

Genetic Testing of the CYP17A1 Gene Analysis in 17 α -Hydroxylase/17,20-Lyase Deficiency

Disorder also known as: Congenital adrenal hyperplasia due to 17 α -hydroxylase deficiency;
Steroid 17 α -hydroxylase deficiency

Clinical Features:

Combined 17 α -hydroxylase/17,20-lyase deficiency is a disorder of steroidogenesis associated with a broad range of clinical presentations. The steroid abnormalities result in a rare form of congenital adrenal hyperplasia (CAH) that accounts for about 1% of cases of CAH overall. The 17 α -hydroxylase deficiency leads to diminished cortisol production, although adrenal insufficiency is rare because hypersecretion of ACTH leads to increased corticosterone production. However, overproduction of mineralcorticoids also occurs due to hypersecretion of ACTH, and this often results in hypokalemia and early-onset hypertension in 85-90% of cases. The steroid abnormalities also affect production of enzymes needed to make hormones involved in sexual development. 46,XY individuals typically have female external genitalia, a blind vaginal pouch, and absence of Mullerian structures, although ambiguous genitalia and hypospadias with cryptorchidism have been reported. 46,XX individuals have normal female external genitalia but typically present at puberty due to lack of development of secondary sexual characteristics (“sexual infantilism”) and absent or irregular menses.

In rare cases, individuals with isolated 17,20-lyase deficiency have been reported. These individuals do not exhibit symptoms of mineralcorticoid excess as 17 α -hydroxylase activity is retained. 46,XY individuals with isolated 17,20-lyase deficiency typically present in infancy with ambiguous genitalia or inguinal hernias.

Genetics:

17 α -Hydroxylase and 17,20-Lyase Deficiency both have an autosomal recessive inheritance pattern. The CYP17A1 gene is located on chromosome 10q24.3. It is approximately 8.7 kb and consists of 8 coding exons. It is expressed in the adrenals and gonads, and it encodes the P450c17 enzyme. The enzyme catalyzes two distinct reactions. The 17 α -hydroxylase activity hydroxylates pregnenolone and progesterone, which is necessary for the synthesis of cortisol. The 17,20-lyase activity converts C21 compounds to C19 compounds, which is necessary for the production of the sex steroids DHEA and androstenedione.

Genotype-phenotype correlations are not well-established at this time. Variants that retain partial catalytic activity have been reported to be associated with a milder clinical phenotype than variants that result in complete inactivation of the enzyme.⁸ However, the severity of hypertension, hypokalemia, and sexual ambiguity varies, even among patients with two

inactivating variants.⁵ Additionally, two sisters with the same genotype were reported to be discordant for the presence of hypertension.¹

Test Methods:

Analysis is performed by bi-directional sequencing of all 8 coding exons and the exon/intron splice junctions of the CYP17A1 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:

CYP17A1 is the only gene known to be associated with 17 α -hydroxylase/17,20-lyase deficiency and isolated 17,20-lyase deficiency. More than 60 patients have been reported in the literature to date, almost all of whom have had two identifiable variants in the CYP17A1 gene by sequencing.

Variant Spectrum:

Most variants in the CYP17A1 gene are missense, nonsense, or frameshift variants, although a few splice site variants have been reported. Variants are scattered throughout the gene, although exon 8, which codes for the heme-binding region of the protein, has been suggested to be a hotspot for variants.³ The Arginine 96 and Tyrosine 329 residues also may be hotspots for variant, as several different amino acid substitutions have been described at these positions in patients from various ethnic backgrounds.^{4,1}

Several founder mutations have been described, including: R362C and W406R, accounting for 32% and 50% of Brazilian alleles, respectively⁵; 4 bp duplication (CATC), accounting for 92% of alleles in Canadian Mennonites and Dutch Freislanders⁶; c.1517_1525del and Y329Kfs, accounting for 32% and 27% alleles in Chinese patients, respectively.^{7,1}

References:

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