Genetics of Congenital Adrenal Hyperplasia

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KEYWORDS

• Congenital adrenal hyperplasia • Genetics • Adrenal insufficiency
• 21-hydroxylase deficiency • Pseudogene • Genetic counseling

KEY POINTS

- Congenital adrenal hyperplasia (CAH) refers to a group of autosomal recessive disorders due to single-gene defects in the various enzymes required for cortisol biosynthesis.
- CAH represents a continuous phenotypic spectrum with more than 95% of all cases caused by 21-hydroxylase deficiency. Genotyping is an important tool in confirming the diagnosis or carrier state, provides prognostic information on disease severity, and is essential for genetic counseling.
- The genes for the various variants of CAH are well characterized, and mutation analysis is widely available.
- Certain ethnic groups have a predilection to certain genotypes, which may have resulted from an ancient founder effect, a hot spot in the gene, unequal crossing-over during meiosis, or gene conversion of point mutations from a pseudogene.
- Several pitfalls in the genetic diagnosis of patients with CAH exist.

INTRODUCTION

Congenital adrenal hyperplasia (CAH) refers to a group of autosomal recessive disorders that impair cortisol biosynthesis. Consequently, overproduction of corticotropin-releasing hormone (CRH) and adrenocorticotropic hormone (ACTH)

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from the hypothalamus and pituitary glands, respectively, results in an increase and accumulation of various steroid precursors proximal to the block. This accumulation leads to defective cortisol synthesis, shunting of the accumulated steroid precursors through alternative pathways, and often adrenal gland hyperplasia. The biochemical defects in CAH translate to a spectrum of clinical consequences, which include adrenal insufficiency, genital ambiguity or disordered sex development, infertility, short stature, hypertension, and an increased risk of metabolic syndrome during adolescence and adulthood. The severity and clinical features of CAH vary depending on the enzymatic defect, its residual activity, age of presentation, and genotype.

CAH represents a continuous phenotypic spectrum (**Table 1**). More than 95% of all cases of CAH are caused by 21-hydroxylase deficiency (21-OHD); 21-OHD is classified into 3 subtypes according to clinical severity: classic salt wasting (SW), classic simple virilizing (SV), and nonclassic CAH (NCCAH; mild or late onset).[1] The classic

Table 1
Types of congenital adrenal hyperplasia

CAH Type	Causative Gene	Clinical Manifestation
21-Hydroxylase deficiency	*CYP21A2*	Classic: 46,XX ambiguous genitalia, adrenal insufficiency, salt-wasting, postnatal virilization Nonclassic: hyperandrogenism during childhood or early adulthood; may be asymptomatic
	CYP21A2 and *TNXB*	CAH-X: in addition to the above, joint hypermobility, joint pain, multiple joint dislocations, midline defects including possible cardiac structural abnormalities
11β-Hydroxylase deficiency	*CYP11B1*	Classic: 46,XX ambiguous genitalia, postnatal virilization, hypertension Nonclassic: hyperandrogenism during childhood or early adulthood; may be asymptomatic
17α-Hydroxylase deficiency	*CYP17A1*	Classic: female phenotype (46,XX or 46,XY sex reversal), hypertension, pubertal delay with absence of secondary sexual characteristics Partial: 46,XY variable degrees of genital ambiguity; 46, XX variable development of secondary sexual characteristics
3β-Hydroxysteroid dehydrogenase type 2 deficiency	*HSD3B2*	Classic: 46,XX and 46,XY ambiguous genitalia, adrenal insufficiency, salt wasting
POR deficiency	POR	46,XX and 46,XY ambiguous genitalia, adrenal insufficiency, severe salt wasting, possible maternal virilization during pregnancy; possible skeletal malformations (Antley-Bixler syndrome); no postnatal virilization
Lipoid CAH	StAR	Classic: phenotypic female (46,XX or 46,XY sex reversal), adrenal insufficiency, severe salt wasting Nonclassic: 46,XY variable degrees of genital ambiguity, adrenal insufficiency
Cholesterol side-chain cleavage enzyme deficiency	*CYP11A1*	Classic: phenotypic female (46,XX or 46,XY sex reversal), adrenal insufficiency, salt wasting Nonclassic: 46,XY variable degrees of genital ambiguity, adrenal insufficiency

Abbreviations: CAH-X, congenital adrenal hyperplasia with *tenascin*-X impairment; POR, P450 oxidoreductase; StAR, steroidogenic acute regulatory protein.