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Genetic Testing for D-2-Hydroxyglutaric Aciduria

Clinical Features:

D-2-hydroxyglutaric aciduria (D2HGA) type 1 [OMIM #600721] and type 2 [OMIM#613657] are rare neurometabolic diseases associated with accumulation of D-2-hydroxyglutaric aciduria (D-2-HG) in urine (1). The cardinal clinical manifestations in both D2HGA subtypes are developmental delay, hypotonia and seizures (1). Age of onset is similar for both subtypes, typically occurring at 0-6 months of age in D2HGA type 1, and 0-2 years of age in D2HGA type 2. Additional clinical features described in some patients with D2HGA include macrocephaly, dysmorphic features and cerebral visual abnormalities. 47% of D2HGA type 2 patients have cardiomyopathy (primarily dilated). Brain MRI findings in D2HGA patients include enlargement of lateral ventricles, enlarged subarachnoid spaces, subdural effusions, subependymal psuedocysts, signs of delayed cerebral maturation and multifocal cerebral white matter abnormalities. Differences between MRI findings patients with D2HGA type 1 compared to type 2 have not been delineated to date.

Molecular and Biochemical Genetics:

Mutations in the *D2HGDH* [OMIM #609186] gene are associate with D2HGA type 1, and mutations in the *IDH2* gene [OMIM #147650] gene are associated with D2HGA type 2 (1). Mutations in either gene are associated with accumulation of D-2-HG in the urine and cerebral spinal fluid. 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). *D2HGDH* encodes D-2-hydroglutarate dehydrogenase, which converts D-2-HG to 2-ketoglutaric acid. Loss of function mutations in *D2HGDH* lead to an accumulation of D-2-HG. To date, missense, nonsense, splice site and frameshift mutations in *D2HGDH* have been described. *IDH2* encodes isocitrate dehydrogenase-2, which normally converts isocitrate to 2-ketoglutaric aciduria. Mutations in *IDH2* associated with D2HGA are gain-of-function missense mutations, which give isocitrate dehydrogenase-2 the ability to convert 2-ketoglutaric aciduria to D-2-HG. This causes D-2-HG to accumulate. D-2-HG has no known physiological function, however its accumulation appears to lead to the clinical manifestations seen in D2HGA (1).

Inheritance:

D2HGDH mutations follow an autosomal recessive inheritance pattern. Parents of an affected child are most likely obligate carriers. Recurrence risk for carrier parents is 25%. Mutations in *IDH2* are inherited in an autosomal dominant manner. *IDH2* mutations are typically *de novo*, and recurrence risk is therefore low. A case of germline mosaicism for an *IDH2* mutation has been reported (1).

Test methods:

We offer full gene sequencing of all 10 coding exons and intron/exon boundaries of *D2HGDH* and all 11 coding exons and intron/exon boundaries of *IDH2* by direct sequencing of amplification products in both the forward and reverse directions.

D-2-Hydroxyglutaric Aciduria Sequencing Panel (*D2HGDH* and *IDH2* sequence analysis)

Sample specifications:	3 to10 cc of blood in a purple top (EDTA) tube
Cost:	$2,025
CPT codes:	81406
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.

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