HMGCL Gene Analysis in 3-Hydroxy-3-Methylglutaryl-CoA Lyase Deficiency (HMG-CoA Lyase Deficiency)

Clinical Features:
3-Hydroxy-3-methylglutaryl-CoA lyase deficiency, commonly known as HMG-CoA lyase deficiency, is a rare inborn error that affects ketogenesis and leucine catabolism. Symptoms usually appear in the first year of life and include metabolic acidosis with hypoketotic hypoglycemia, hyperammonemia, abnormal liver function tests, vomiting and hypotonia. Other signs are hepatomegaly, macrocephaly, and less frequently microcephaly, seizures, acute pancreatitis, dilated cardiomyopathy and arrhythmia. Abnormal cerebral white matter foci on MRI has also been reported. Without treatment, rapid progression to coma and death or permanent neurological damage may occur. With treatment, many patients do well; however recurrent metabolic decompensation continues to occur especially with prolonged fasting or intercurrent illness. This disorder is fatal in approximately 20% of cases with the symptoms becoming milder after childhood. The incidence of HMG-CoA lyase deficiency is estimated at less than 1/100,000.[1]

Genetics:
HMG-CoA lyase deficiency is caused by pathogenic variants in the *HMGCL* gene that encodes mitochondrial and peroxisomal 3-hydroxy-3-methylglutaryl-CoA lyase. In mitochondria this enzyme catalyzes the last step of both leucine degradation and ketogenesis, while its role in peroxisomes is unknown. Urine organic acid profiles show increased quantities of 3-hydroxy-3-methylglutaric, 3-hydroxyisovaleric, 3-methyl-glutaconic and 3-methylglutaric acids, 3-methylcrotonylglycine may also be present. The *HMGCL* gene is located on chromosome 1p36.11 and has 9 exons.

Inheritance Pattern:
Autosomal Recessive

Test Methods:
Variant analysis of the *HMGCL* gene is performed on genomic DNA from the submitted specimen using bi-directional sequence analysis of exons 1-9, and the corresponding intron/exon boundaries. If sequencing identifies a variant on only one allele of the *HMGCL* 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 36 Saudi Arabian and 9 Portuguese patients diagnosed with HMG-CoA lyase deficiency based on urine organic acid analysis, variants were identified on 68/72 and 17/18 *HMGCL* alleles respectively.[2,3] In 24 ethnically diverse patients diagnosed with HMG-CoA lyase deficiency, variants were identified on 47/48 alleles.[5] The methods used by GeneDx are expected to be greater than 99% sensitive at detecting variants identifiable by sequencing.

Variant Spectrum:

HMGCL variants are distributed throughout the *HMGCL* gene with most variants being missense, followed by nonsense, small deletions/insertions, large deletions and splice site variants.[1] Two common variants in exon 2 have been found in approximately 87% of Saudi Arabian patients (c.122 G>A) and 94% of patients from the Iberian Peninsula (Portugal and Spain) (c.109 G>A), respectively.[1] In most other countries only a few affected patients have been reported with no common variants apparent.[1] Genotype-phenotype correlations have not been established.[1]

References:

1. Pie et al., (2007) Mol Genet Metab 92:198-209.
2. Al-Sayed et al., (2006) BMC Med Genet 7:86.
3. Cardoso et al., (2004) Mol Genet Metab 82:334-338.
4. Muroi et al., (2000) Hum Genet 107:320-326.
5. Menao et al., (2009) Hum Mutat 30:E520-9.