GAA Gene Analysis in Pompe Disease / Glycogen Storage Disease II

Clinical Features:
Pompe Disease / Glycogen Storage Disease II (GSDII) is a rare lysosomal storage disease. Patients have been classified as infantile, juvenile or adult onset types. More recently, it has been recognized that there is a continuum of phenotypes between the classical infantile onset and the adult form. Infantile GSDII presents during the first weeks or months of life with poor feeding, failure to thrive, macroglossia, severe hypotonia, cardiomegaly, mild hepatomegaly, and respiratory insufficiency. There is often a rapid progression to cardiac failure and death typically occurs within the first year. Later onset forms are characterized by skeletal muscle weakness, respiratory insufficiency and hepatomegaly. Cardiac involvement is usually absent or mild. The adult onset form presents in the third to sixth decade and is similar to the juvenile form but with a slower progression of skeletal muscle weakness.[1]

GSDII is caused by pathogenic variants in the GAA gene that encodes the enzyme alpha-1, 4-glucosidase, which degrades alpha-1, 4 and alpha-1,6 linkages in glycogen, maltose and isomaltose. Enzyme deficiency leads to lysosomal accumulation of glycogen which may eventually lead to cardiac failure and/or skeletal muscle dysfunction. The severity of the disease is related to the degree of enzyme deficiency. The GAA gene is located on chromosome 17q25.2-q25.3 and contains 20 exons, the first of which is not translated. The incidence of GSDII has been estimated at 1 in 40,000 in the western world.[1,2]

Inheritance Pattern/Genetics:
Autosomal Recessive

Test Methods:
Variant analysis of the GAA gene is performed on genomic DNA from the submitted specimen using bi-directional sequence analysis of coding exons (2-20), and corresponding intron/exon boundaries. If sequencing identifies a variant on only one allele of the GAA gene, and if clinically indicated, reflex deletion/duplication testing (ExonArrayDx) 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:
In patients with GSDII diagnosed by deficiency of the alpha-1, 4-glucosidase enzyme, sequence analysis identified two variants in approximately 82-93% of cases.[3,4]

GAA variants are spread throughout the gene and include missense, nonsense, splicing, and both small and large deletions and insertions. There are over 250 different variants described, the majority of which are private, but some are common in certain ethnic groups. A large deletion of exon 18 has been identified in 5-8% of GAA alleles in patients with both infantile and adult-onset GSDII from diverse ethnic backgrounds.[5,6, 8, 9] This variant occurs at even higher frequency in the Dutch population (13% of patients in one study in which 58% of patients were Dutch), and has been proposed to be a founder mutation in this population. [7,10] The most common variant among adults is c.-32-13 T>G occurring in approximately 77% of patients from diverse ethnic backgrounds with adult-onset GSDII. The majority of GSDII patients are compound heterozygotes despite the high frequency of the c.-32-13 T>G variant. A genotype-phenotype correlation has been identified.[1,2,3]

References:

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