PTS Gene Analysis in 6-Pyruvoyl-Tetrahydropterin Synthase (PTPS) Deficiency

CLINICAL FEATURES

Persistent hyperphenylalaninemia may be caused by defects in metabolism or regeneration of tetrahydrobiopterin. 6-pyruvoyl-tetrahydropterin synthase (PTPS) deficiency is an inborn error of tetrahydrobiopterin (BH4) synthesis that accounts for approximately 60% of all tetrahydrobiopterin deficiencies.[1] BH4 is a cofactor essential for phenylalanine, tryptophan and tyrosine hydroxylases. The decreased activities of the latter two enzymes is likely the cause of the neurologic symptoms associated with this disorder.[2] Approximately 80% of individuals with PTPS deficiency present with the severe "typical" form characterized by early onset of severe neurological symptoms including microcephaly, psychomotor retardation, tonal abnormalities, seizures, hypothermia and hyperthermia (without infections), swallowing difficulties and hypersalivation.[3] Other features include intellectual disability and microcephaly. The clinical course of severe PTPS deficiency may be similar to that in other inborn errors of BH4 metabolism namely dihydropteridine reductase deficiency and GTP cyclohydrolase I deficiency. Less severely affected individuals are classified as having a mild/peripheral or "atypical" form of PTPS deficiency with symptoms ranging from transient hyperphenylalaninemia to cases where a mild form progresses into a severe form.

INHERITANCE

Autosomal Recessive

GENETICS

PTPS deficiency is caused by pathogenic variants in the *PTS* gene that encodes 6-pyruvoyl-tetrahydropterin synthase, which is required for the second step of the de novo biosynthesis of BH4. The severe form of PTPS deficiency causes hyperphenylalaninemia (HPA) and monoamine neurotransmitter deficiency as measured in cerebrospinal fluid (CSF). The mild form may result in HPA only, transient HPA only, or HPA with normal CSF neurotransmitters initially with progression to very low neurotransmitter levels later in life. Individuals with CSF neurotransmitter abnormalities are typically treated with a combination of BH4 and neurotransmitter precursors, L-dopa/carbidopa and 5-hydroxytryptophan while those with HPA alone require monotherapy with BH4. The PTS gene is located on chromosome 11q22.3-q23.3 and has 6 exons. It is estimated that the prevalence of BH4 deficiencies is approximately 1/1,000,000 individuals,[4] and that they account for about 2% of infants with hyperphenylalaninemia identified by newborn screening.[5] Mild cases, in particular may be misdiagnosed or go undiagnosed.[5]

TEST METHODS

Using genomic DNA extracted from the submitted specimen, the complete coding regions and splice site junctions of the PTS gene are enriched using a proprietary targeted capture system developed by GeneDx for next-generation sequencing with CNV calling (NGS-CNV). The enriched targets aresimultaneously sequenced with paired-end reads on an Illumina platform. Bi-directional sequence reads are assembled and aligned to the reference sequence 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; however, technical limitations and inherent sequence properties effectively reduce this resolution for some genes. Alternative sequencing or copy number detection methods are used to analyze or confirm regions with inadequate sequence or copy number data by NGS. 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.

VARIANT SPECTRUM

PTS variants have been described spanning all six exons and the first four introns of the gene. The majority are missense variants; nonsense, splicing, small deletions/insertions, and exonic deletions have also been described.[6] A c.243G>A variant in exon 4 (E81E) has been described that leads to a splicing defect and skipping of exon 4.[7] Most affected individuals are compound heterozygotes for private variants, although several variants, including N52S and P87S, appear to be frequent in the Asian population.[7] Several variants proposed to be associated with mild disease have been described.[5]

REFERENCES:

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