GCDH Gene Analysis in Glutaric aciduria Type I (GA1)

Clinical Features:
Glutaric aciduria type I (GA1) is a rare autosomal recessive disorder affecting the catabolism of the amino acids lysine, hydroxylysine and tryptophan. There is wide variation in disease severity, even reported among affected siblings.[1] Some patients are asymptomatic even without treatment, whereas others have severe neurologic phenotype characterized by progressive dystonia, spasticity and opisthotonos. Macrocephaly is a common feature, and may be present at birth or develop in the first few weeks or months. Fronto-temporal atrophy may be apparent on neuroimaging and may preceed neurologic symptoms. Affected children are generally well at birth and may present with irritability, feeding difficulties repeated fevers, insomnia, or hypotonia.[1,4]

Genetics:
GA1 has an autosomal recessive inheritance pattern. GA1 is caused by pathogenic variants in the GCDH gene on chromosome 19p13.2, encoding a polypeptide of 438 amino acids, including a 44 amino acid leader peptide which is removed to form the mature enzyme. Deficient enzyme activity can result in the accumulation of glutaric and 3-hydroxyglutaric acids with secondary carnitine deficiency, although some affected individuals show normal patterns of urine organic acids and plasma acylcarnitines, and therefore escape detection by newborn screening. Enzymatic or molecular testing of the GCDH gene is used to make the diagnosis of GA1 in individuals with clinical features of the disorder without consistent biochemical findings The incidence of GA1 has been estimated to be 1/40,000 in Caucasians.[6]

Test Methods:
Variant analysis of the GCDH gene is performed on genomic DNA from the submitted specimen using bi-directional sequence analysis of the coding exons 1-11, and corresponding intron/exon boundaries. If sequencing identifies a variant on only one allele of the GCDH 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 an unequivocal diagnosis of GA1 based on enzyme studies, variant analysis is expected to identify greater than 95% of mutant alleles. [1,2,4]

Variant Spectrum:

More than 150 variants in the GCDH gene have been identified to date. Most patients are compond heterozygotes. The variant R402W has been found in relatively high frequency (10-28% of alleles) in European populations and single prevalent variants have been found in small isolated ethnic groups.[1,3] Missense, nonsense, small deletions/insertions and splice site variants have been reported. There is no obvious correlation between the severity of the clinical phenotype and genotype, however the severity of organic aciduria has been correlated with certain variants.[2,5]

References:

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