POR Gene Analysis for P450 Oxidoreductase Deficiency

Clinical Features:

The POR gene is ubiquitously expressed and produces an 82-kDA membrane-bound protein that plays an important role in steroid and cholesterol synthesis. Cytochrome P450 oxidoreductase (POR) deficiency is a disorder of steroidogenesis associated with a broad range of clinical presentations.[1,2] Steroid abnormalities occur in all patients, consistent with a form of congenital adrenal hyperplasia (CAH) causing deficiencies of both 21-hydroxylase and 17α-hydroxylase/17,20-lyase; therefore, some patients with POR deficiency may have an abnormal newborn screen for 21-hydroxylase deficiency. Like classical CAH, the steroid abnormalities may lead to cortisol deficiency, which can be life-threatening without treatment in some cases.[1] Disordered sex development can be observed in both males and females, and ambiguous genitalia is a common finding. At the severe end of the spectrum, patients may also have skeletal and craniofacial findings consistent with Antley-Bixler syndrome (ABS), including craniosynostosis, brachycephaly, severe midface hypoplasia, radiohumeral synostosis, and multiple joint contractures. [1,2]

Genetics:

Cytochrome P450 oxidoreductase (POR) and ABS are both associated with autosomal recessive pattern of inheritance.

Test Methods:

Genomic DNA is extracted from the submitted specimen. For skin punch biopsies, fibroblasts are cultured and used for DNA extraction. The DNA is enriched for the complete coding regions and splice site junctions of the requested gene 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 reference sequences 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 at the exon-level; 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 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, but less for 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 identify most deletions and duplications involving coding exons but are less reliable for detecting copy number variants of less than 500 base pairs. Assessment of copy number events also depends on the inherent sequence properties of the targeted regions, including shared homology and exon size. Mosaicism detection is limited and balanced chromosome aberrations cannot be identified.

Clinical Sensitivity:

POR is the only gene known to be associated with P450 oxidoreductase deficiency (PORD). The majority of POR variants identified are sequencing variants, however, copy number variants have been reported in individuals with PORD and ABS in the literature.[2,6]

Antley-Bixler syndrome is genetically heterogenous. Variants in the POR gene have been identified in patients with skeletal and craniofacial features of ABS who also have genital anomalies and/or disordered steroidogenesis, whereas variants in the FGFR2 gene have been identified in patients with a clinical diagnosis of ABS in the absence of genital or steroid anomalies.[3,4] It has been reported that 19/32 (59%) patients with a clinical diagnosis of ABS had at least one identifiable variant in the POR gene, including 15/15 (100%) with abnormal steroids and/or genitalia.[3] Variants resulting in a more significant decrease in cytochrome P450 oxidoreductase functional activity are more frequently associated with the presence of skeletal and craniofacial abnormalities.[4,5]

References:

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