SUMF1 Gene Analysis in Multiple Sulfatase Deficiency

Clinical Features:
Multiple sulfatase deficiency (MSD) is a rare disorder characterized by impaired activity of all known sulfatases. Thus MSD results in features associated with deficiencies of single sulfatases: mucopolysaccharidosis II (Hunter syndrome), IIA (Sanfilippo syndrome A), IIID (Sanfilippo syndrome D), IVA (Morquio syndrome A) and VI (Maroteaux-Lamy syndrome), metachromatic leukodystrophy, X-linked ichthyosis, and X-linked recessive chondrodysplasia punctata. MSD is associated with a broad range of symptoms that have been classified into four clinical forms.[1] The severe neonatal form of MSD is diagnosed in the first months of life with coarse facies, cataract and hydrocephalus; death usually ensues within the first year. The severe late-infantile form of MSD has onset within the first year of life with neurological problems similar to late-infantile metachromatic leukodystrophy.[1] Mild-late onset MSD is the more common presentation, characterized with onset of symptoms between 2 years and 4 years with facial dysmorphism, visceromegaly, dysostosis multiplex, cardiomyopathy and milder and slower neurodegeneration including vision and hearing loss.[1] Juvenile MSD is a rare subtype that is associated with only a few of the MSD symptoms, such as ichthyosis and intellectual disability.[1] The prevalence of MSD has been estimated at less than 1 in 1,000,000 births.[1]

Genetics:
MSD is caused by pathogenic variants in the *SUMF1* gene that encodes the formylglycine generating enzyme (FGE) that catalyzes the conversion of a highly conserved cysteine within the catalytic domain of sulfatases into a C-alpha-formylglycine which is required for generating catalytically active sulfatases. Defective FGE results in impaired activity of sulfatases and the accumulation of sulfated lipids and acid mucopolysaccharides. Variable residual activity of the different sulfatases has been described.[2] The *SUMF1* gene is located on chromosome 3p26.1 and has 9 exons.

Inheritance Pattern:
Autosomal Recessive

Test Methods:
Variant analysis of the *SUMF1* 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 *SUMF1* 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. The methods used by GeneDx are expected to be greater than 99% sensitive at detecting variants identifiable by sequencing.

Test Sensitivity:

In 20 patients of different ethnic backgrounds with MSD diagnosed by clinical presentation and decreased levels of at least three different sulfatases, sequence analysis of the *SUMF1* gene identified variants on 95% of alleles (38/40).[2]

Variant Spectrum:

At this time, greater than 50 variants in the *SUMF1* gene have been reported, the vast majority of which are missense variants. Nonsense, splice site, small deletion/insertions, gross deletions, and frameshift variants have also been described. Genotype/phenotype correlations are not well established.[3]

References:

1. Artigalas et al., (2009) Metab Brain Dis 24:493-500.
2. Cosma et al., (2004) Hum Mutat 23:576-581.
3. Schlotawa et al., (2008) Hum Mutat 29:205.