



CLIA #: 52D1027685 • CAP #: 7185561
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Phenylalanine Hydroxylase Deficiency via *PAH* Gene Sequencing

Brief Description of Clinical Features: Phenylalanine Hydroxylase (PAH) Deficiency (OMIM 261600) is a defect in the enzymatic conversion of phenylalanine to tyrosine. PAH Deficiency may lead to phenylketonuria (PKU), one of the first recognized human monogenetic disorders. If uncorrected by diet, childhood PAH Deficiency results in blood phenylalanine levels >1000 µM. Such levels interfere with normal brain development and lead to profound mental retardation. It is also critically important that women with PAH Deficiency carefully control their phenylalanine levels in the months before and during pregnancy. Beginning in the 1960's, nearly all cases of PAH Deficiency in America, Canada and Western Europe have been detected by routine neonatal screening with Guthrie Cards. Incidence in the U.S. is roughly 1/15,000 newborns. Subclinical levels of hyperphenylalaninemia may be detected by tandem mass spectrometry. For more information see Scriver, Hum Mut 2007, in press; Mitchell and Scriver, GeneReviews, www.genetests.org, 2007.

Genetics: PAH Deficiency exhibits autosomal recessive inheritance, with genetic and non-genetic modifying factors. Over 500 *PAH* causative mutations have been listed in the PAH database (Scriver et al. Hum Mut 21:333-344, 2003; www.pahdb.mcgill.ca). Causative mutations are about 60% missense, 15% frameshift, 10% splicing, and 5% nonsense. In the outbred U.S. populations, no mutations are common. Mutations are located throughout the length of the gene. Some correlations have been made between genotype and phenotype (Kayaalp et al. Am J Hum Genet 61:1309-1317, 1997).

Description of This Particular Test: This test involves bidirectional DNA sequencing of all 13 exons of the *PAH* gene. The full coding region of each exon plus ~50 bp of flanking non-coding DNA on either side are sequenced. We will sequence any single exon or pair of exons in family members of patients with known mutations, and to confirm research results (\$190-340).

Reference Sequences: Genomic: NC_000012.10 mRNA: NM_000277.1 protein: NP_000268.1

Indications for Test: All individuals with PAH Deficiency or even modest hyperphenylalaninemia are candidates for this test.

Sensitivity of Test: Based on the literature, we estimate that sequencing will detect at least one likely causative mutation in >99% of hyperphenylalaninemia patients and two likely causative mutations in >90% of patients. Larger deletions, not detectable by sequencing, have been reported in 0.4% and 3% of patients in two European populations (Kozak et al. Mol Genet Metab 89:300-309, 2006; Moller et al. Hum Mut, Mut. in Brief #952, 2007). Also, up to 2% of cases of hyperphenylalaninemia are due not to PAH Deficiency, but rather to defects in tetrahydrobiopterin metabolism (Mitchell and Scriver 2007).

Turn Around Time: Maximum of 40 days, although many tests are completed in 2-3 weeks.

Specimen Requirements: See page 4 of the Requisition Form.

Price: Sequencing of complete coding regions of *PAH* Gene **\$ 690**

CPT Codes:

Sample Ascertainment	83890	\$ 30	DNA Isolation	83891	\$ 40
Amplification x10	83898	\$ 200	Sequencing x10	83904	\$ 290
Separation	83894	\$ 50	Interpretation/Report	83912	\$ 80

Accreditation Info. CLIA ID #: 52D1027685 (expires 1/18/13) (CAP#: 7185561, AU ID: 1407125 expires 12/20/12)

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