skeletal muscle. The disease is characterized by muscle fatigue, stiffness, myalgia, and weakness often caused by activity and improved by rest. If activity is continued after symptoms appear, severe, painful muscle cramping and contracture may occur; this may be accompanied by myoglobinuria and can lead to rhabdomyolysis with possible renal failure if not treated properly. Onset of symptoms is usually in early childhood; however, individuals are often not diagnosed until after age 30.[1]Two individuals were reported who were diagnosed in their 70s due to very late-onset myopathy with no previous history of exercise intolerance.[6]A subset of patients have fixed muscle weakness and wasting with age. Serum creatine kinase (CK) is generally elevated.[1]The potential risk of statins in individuals with McArdle disease is still under investigation; several case reports suggested that statin use may uncover the underlying muscle disease.[1,2] In one U.S. study, the incidence of GSD V was estimated to be about 1 in 100,000.[3]

GENETICS
GSD V is caused by pathogenic variants in the *PYGM* gene that encodes the skeletal muscle isoform of glycogen phosphorylase known as myophosphorylase. Myophosphorylase deficiency leads to the inability to use muscle glycogen. The enzyme initiates glycogen breakdown by removing the 1,4-alpha-glucosyl units from its outer branches. The active form of myophosphorylase is a homotetramer. The *PYGM* gene is located on chromosome 11q13, contains 20 exons, and encodes a protein of 842 amino acids.

INHERITANCE PATTERN
Autosomal Recessive

TEST METHODS
Using genomic DNA extracted from the submitted specimen, the complete coding regions and splice site junctions of the PYGM gene are enriched using a proprietary targeted capture system developed by GeneDx for next-generation sequencing with CNV calling (NGS-CNV). The enriched targets are simultaneously sequenced with paired-end reads on an Illumina platform. Bi-directional sequence reads are assembled and aligned to the reference sequence based on NCBI RefSeq transcripts and human genome build GRCh37/UCSC hg19. After gene specific filtering, data are analyzed to identify sequence variants and most deletions and duplications involving coding exons; however, technical limitations and inherent sequence properties effectively reduce this resolution for some genes. Alternative sequencing or copy number detection methods are used to analyze or confirm regions with inadequate sequence or copy number data by NGS. Reportable variants include pathogenic variants, likely pathogenic variants and variants of uncertain significance. Likely benign and benign variants, if present, are not routinely reported but are available upon request.

The technical sensitivity of sequencing is estimated to be >99% at detecting single nucleotide events. It will not reliably detect deletions greater than 20 base pairs, insertions or rearrangements greater than 10 base pairs, or low-level mosaicism. The copy number assessment methods used with this test cannot reliably detect copy number variants of less than 500 base pairs or mosaicism and cannot identify balanced chromosome aberrations. Assessment of exon-level copy number events is dependent on the inherent sequence properties of the targeted regions, including shared homology and exon size.

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VARIANT SPECTRUM

Variants identified in the PYGM gene include missense, nonsense, splice-site, small deletions/insertions, and large deletions.[8]The most common variant in the Caucasian population is a single base pair substitution, c.148G>T; p.Arg50X (p.R50X) (initially reported as p.R49X).[4]Other common variants are p.Gly205Ser (p.G205S), which accounts for about 10% of variants in American patients and 9% of mutant alleles in Spanish patients,[6]and p.Tyr85X, common in the central European population. Other common variants have been reported in Spanish (p.Trp798Arg; 16.5%) and Japanese (p.Phe710del; 64%) populations.[6] Most other variants are private. At this time, genotype-phenotype correlations have not been established.[1,4,5] Somatic mosaicism has been reported previously.[7]

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