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] One paper reports two individuals 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; however several case reports have suggested that statin use may cause an adverse muscle reaction in these patients or 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:
Variant analysis of the *PYGM* gene is performed on genomic DNA from the submitted specimen using bi-directional sequence analysis of coding exons and corresponding intron/exon boundaries. If sequencing identifies a variant on only one allele of the *PYGM* gene, and if clinically indicated, reflex deletion/duplication testing will be performed at no additional charge to evaluate for a deletion/duplication of one or more exons of this gene. Variants found in the first person of a family to be tested are confirmed by repeat analysis using sequencing, restriction fragment analysis or another appropriate method.

Test Sensitivity:

Two large cohort studies identified variants in all 56 and 54 patients.[4,5] Sequence analysis is expected to identify close to 100% of the variants in the *PYGM* gene. The methods used by GeneDx are expected to be greater than 99% sensitive at detecting variants identifiable by sequencing.

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]

References:

1. Quinlivan et al. (2010) Journal Of Neurology, Neurosurgery, And Psychiatry 81 (11):1182-8 (PMID: 20861058)
2. Vladutiu, et al. (2008) Current Opinion In Rheumatology 20 (6):648-55 (PMID: 18946323)
3. Haller, et al. (2000) Archives Of Neurology 57 (7):923-4 (PMID: 10891971)
4. Deschauer et al. (2007) Journal Of Neurology 254 (6):797-802 (PMID: 17404776)
5. Martin et al. (2001) Annals Of Neurology 50 (5):574-81 (PMID: 11706962)
6. Chéraud et al. (2018) Muscle Nerve 57 (1):157-160 (PMID: 28120463)
7. Qin et al. (2016) J Mol Diagn 18 (3):446-53 (PMID: 26944031)
8. Stenson et al. (2014) Human Genetics 133 (1):1-9 (PMID: 24077912)