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Genetic Testing for Combined D-2 and L-2-Hydroxyglutaric Aciduria

Clinical Features:

Combined D-2 and L-2-hydroxyglutaric aciduria (D,L-2-HGA) [OMIM #615182] is a rare neurometabolic disease (1). Affected individuals typically have severe neonatal epileptic encephalopathy and absence of developmental progress (2). Death in the first year of life is common. Enlarged ventricles, subependymal pseudocysts and delayed gyration and myelination are typical brain MRI findings in affected patients (1).

Molecular and Biochemical Genetics:

Homozygous and compound heterozygous mutations of the *SLC25A1* gene [OMIM #190315] gene are associated with D,L-2-HGA (2). Missense, nonsense and frameshift mutations have been described. The *SLC25A1* gene plays a role transporting citrate from the mitochondria to the cytosol, where it is converted into acetyl coenzyme A. Acetyl coenzyme-A is essential for fatty acid and sterol synthesis. Individuals with D,L-2-HGA have increased levels of both D-2 hydroxyglutaric acid and L-2 hydroxyglutaric acid in the urine. It is hypothesized that the increased excretion of these two compounds is related to impaired citrate transport from the mitochondria and disruption of the Krebs cycle caused by *SLC25A1* mutations (2). Conventional urine organic acid screening with gas chromatography mass spectrometry (GC-MS) can detect increased 2-HG (2-hydroxyglutaric acid), but does not differentiate between enantiomeric D-2-HG and L-2-HG (1).

Inheritance:

SLC25A1 mutations follow an autosomal recessive inheritance pattern. Parents of an affected child are most likely obligate carriers. Recurrence risk for carrier parents is 25%.

Test methods:

We offer full gene sequencing of all coding exons and intron/exon boundaries of *SLC25A1* by direct sequencing of amplification products in both the forward and reverse directions.

SLC25A1 sequence analysis

Sample specifications:	3 to10 cc of blood in a purple top (EDTA) tube
Cost:	$1,675
CPT codes:	81405
Turn-around time:	4 weeks

Results:

Results, along with an interpretive report, will be faxed to the referring physician. Additional reports will be provided as requested. All abnormal results will be reported by telephone.

References:

1. Kranendijk M, Struys EA, Salomons GS et al. Progress in understanding 2-hydroxyglutaric acidurias. J Inherit Metab Dis 2012: 35: 571-587.
2. Nota B, Struys EA, Pop A et al. Deficiency in SLC25A1, encoding the mitochondrial citrate carrier, causes combined D-2- and L-2-hydroxyglutaric aciduria. Am J Hum Genet 2013: 92: 627-631.