QDPR Gene Analysis in Dihydropteridine Reductase (DHPR) Deficiency

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] Affected individuals typically exhibit severe neurological symptoms including psychomotor retardation, tonal abnormalities, myoclonic epilepsy, hyperthermia without infections, swallowing difficulties, hypersalivation, intellectual disability and microcephaly. Hyperphenylalaninemia and deficiency of the neurotransmitters dopamine, epinephrine and serotonin, particularly in the CSF, are characteristic. 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. The QDPR gene is located on chromosome 4p15.3 and has 7 exons. It is estimated that the prevalence of BH4 deficiencies is approximately 1/1,000,000 individuals, and accounts for about 2% of infants with hyperphenylalaninemia identified by newborn screening. [3,4] Mild cases may be misdiagnosed or go undiagnosed.[4]

TEST METHODS

Using genomic DNA extracted from the submitted specimen, the complete coding regions and splice site junctions of the QDPR gene 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 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

Variants in QDPR have been described across the gene. The majority are missense variants with nonsense, splicing, and small deletions/insertions also described.[7] Most patients are compound heterozygotes for private mutations.[5,6]

REFERENCES:

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