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 hydroxylase, and tryptophan and tyrosine hydroxylases; decreased activities of the latter enzymes is likely the cause of the neurologic symptoms associated with this disorder.[2] Approximately 80% of patients 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 patients 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 the 6-pyruvoyl-tetrahydropterin synthase, which is required for the second step of the de novo biosynthesis of BH4 starting from GTP. 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 in HPA with normal CSF neurotransmitters initially with progression to very low levels later in life. Patients 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. The overall frequency of BH4 deficiency is approximately 1/1,000,000.[4]

Test Methods:
Variant analysis of the *PTS* gene is performed on genomic DNA from the submitted specimen using bi-directional sequence analysis of exons 1-6, and the corresponding intron/exon

boundaries. If sequencing identifies a variant on only one allele of the *PTS* gene, and if clinically indicated, reflex deletion/duplication testing (ExonArrayDx) will be performed at no additional charge to evaluate for 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 a study of 25 Chinese patients with deficient PTPS enzyme activity, variant analysis identified a sequence variant in 98% of alleles.[5] In multiple smaller studies of patients from varied ethnic backgrounds with deficient PTPS enzyme activity, variants were found on 83-100% of alleles.[6-11] The methods used by GeneDx are expected to be greater than 99% sensitive at detecting variants identifiable by sequencing.

Variant spectrum:

More than 50 *PTS* variants have been described and are spread across all six exons and the first three introns. The majority are missense variants with nonsense, splicing and small deletions/insertions also described.[12] A silent missense change (E81E) found in exon 4 leads to a splicing defect and skipping of exon 4.[13] Most patients are compound heterozygotes for private variants, although two variants, N52S and P87S, appear to be frequent in the Asian population.[13] A genotype-phenotype correlation has not been identified.

References:

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