

QDPR Gene Analysis in Dihydropteridine Reductase (DHPR) Deficiency

Disorder also known as: Quinoid Dihydropteridine Reductase (QDPR) Deficiency, tetrahydrobiopterin deficiency, atypical hyperphenylalaninemia and phenylketonuria (aPKU)

Clinical Features:

Dihydropteridine reductase (DHPR) deficiency is an inborn error of tetrahydrobiopterin (BH₄) recycling that accounts for approximately one-third of all tetrahydrobiopterin deficiencies.^{1,2} Patients typically exhibit severe neurological symptoms including psychomotor retardation, tonal abnormalities, myoclonic epilepsy, hyperthermia without infections, swallowing difficulties and hypersalivation. Other features include mental retardation and microcephaly. The clinical course of untreated DHPR deficient patients is similar to that in some of the other inborn errors of BH₄ metabolism namely 6-pyruvoyl-tetrahydropterin synthase deficiency and GTP cyclohydrolase I deficiency.

Inheritance:

Autosomal Recessive

Genetics:

DHPR deficiency is caused by pathogenic variants in the *QDPR* gene that encodes the dihydropteridine reductase enzyme, which is involved in the regeneration of dihydrobiopterin formed during the hydroxylation of phenylalanine, tyrosine and tryptophan. DHPR deficiency is characterized by hyperphenylalaninemia that may be detected on newborn screening and deficiency of the neurotransmitters dopamine, epinephrine and serotonin in the central nervous system. The *QDPR* gene is located on chromosome 4p15.3 and has 7 exons.

Test Methods:

Variant analysis of the *QDPR* gene is performed on genomic DNA from the submitted specimen using bi-directional sequence analysis of the 7 coding exons, and the corresponding intron/exon boundaries. If sequencing identifies a variant on only one allele of the *QDPR* gene, and if clinically indicated, reflex deletion/duplication testing (ExonArrayDx) will be performed at no additional charge to evaluate for a 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 number of small studies with a collective total of 30 patients from different families with a clinical diagnosis of DHPR deficiency and deficient dihydropteridine reductase enzyme activity, all individuals were found to have two variants in the *QDPR* gene.^{3,4,5} The methods used by GeneDx are expected to be greater than 99% sensitive at detecting variants identifiable by sequencing.

Variant spectrum:

Greater than 30 QDPR variants have been described and are spread over the entire gene. The majority are missense variants with nonsense, splicing, and small deletions/insertions also described.⁶ Most patients are compound heterozygotes for private mutations.^{3,4} Only 3 variants have been identified more than once, all in patients from the Mediterranean.³ A genotype-phenotype correlation has been identified.⁶

References:

1. Kalkanoglu et al., (2001) *Prenat Diagn* 21:868-870 (PMID: 11746132).
2. Farrugia et al., (2007) *Mol Genet Metab* 90:277-283 (PMID: 17188538).
3. Dianzani et al., (1998) *Hum Mutat* 12:267-273 (PMID: 9744478).
4. Romstad et al., (2000) *Hum Genet* 107:546-553 (PMID: 11153907).
5. Smooker et al., (1999) *Hum Mutat* 13(6):503-4 (PMID: 10408783).
6. BIOMDB: Database of Mutations Causing Tetrahydrobiopterin Deficiencies (database online) (http://www.biopku.org/BioPKU_DatabasesBIOMDB.asp) curated by N. Blau, Beat Thöny