PAH Gene Analysis in Phenylketonuria

Disorder also known as: PKU; Phenylalanine hydroxylase deficiency, PAH deficiency; Hyperphenylalanemia; HPA; Mild hyperphenylalanemia

Clinical Features:
Phenylketonuria (PKU) is a well-characterized, treatable, biochemical disorder which results in dietary intolerance to the essential amino acid phenylalanine. It is the most common inborn error of amino acid metabolism in the Caucasian population with an average incidence of 1 in 10,000. Classic PKU is caused by complete or near-complete deficiency of phenylalanine hydroxylase activity secondary to variants in the PAH gene. The primary route for phenylalanine metabolism is hydroxylation of phenylalanine to tyrosine catalyzed by phenylalanine hydroxylase; consequently a deficiency of this enzyme leads to an elevation of the plasma phenylalanine (phe) concentration (~ 1000 μmol/L). Without dietary restriction of phenylalanine, children with classic PKU will develop severe and irreversible mental retardation. Other clinical features evident in untreated children can include microcephaly, epilepsy, behavioral problems, eczema, hypopigmentation, decreased myelin formation and musty urine odor. Patients with hyperphenylalaninemia due to tetrahydrobiopterin (BH4) deficiency will not be expected to have pathogenic variants in PAH. BH4 deficiency is due to defects in the enzymes involved in the synthesis or regeneration of tetrahydrobiopterin (BH4), a cofactor for phenylalanine hydroxylase enzyme. BH4 deficient hyperphenylalaninemia is a genetically heterogeneous group of disorders caused by variants in genes (GCH1, PTS, QDPR, PCBD) of the BH4 pathway.

Genetics:
Autosomal recessive.

Test Methods:
Analysis is performed by bi-directional sequencing of the coding regions (exons 1-13) and splice sites of the PAH gene. If sequencing identifies a variant on only one allele of the PAH 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:
Bi-directional sequencing of the entire coding region and intron-exon boundaries of the PAH gene by GeneDx will identify more than 95% of variants. Some variants, such as large deletions or variants in the promoter region will not be detected by this method. If both variants are not detected by sequencing, targeted array CGH analysis with exon-level resolution (ExonArrayDx) will be performed to evaluate for a deletion or duplication of one or more exons of the PAH gene.

References:
1. PAHdb: http://www.pahdb.mcgill.ca