Genetic Testing of the POR Gene Analysis in P450 Oxidoreductase Deficiency and ABS

Disorder also known as: POR deficiency; Congenital adrenal hyperplasia with combined P450C17 and P450C21 deficiencies; Antley-Bixler syndrome

Clinical Features:
Cytochrome P450 oxidoreductase (POR) deficiency is a disorder of steroidogenesis associated with a broad range of clinical presentations. 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 in some cases can be life-threatening without treatment.[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, including craniosynostosis, brachycephaly, severe midface hypoplasia, radiohumeral synostosis, and multiple joint contractures.

Genetics:
Cytochrome P450 oxidoreductase (POR) and ABS both have an autosomal recessive pattern of inheritance. The POR gene is located on chromosome 7q11.2. It is approximately 32-kb and consists of 15 coding exons. It is ubiquitously expressed and produces an 82-kDA membrane-bound protein that plays an important role in steroid and cholesterol synthesis. The protein has two distinct domains, one containing both an NADPH-binding site and an FAD-binding site and the other containing the FMN domain. The POR protein binds NADPH and accepts a pair of electrons through its FAD component. The electrons are transferred to the FMN moiety and then are distributed to other cytochrome P450 enzymes, including CYP17A1, CYP21A2, CYP51A1, and CYP19A1.

Test Methods:
Analysis is performed by bi-directional sequencing of all 15 coding exons and the exon/intron splice junctions of the POR 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:
POR is the only gene known to be associated with P450 oxidoreductase deficiency; however, the sensitivity of POR sequencing is not well established at this time. An estimated 12% of

patients reported to date have only one identifiable variant in the POR gene, indicating that some variants lie outside of the coding exons and would not be detected with current methodology.[2]

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] In the largest study to date, 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]

Variant Spectrum:

To date, more than 30 inactivating variants have been identified in the POR gene. Although there is no evidence of any variant hotspots, there are a small number of recurrent variants, including the A287P variant in Caucasians and the R457H variant in Japanese patients.[1,3] The majority of variants are missense changes located in the central electron transfer domain; however, frameshift variants, small deletions, insertions, and splice site variants have also been identified and are scattered throughout the gene. Genotype-phenotype correlations have not been well established for the clinical features of POR deficiency at this time, although 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.[5,4]

References:

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3. Huang et al. (2005) Am J Hum Genet 76:729-749.
4. Reardon et al. (2000) J Med Genet 37:26-32.
5. Fluck et al. (2004) Curr Opin Pediatr 18:435-441.