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

Mendelian Inheritance in Man Numbers: 261640 –PTPS deficiency; 612719- PTS gene

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 (BH_4) synthesis that accounts for approximately 60% of all tetrahydrobiopterin deficiencies. BH_4 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. Infants develop neurological symptoms even though blood phenylalanine levels are normal. 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. Other features include mental retardation and microcephaly. The clinical course of severe PTPS deficiency may be similar to that in other inborn errors of BH_4 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 hyperphenylalanemia to cases where a mild form progresses into a severe form.

Inheritance pattern: Autosomal Recessive

Genetics and biochemical features:
PTPS deficiency is caused by mutations in the PTS gene that encodes the 6-pyruvoyl-tetrahydropterin synthase, which is required for the second step of the de novo biosynthesis of BH_4 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 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 BH_4 and neurotransmitter precursors, L-dopa/carbidopa and 5-hydroxytryptophan while those with HPA alone require monotherapy with BH_4. The PTS gene is located on chromosome 11q22.3-q23.3 and has 6 exons. The overall frequency of BH_4 deficiency is approximately 1/1,000,000.

Reasons for referral:
1. Confirmation of biochemical diagnosis
2. Carrier testing
3. Genetic counseling
4. Prenatal diagnosis in at risk pregnancies

Test method:
Mutation analysis of the PTS gene is performed on genomic DNA from the submitted specimen using bidirectional sequence analysis of exons 1-6, and the corresponding intron/exon boundaries. If sequencing identifies a mutation 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. Mutations 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, mutation analysis identified a sequence variant in 98% of alleles. In multiple smaller studies of patients from varied ethnic backgrounds with deficient PTPS enzyme activity, mutations were found on 83-100% of alleles.

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

Specimen Requirements and Shipping/Handling:
- **Blood**: A single tube with 1-5 mL whole blood in EDTA (1-2mL for infants). Ship overnight at ambient temperature, using a cool pack in hot weather. Specimens may be refrigerated for one week prior to shipping.
- **Buccal Brushes**: Can be used as an alternative to blood for PTS sequencing only. Gene deletion/duplication testing requires submission of a blood sample. When sending a buccal sample, use a GeneDx buccal kit (others not accepted). Submit by mail. Buccal brushes are not accepted on children under 6 months of age.
- **Prenatal Diagnosis**: For prenatal testing for a known mutation in the PTS gene, please refer to the specimen requirements table on our website at: [http://www.genedx.com/test-catalog/prenatal/](http://www.genedx.com/test-catalog/prenatal/). Ship specimen overnight at ambient temperature, using a cool pack in hot weather.

Required Forms:
- Sample Submission (Requisition) Form – complete all pages
- Payment Options Form or Institutional Billing Instructions

For test codes, prices, CPT codes, and turn-around-times, please refer to the “6-Pyruvoyl-Tetrahydropterin Synthase (PTPS) Deficiency” page on our website: [www.genedx.com](http://www.genedx.com)