Disorders of Hyperphenylalaninemia and Biopterin Metabolism Panel

PANEL GENE LIST

PAH, PTS, GCH1, SPR, QDPR, PCBD1, DNAJC12

CLINICAL FEATURES

Disorders of hyperphenylalaninemia and biopterin metabolism are clinically and genetically heterogeneous. Defects in the PAH gene, which encodes the enzyme phenylalanine hydroxylase, account for ~98% of cases of hyperphenylalaninemia.[1] PAH deficiency is a condition with a broad phenotypic spectrum that ranges from classic phenylketonuria (PKU) to mild hyperphenylalaninemia (HPA), depending on phenylalanine levels. Most individuals with untreated classic PKU exhibit severe irreversible intellectual disability and microcephaly, epilepsy, behavioral problems, eczema, and hypopigmentation may also be present. Untreated mild HPA may result in mild symptoms depending on the phenylalanine level. [1] Hyperphenylalaninemia is detectable by newborn screening and includes disorders caused by defects in the synthesis or regeneration of tetrahydrobiopterin (BH4), an important metabolic cofactor for phenylalanine hydroxylase which accounts for ~2% of cases of hyperphenylalaninemia.[1,2] Variants in PTS, GCH1, and SPR lead to defective BH4 biosynthesis, while variants in QDPR and PCBD1 lead to defective BH4 regeneration.[2,3] Individuals affected with disorders of biopterin metabolism may present with neurological dysfunction, developmental delay, intellectual disability, axial hypotonia, peripheral spasticity, dystonia, microcephaly, and seizures.[2] Phenylalanine in plasma, and CSF biopterin, neopterin, homovanillic acid, and 5-hydroxyindoleacetic acid are biochemical tests that can help distinguish between disorders of biopterin metabolism.[2] These disorders, with the exception of sepiapterin reductase deficiency (SPR) and the dominant form of GTP cyclohydrolase I deficiency (GCH1) which typically are not associated with hyperphenylalaninemia, are detectable by newborn screening.[2] Lastly, a rare form of non-BH4 deficient hyperphenylalaninemia is caused by pathogenic variants in DNAJC12. The protein encoded by DNAJC12 has been shown to interact with phenylalanine, tyrosine, and tryptophan hydroxylases.[4] Clinical findings in affected individuals may include progressive neurodevelopmental delay, dystonia, and deficiencies of several neurotransmitters and metabolites, including dopamine, serotonin, homovanillic acid, and 5-hydroxyindoleacetic acid.[4] The confirmation of a clinical diagnosis with molecular testing can help direct treatment and medical management in individuals with these disorders.

INHERITANCE PATTERN

Variants in the seven genes on this panel are inherited in an autosomal recessive manner. Variants in *GCH1* are also inherited in an autosomal dominant manner.

GENETICS

Many types of variants have been reported in *PAH, PTS, GCH1, SPR, QDPR, PCBD1, and DNAJC12*, with missense variants being the most common.[5]

TEST METHODS

Using genomic DNA from the submitted specimen, the complete coding regions and splice site junctions of the genes on this panel are enriched using a proprietary targeted capture system developed by GeneDx for next-generation sequencing with CNV calling (NGS-CNV). The enriched targets are simultaneously sequenced with paired-end reads on an Illumina platform. Bi-directional sequence reads are assembled and aligned to reference sequences based on NCBI RefSeq transcripts and human genome build GRCh37/UCSC hg19. After gene specific filtering, data are analyzed to identify sequence variants and most deletions and duplications involving coding exons. Alternative sequencing or copy number detection methods are used to analyze or confirm regions with inadequate sequence or copy number data. Reportable variants include pathogenic variants, likely pathogenic

variants and variants of uncertain significance. Likely benign and benign variants, if present, are not routinely reported but are available upon request. The technical sensitivity of sequencing is estimated to be >99% at detecting single nucleotide events. It will not reliably detect deletions greater than 20 base pairs, insertions or rearrangements greater than 10 base pairs, or low-level mosaicism. The copy number assessment methods used with this test cannot reliably detect copy number variants of less than 500 base pairs or mosaicism and cannot identify balanced chromosome aberrations. Assessment of exon-level copy number events is dependent on the inherent sequence properties of the targeted regions, including shared homology and exon size.

CLINICAL SENSITIVITY

Based on previous studies of patients with disorders of hyperphenylalaninemia and biopterin metabolism, this test is expected to detect >98% of pathogenic variants in PAH, SPR and QDPR, and >92% of pathogenic variants in the PTS gene.1,3,6-8 Based on the mutation spectrum of autosomal recessive GCH1 deficiency, the test sensitivity is expected to be similar to the above tests, but clinical sensitivity is difficult to estimate based on the presence of an autosomal dominant intermediate form of GCH1 deficiency. The clinical sensitivity for disorders of hyperphenylalaninemia due to PCBD1 and DNAJC12 pathogenic variants is difficult to accurately estimate at this time due to the low number of variants in these genes that have been reported to date.

Gene Name	Associated Disorder(s)	OMIM#
PAH	Phenylketonuria; Hyperphenylalaninemia, non-PKU mild	612349 (AR)
PTS	Hyperphenylalaninemia, BH4-deficient, A	612719 (AR)
GCH1	Dystonia, DOPA-responsive, with or without hyperphenylalaninemia; Hyperphenylalaninemia, BH4-deficient, B	600225 (AD/AR)
SPR	Dystonia, dopa-responsive, due to sepiapterin reductase deficiency	182125 (AR)
QDPR	Hyperphenylalaninemia, BH4-deficient, C	612676 (AR)
PCBD1	Hyperphenylalaninemia, BH4-deficient, D	126090 (AR)
DNAJC12	Hyperphenylalaninemia, mild, non-BH4-deficient	606060 (AR)

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