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# Congenital Adrenal Hyperplasia

*CYP21A2, CYP11B1,  
CYP17A1, HSD3B2, STAR*



**Frequently Used Abbreviations:** **ACTH:** adrenocorticotrophic hormone; **AIRE:** autoimmune regulator; **CAH:** congenital adrenal hyperplasia; **DSD:** disorder of sexual development; **3 $\beta$ -HSD:** 3 $\beta$ -hydroxysteroid dehydrogenase; **17-OHP:** 17-hydroxyprogesterone; **STAR:** steroid acute regulatory

## Introduction

Congenital adrenal hyperplasia (CAH) refers to a family of inherited disorders caused by enzymatic defects in adrenal steroid biosynthesis. In patients with CAH, reduced cortisol synthesis interrupts feedback inhibition of adrenocorticotrophic-hormone (ACTH) release from the pituitary, leading to continual stimulation of the adrenals by ACTH and, consequently, adrenal hyperplasia. Incidence of “classic” CAH, which presents in infancy with signs of adrenal insufficiency and/or ambiguous genitalia, has been estimated at 1:15,000. Prevalence of the “non-classic” form of CAH, which typically presents later in life and with much milder symptoms, may be as high as 1:100.<sup>1-4</sup>

The three major types of adrenal steroid hormones, glucocorticoids, mineralocorticoids, and adrenal androgens, are each produced through a separate biosynthetic pathway. All three pathways, however, share common precursor molecules. If an enzymatic block occurs in any of the three biosynthetic pathways, precursor molecules are shunted into the remaining functional pathway(s). Therefore, defects in a specific biosynthetic enzyme can simultaneously lead to deficiency in one or two types of adrenal steroids and overproduction of the remaining type(s). Presentation and treatment of CAH depend on 1) which of the three major biosynthetic pathways is/are affected by the enzymatic defect in adrenal steroid synthesis, 2) the severity of the enzymatic defect, and 3) whether gonadal steroid synthesis is also affected. The pattern of elevated biosynthetic precursor molecules is highly diagnostic of the type of CAH. Genetic testing can also be used for the differential diagnosis of CAH, since the genes coding for the enzymes involved in steroid biosynthesis have been identified. Loss-of-function mutations in the gene *CYP21A2* account for about 90% of all cases of CAH. Other, rarer forms of CAH are due to loss-of-function mutations in the genes *CYP11B1*, *CYP17A1*, *HSD3B2*, or *STAR* (lipoid CAH). All known forms of CAH show autosomal recessive inheritance. Genetic testing may be more sensitive than biochemical testing in cases of mild enzymatic defects. In addition, genetic testing can facilitate carrier detection, genetic counseling, and the early diagnosis and treatment of affected family members.

## Genetic Causes of CAH

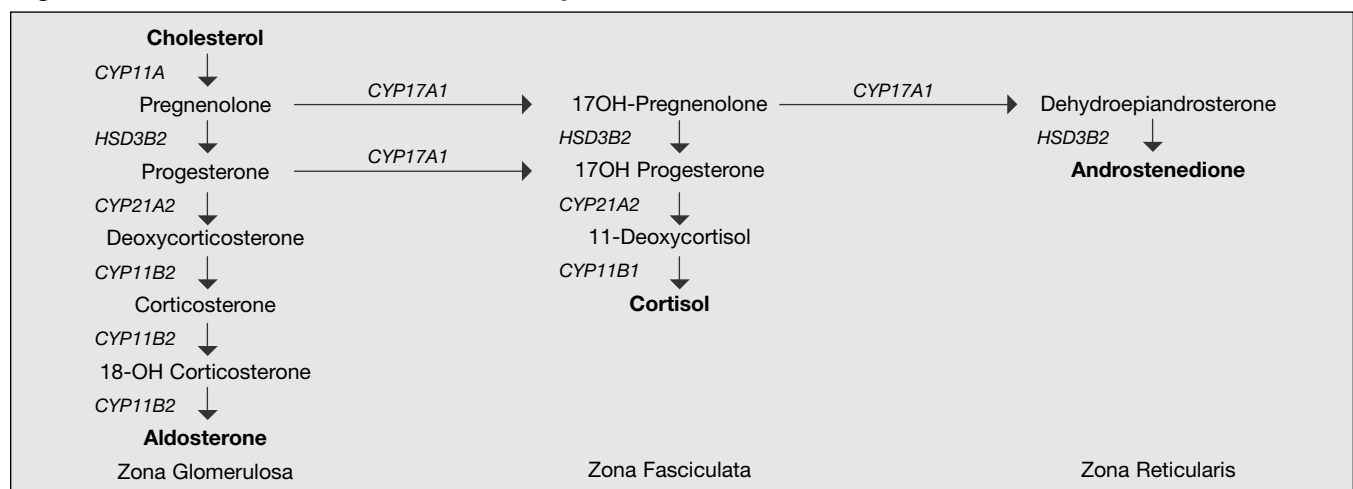
Figure 1 shows the normal biosynthetic pathways for mineralocorticoids, glucocorticoids, and adrenal androgens. Each step is catalyzed by a specific enzyme. The genes coding for these enzymes are indicated in italics. CAH can be caused by a defect in any one of several of these genes.

### 21-Hydroxylase Deficiency

Loss-of-function mutations in the gene *CYP21A2* account for about 90% of all cases of CAH.<sup>1-3</sup> *CYP21A2* codes for the cytochrome P-450 enzyme steroid 21-hydroxylase, which catalyzes the conversion of 17-hydroxyprogesterone (17OH progesterone, 17-OHP) to 11-deoxycortisol in the

glucocorticoid biosynthetic pathway and the conversion of progesterone to deoxycorticosterone in the mineralocorticoid biosynthetic pathway. Defects in 21-hydroxylase disrupt glucocorticoid and mineralocorticoid synthesis and may cause primary adrenal insufficiency and salt wasting. Precursors accumulating “upstream” of the enzymatic block are shunted into the biosynthetic pathway for adrenal androgens. The resulting overproduction of adrenal androgens leads to prenatal and/or postnatal virilization in genetic females and postnatal virilization in genetic males. The degree of virilization depends on the extent to which 21-hydroxylase activity is impaired, which also determines the degree of glucocorticoid and mineralocorticoid deficiency.

**Figure 1: Genes Associated with Steroid Biosynthesis in the Adrenal Cortex**



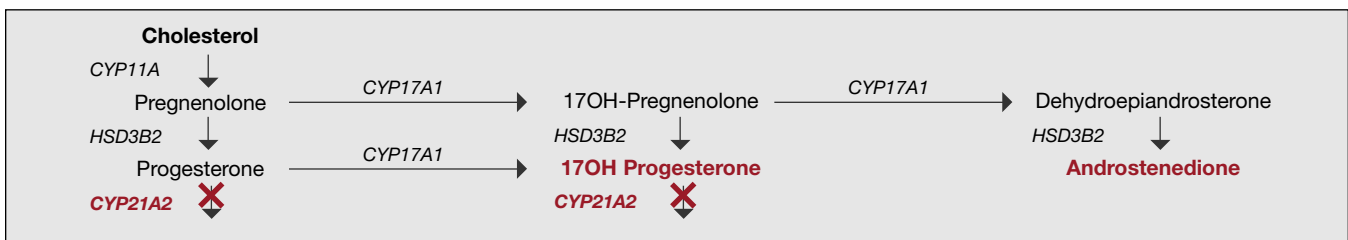
In the classic form of 21-hydroxylase deficiency, genetic females are born with ambiguous genitalia, and both males and females suffer from glucocorticoid deficiency and undergo premature adrenarche if left untreated. The classic form of 21-hydroxylase deficiency is further divided into the salt-wasting form [see Figure 2A], which is associated with mineralocorticoid deficiency, glucocorticoid deficiency, and adrenal androgen excess, and the simple-virilizing form [see Figure 2B], which is characterized by glucocorticoid deficiency and adrenal androgen excess only. The salt-wasting form is the most severe form of 21-hydroxylase deficiency and accounts for up to 75% of all classic cases. The non-classic form of 21-hydroxylase

deficiency is not associated with mineralocorticoid or glucocorticoid deficiency [see Figure 2C], but is characterized by mild adrenal androgen excess only.

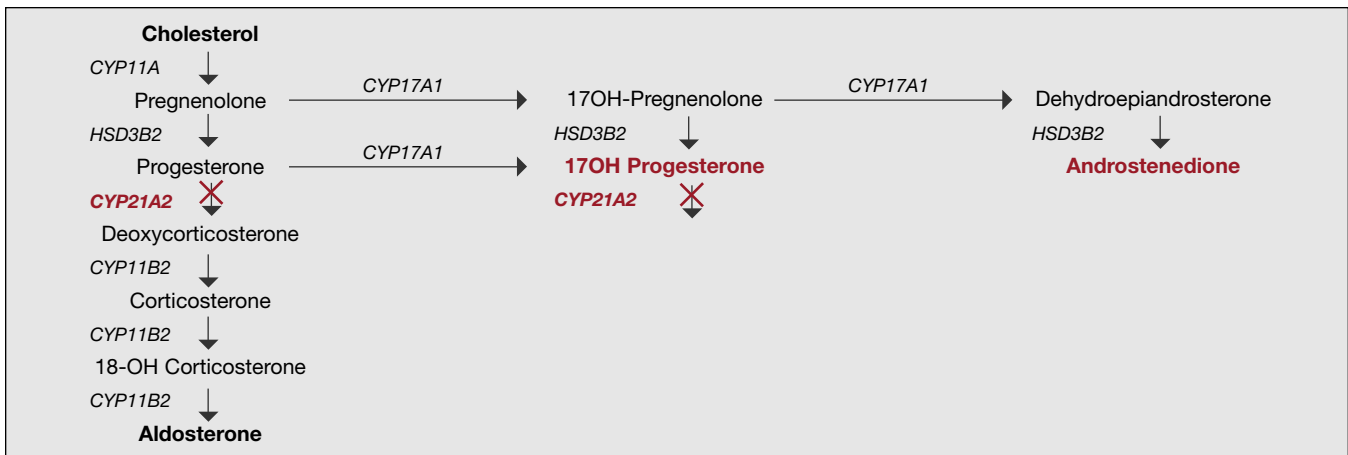
### 11 $\beta$ -Hydroxylase Deficiency

Loss-of-function mutations in the gene *CYP11B1* account for about 5-8% of all cases of CAH in Western Europe and the US.<sup>4,5</sup> *CYP11B1* codes for the cytochrome P-450 enzyme 11 $\beta$ -hydroxylase, which catalyzes the conversion of 11-deoxycortisol to cortisol in the glucocorticoid biosynthetic pathway. Defects in 11 $\beta$ -hydroxylase disrupt glucocorticoid synthesis, and precursors accumulating “upstream” of the

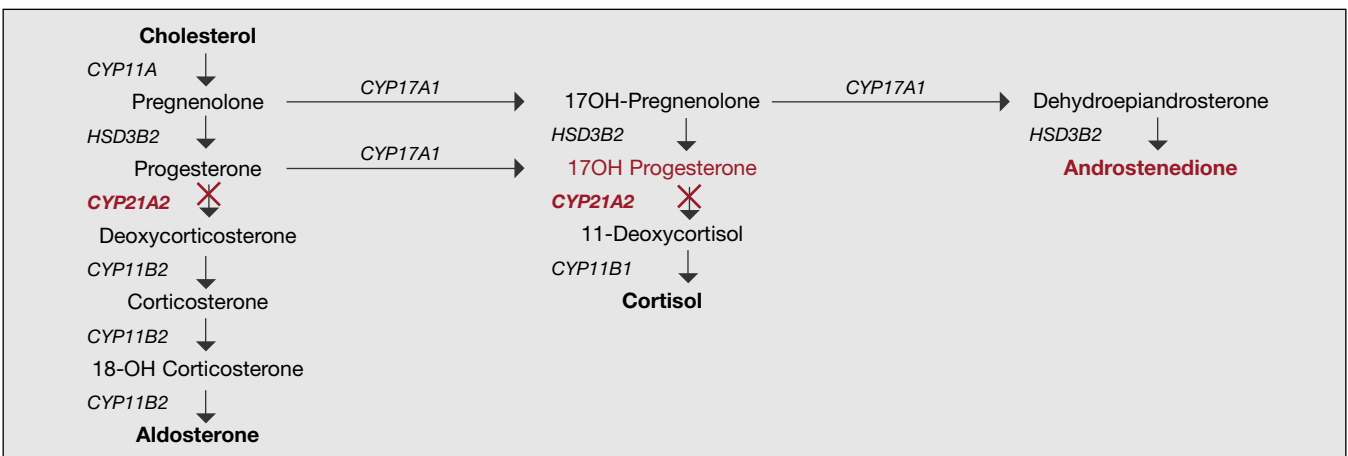
**Figure 2: 21-Hydroxylase Deficiency**  
**A. Salt-Wasting Classic Form**



**B. Simple-Virilizing Classic Form**



**C. Non-Classical Form**



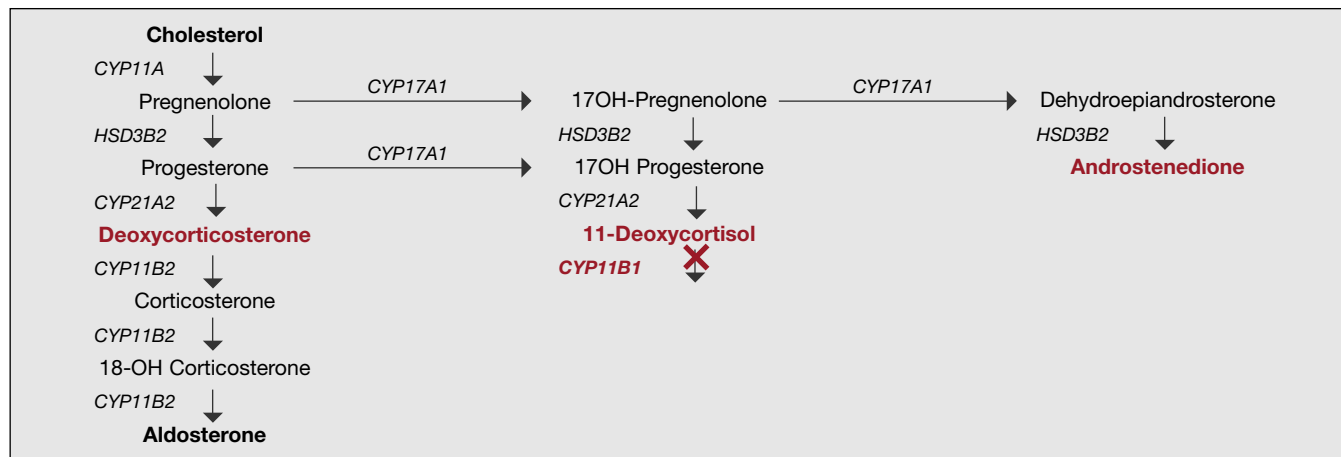
enzymatic block are shunted into the biosynthetic pathways for mineralocorticoids and adrenal androgens. Patients are protected from an adrenal crisis by presence of corticosterone, which possesses glucocorticoid activity. However, increased levels of deoxycorticosterone can give rise to hypertension, since this intermediate product in the mineralocorticoid biosynthetic pathway shows weak mineralocorticoid activity. Overproduction of adrenal androgens leads to prenatal and/or postnatal virilization in genetic females and postnatal virilization in genetic males. The degree of virilization depends on the extent to which 11 $\beta$ -hydroxylase activity is impaired, which also determines the degree of excess mineralocorticoid activity. In the classic form of 11 $\beta$ -hydroxylase deficiency, which accounts for about two thirds of all cases, genetic females are born with ambiguous genitalia, and both males and females are affected by postnatal hyperandrogenism if untreated [Figure 3A]. Hypertension due to excessive salt retention may also be present. The non-classic form of 11 $\beta$ -hydroxylase deficiency is characterized by mild adrenal androgen excess only [Figure 3B].

### 17 $\alpha$ -Hydroxylase Deficiency

Loss-of-function mutations in the gene **CYP17A1** account for about 1% of CAH in most populations, but represent the second most common cause of CAH in Brazil.<sup>6</sup> **CYP17A1** codes for a cytochrome P-450 enzyme with both 17 $\alpha$ -hydroxylase and 17,20-lyase activities, which performs a gatekeeper function for the entry of precursor molecules into the glucocorticoid and adrenal androgen biosynthetic pathways: 17 $\alpha$ -hydroxylase activity controls the branch point from the mineralocorticoid to the glucocorticoid biosynthetic pathway, and 17,20-lyase activity regulates the branch point from the glucocorticoid to the adrenal androgen biosynthetic pathway [see Fig. 4]. Defects in **CYP17A1** that disrupt both the hydroxylase and the lyase activity affect the synthesis of glucocorticoids and androgens in the adrenal cortex as well as steroid synthesis in the gonads.<sup>7</sup> Mineralocorticoid synthesis is not affected, but the block in the entry point to the glucocorticoid biosynthetic pathway leads to an increase in mineralocorticoid precursors such as deoxycorticosterone and corticosterone. This increase in the concentration of corticosterone, which exhibits glucocorticoid activity, compensates for the absence of cortisol and protects patients from an adrenal crisis. Increases in the

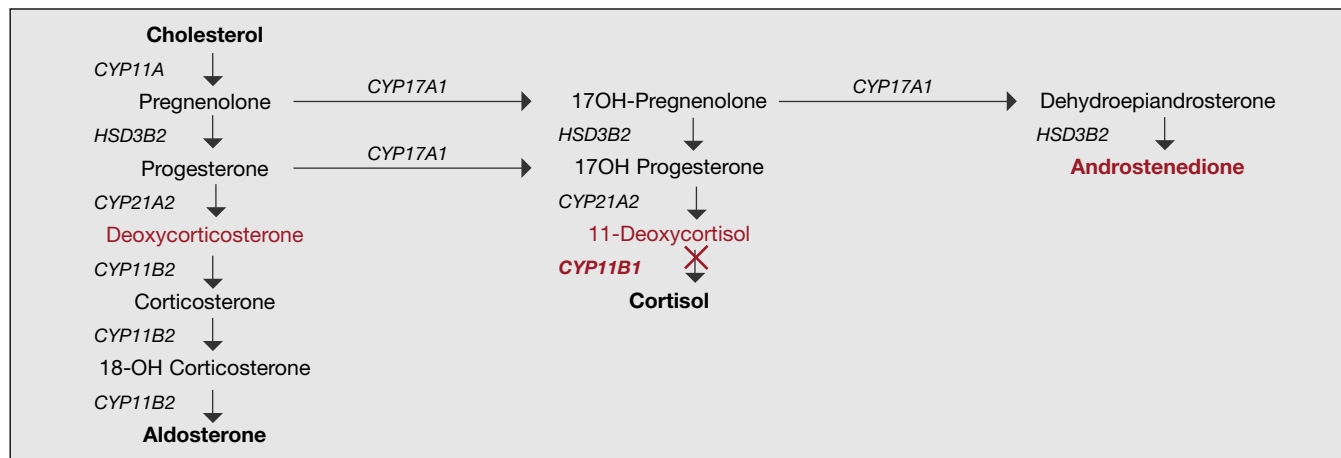
**Figure 3: 11 $\beta$ -Hydroxylase Deficiency**

**A. Classic Form**



**Figure 3: 11 $\beta$ -Hydroxylase Deficiency**

**B. Non-Classical Form**



levels of deoxycorticosterone and corticosterone are also believed to be the cause of the hypertension frequently observed in patients with  $17\alpha$ -hydroxylase deficiency, since both intermediates possess weak mineralocorticoid activity. Disruption of adrenal androgen production and gonadal steroid synthesis causes female or ambiguous external genitalia in 46XY males, and lack of pubertal progression and primary or, more rarely, secondary amenorrhea in 46XX females.

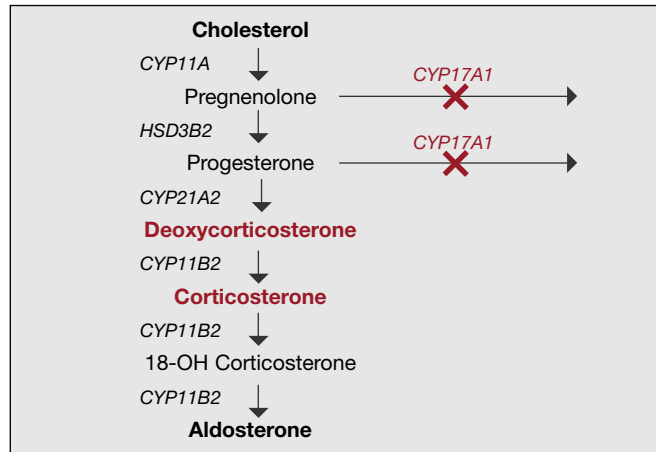
### 3 $\beta$ -Hydroxysteroid Dehydrogenase Deficiency

Loss-of-function mutations in the gene *HSD3B2* account for about 1% of CAH.<sup>8</sup> *HSD3B2* codes for the enzyme 3 $\beta$ -hydroxysteroid dehydrogenase (3 $\beta$ -HSD), which catalyzes the conversion of pregnenolone to progesterone in the mineralocorticoid biosynthetic pathway and the conversion of 17OH-pregnenolone to 17OH-progesterone in the glucocorticoid biosynthetic pathway. 3 $\beta$ -hydroxysteroid dehydrogenase is also necessary for conversion of dehydroepiandrosterone to androstenedione in the adrenals and for the biosynthesis of sex steroids in the gonads. In 46XY males, 3 $\beta$ -HSD deficiency is associated with ambiguous genitalia due to impaired testosterone synthesis in the gonads. In 46XX females, 3 $\beta$ -HSD deficiency may lead to premature adrenarche, amenorrhea, or ambiguous genitalia due to conversion of androgen precursors to androgens in peripheral tissues. Severe defects in 3 $\beta$ -HSD activity also cause deficiency in both mineralocorticoids and glucocorticoids and lead to salt wasting and primary adrenal insufficiency in males and females (salt-wasting form) [Figure 5].

### Congenital Lipoid Adrenal Hyperplasia

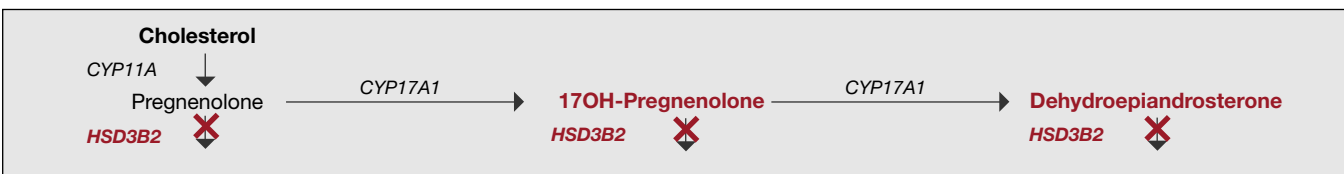
Loss-of-function mutations in the gene *STAR*, which are associated with congenital lipoid adrenal hyperplasia (lipoid

**Figure 4: 17 $\alpha$ -Hydroxylase Deficiency**

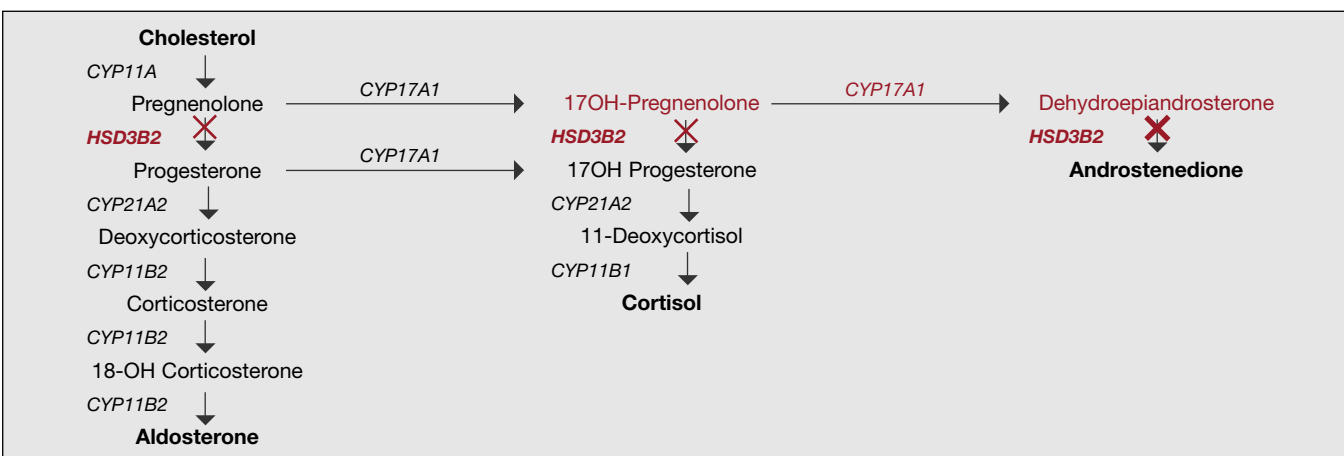


CAH), account for a small percentage of CAH in most populations, but appear to be more common in individuals of Japanese, Korean, or Palestinian ancestry.<sup>9</sup> *STAR* codes for the steroid acute regulatory protein, which fulfills a gatekeeper function for all of steroid biosynthesis by catalyzing the transfer of cholesterol from the cytosol into mitochondria, where the initial steps of steroidogenesis take place. Absence of functional StAR protein reduces cholesterol import into mitochondria by a factor of about ten, leading to impaired biosynthesis of all steroids and accumulation of cholesterol lipid droplets in the cytoplasm of affected cells. However, StAR-protein independent cholesterol import may allow for enough steroid synthesis to prevent acute symptoms in the absence of functional StAR protein, and only the gradual accumulation of lipid droplets leads to complete cessation of all steroidogenesis through

**Figure 5: 3 $\beta$ -Hydroxysteroid Dehydrogenase Deficiency**  
A. Salt-Wasting Form



### B. Non-Salt-Wasting Form



generalized damage to the affected cells. For this reason, defects in *STAR* cause damage to steroidogenic target organs such as the adrenals and the gonads only if they are stimulated to produce steroids.

This “two hit” model of lipoid CAH explains why 46XY infants with lipoid CAH are born as phenotypic females, while onset of acute primary adrenal insufficiency and salt wasting may not occur until several weeks or even months after birth. The fetal testis is stimulated and thus damaged by absence of functional StAR early in gestation, leading to lack of testosterone and preventing development of male external genitalia. In the adrenals, in contrast, stimulation prior to birth affects primarily the fetal zone. The definitive zone, which postnatally develops into the zona glomerulosa and zona fasciculata, may therefore remain partially functional for several weeks or months after birth in individuals with reduced StAR-protein activity. Similarly, the ovaries in 46XX individuals remain hormonally silent until puberty, when individual ovarian follicles are stimulated and, in individuals with lipoid CAH, thus damaged during each cycle. However, while 46XX individuals with lipoid CAH can spontaneously enter puberty and may undergo menarche, their cycles remain anovulatory because lack of StAR-protein activity prevents the progesterone surge necessary for ovulation.

### Clinical Presentation of CAH

Presentation of CAH depends on the underlying genetic defect and the severity of the enzymatic impairment [Table 1].

#### Clinical Presentation of 21-Hydroxylase Deficiency

Three forms of 21-hydroxylase deficiency are distinguished: the salt-wasting classic form, the simple-virilizing classic form, and the non-classic form. Both classic forms of 21-hydroxylase deficiency lead to ambiguous genitalia in genetically female infants and to primary adrenal insufficiency in males and females, presenting with symptoms such as

hyperpigmentation of the skin and mucosal membranes, failure to thrive, vomiting, and hypoglycemia. The salt-wasting form also causes acutely life-threatening renal sodium wasting and hyponatremic dehydration. In both male and female children, poorly treated 21-hydroxylase deficiency leads to rapid growth and advanced bone age, resulting in premature adrenarche and reduced adult height. Continued postnatal virilization may cause premature penile (but not testicular) growth in genetic males and clitoral growth in genetic females.

The non-classic form of 21-hydroxylase deficiency is not associated with primary adrenal insufficiency and/or ambiguous genitalia and presents in girls or women with milder symptoms of androgen excess, such as hirsutism, cystic acne, or oligomenorrhea.

#### Clinical Presentation of 11 $\beta$ -Hydroxylase Deficiency

11 $\beta$ -Hydroxylase deficiency presents in both classic and non-classic forms. The classic form is associated with ambiguous genitalia in genetically female infants. In both male and female children, poorly treated 11 $\beta$ -hydroxylase deficiency can lead to hypertension due to excessive salt retention, rapid growth, and advanced bone age, resulting in reduced adult height and postnatal hyperandrogenism. Continued postnatal virilization may cause premature penile (but not testicular) growth in genetic boys and clitoral growth in genetic girls.

The non-classic form of 11 $\beta$ -hydroxylase deficiency is not associated with hypertension or ambiguous genitalia and presents in girls or women with milder symptoms of androgen excess, such as hirsutism, cystic acne, or oligomenorrhea.

#### Clinical Presentation of 17 $\alpha$ -Hydroxylase Deficiency

17 $\alpha$ -Hydroxylase deficiency is associated with a 46XY disorder of sexual development (DSD) and typically presents with low-renin hypertension and lack of pubertal progression in

**Table 1: Symptoms Associated with CAH**

Symptoms						
Gene	Protein	Form of CAH	External Genitalia	Glucocorticoid Activity	Mineralocorticoid Activity	Hirsutism in Women
CYP21A2	21-hydroxylase	classic, salt-wasting	ambiguous in XX	deficient	deficient	yes
		classic, simple virilizing	ambiguous in XX	deficient	clinically normal	yes
		non-classic	normal	clinically normal	clinically normal	yes
CYP11B1	11 $\beta$ -hydroxylase	classic	ambiguous in XX	clinically normal	excessive or clinically normal	yes
		non-classic	normal	clinically normal	clinically normal	yes
CYP17A1	17 $\alpha$ -hydroxylase		female or ambiguous in XY	clinically normal	excessive or, rarely, clinically normal	no
HSD3B2	3 $\beta$ -hydroxysteroid dehydrogenase	salt-wasting (classic)	ambiguous in XY; ambiguous or normal in XX	deficient	deficient	yes
		non-salt-wasting (non-classic)	ambiguous in XY; ambiguous or normal in XX	clinically normal	clinically normal	probably
STAR	steroid acute regulatory protein	lipoid CAH	female in XY	deficient	deficient	no

adolescent phenotypic females. In cases of partial  $17\alpha$ -hydroxylase deficiency, 46XY individuals may present with ambiguous genitalia at birth and 46XX individuals with primary or secondary amenorrhea or ovarian cysts in adolescence or early adulthood. Hypertension may or may not be present with partial  $17\alpha$ -hydroxylase deficiency. Both 46XX and 46XY individuals with  $17\alpha$ -hydroxylase deficiency are typically infertile.

### **Clinical Presentation of $3\beta$ -Hydroxysteroid Dehydrogenase Deficiency**

$3\beta$ -HSD deficiency presents in salt-wasting and a non-salt-wasting forms. Both forms are associated with ambiguous genitalia in genetic males and with premature adrenarche, amenorrhea, or ambiguous genitalia in genetic females. The salt-wasting form also causes renal sodium wasting and primary adrenal insufficiency. The severity of female virilization or male undervirilization is not correlated to the presence or absence of the salt-wasting phenotype.

### **Clinical Presentation of Lipoid CAH**

Lipoid CAH is associated with a 46XY DSD and is seen almost exclusively in phenotypic females. Symptoms of primary adrenal insufficiency and/or salt wasting typically become apparent within the first days or weeks of life, but may be delayed for up to several months after birth. Lipoid CAH may be associated with massive adrenal enlargement, since lack of cortisol biosynthesis prevents feedback inhibition of corticotropin releasing hormone and adrenocorticotrophic hormone (ACTH) release from hypothalamus and pituitary, respectively, allowing continual stimulation of the adrenals.

In postpubertal 46XX females, lipoid CAH may also cause hyperplasia of the ovaries and can lead to large ovarian cysts. Both 46XX and 46XY individuals with lipoid CAH are infertile.

## **Diagnosis of CAH**

### **Diagnosis of 21-Hydroxylase Deficiency**

The classic form of 21-hydroxylase deficiency is suggested by ambiguous genitalia in infants or, in genetically male infants, by symptoms of primary adrenal insufficiency. Diagnosis of primary adrenal insufficiency is based on detection of high serum ACTH in the presence of low or normal serum cortisol or the lack of an increase in serum cortisol levels in response to cosyntropin administration. Detection of elevated 17-OHP levels, which in many states are determined as part of routine newborn screening, is also indicative of 21-hydroxylase deficiency. However, most elevated 17-OHP levels detected on a newborn screening test are false positives and warrant additional testing.

The non-classic form of 21-hydroxylase deficiency is suspected in girls or women with hirsutism or oligomenorrhea. Diagnostic steroid precursors are the same as for the classic form, although increases in concentration tend to be less dramatic.

### **Diagnosis of $11\beta$ -Hydroxylase Deficiency**

The classic form of  $11\beta$ -hydroxylase deficiency is suggested by ambiguous genitalia in infants or by low-renin hypertension

in children. Detection of elevated deoxycorticosterone and/or 11-deoxycortisol levels also indicates  $11\beta$ -hydroxylase deficiency.

The non-classic form of  $11\beta$ -hydroxylase deficiency is suspected in girls or women with hirsutism or oligomenorrhea. Diagnostic steroid precursors are the same as for the classic form, although increases in concentration tend to be less dramatic.

### **Diagnosis of $17\alpha$ -Hydroxylase Deficiency**

$17\alpha$ -Hydroxylase deficiency is indicated by low-renin hypertension in infants with ambiguous genitalia, 46XY infants with DSD, or adolescent females with lack of pubertal progression. Elevation in deoxycorticosterone and corticosterone, especially in response to cosyntropin stimulation, is diagnostic of  $17\alpha$ -hydroxylase deficiency. In 46XY individuals, it is important to differentiate  $17\alpha$ -hydroxylase deficiency from androgen insensitivity syndrome or  $5\alpha$ -reductase deficiency as the cause of ambiguous or female genitalia, since hypertension associated with  $17\alpha$ -hydroxylase deficiency can lead to life-threatening complications if left untreated.

### **Diagnosis of $3\beta$ -Hydroxysteroid Dehydrogenase Deficiency**

$3\beta$ -HSD deficiency is indicated by salt-wasting in undervirilized 46XY infants and in 46XX infants with variable degrees of virilized genitalia, after exclusion of 21-hydroxylase deficiency.  $3\beta$ -HSD deficiency may also be considered as a cause of premature adrenarche or amenorrhea in females, after exclusion of the more common non-classic forms of CAH. Increased levels of pregnenolone, 17OH-pregnenolone, and dehydroepiandrosterone in response to cosyntropin stimulation are diagnostic of  $3\beta$ -HSD deficiency.

### **Diagnosis of Lipoid CAH**

Diagnosis of lipoid CAH is suggested by massive adrenal enlargement in phenotypically female infants with symptoms and biochemical signs of primary adrenal insufficiency and/or salt wasting.

## **Genetic Diagnosis of all Types of CAH**

Since published studies have established a causal relationship between specific types of CAH and variants in *CYP21A2*, *CYP11B1*, *HSD3B2*, *CYP17A1*, or *STAR*, a differential diagnosis of CAH can be achieved through genetic testing. In the case of 21-hydroxylase deficiency, genetic testing can also suggest the form of 21-hydroxylase deficiency present, since certain mutations in *CYP21A2* are found predominantly in association with a specific form of the disease [see Genetics of CAH].

In addition, genetic testing can be used to confirm a positive newborn screening test, identify carriers of CAH-associated mutations, and diagnose CAH in family members of patients at or before birth.

## **Treatment of CAH**

Glucocorticoid replacement therapy is used for all forms of CAH. Dosing has to be carefully calibrated, since excessive glucocorticoid treatment can result in significantly reduced

adult height. Glucocorticoid treatment may also trigger true precocious puberty, which can be treated with long-acting gonadotropin-releasing-hormone analogues. In the case of the simple-virilizing form of 21-hydroxylase deficiency, addition of mineralocorticoid replacement may reduce the glucocorticoid dose required for maintaining acceptable 17-OHP levels.

Mineralocorticoid replacement is indicated for all salt-wasting forms of CAH (21-hydroxylase deficiency, 3 $\beta$ -HSD deficiency, and lipoid CAH). In young children, dietary sodium supplements may also be necessary.

Estrogen replacement can induce development of secondary female characteristics in phenotypically female individuals with 17 $\alpha$ -hydroxylase deficiency, reduce adult height in 46XY phenotypically female individuals with 17 $\alpha$ -deficiency, and prevent hypergonadotropic hypogonadism and ovarian cysts in 46XX individuals with 17 $\alpha$ -hydroxylase deficiency or lipoid CAH.

Dexamethasone treatment during pregnancy has been shown to minimize genital virilization in fetuses affected with 21-hydroxylase or 11 $\beta$ -hydroxylase deficiency. Careful consideration of the benefits and risks of prenatal diagnosis and treatment should be given before initiating therapy.

In patients with ambiguous genitalia, families should receive appropriate counseling, sex should be assigned, and surgical correction of genital anomalies should be considered. Removal of dysgenetic gonads may be recommended to reduce the risk of malignancy.

## Genetics of CAH

All forms of CAH show autosomal recessive inheritance and affect both males and females, although ambiguous genitalia may occur in only one sex depending on the gene affected. In compound heterozygotes, the phenotype is typically determined by the "milder" mutation. Due to the high carrier frequency for *CYP21A2* mutations, such compound heterozygosity for deleterious mutations is relatively common in patients with CAH.

Most 21-hydroxylase deficiency is due to transfer of one or more deleterious mutations from the closely related pseudogene *CYP21P* to *CYP21A2*, a process known as gene conversion, and about 20% of 21-hydroxylase deficiency involves large

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deletions in *CYP21A2* caused by unequal recombination events between *CYP21A2* and *CYP21P*. Homozygous large gene conversions and large deletions are generally associated with the salt-wasting form, while homozygous mutations causing an amino acid change from isoleucine to asparagine at position 173 in 21-hydroxylase typically lead to the simple virilizing form, and homozygous mutations resulting in an amino acid change from valine to leucine at position 282 or from proline to leucine at position 31 have been linked to the non-classic form. (Please note that these mutations are often designated as Ile172Asp, Val281Leu, and Pro30Leu, especially in older publications.)

## Genetic Testing for CAH

Genetic testing for CAH can confirm a diagnosis of CAH and allow a differential diagnosis of the various types of the condition, which may require different treatment. Genetic testing can also identify carriers of CAH-associated mutations, facilitating genetic counseling and the diagnosis of CAH in family members of patients. In mild cases, where elevations in steroid hormone precursors may be subtle, genetic testing may be more accurate than biochemical testing.

### How Is Genetic Testing for CAH Performed?

DNA for testing is obtained from leukocytes present in a small blood sample. The gene coding sequences are amplified in a highly specific manner through a polymerase chain reaction (PCR), and all PCR products are fully sequenced. Presence of the most common large deletion in *CYP21A2* is indicated by detection of a deletion-specific PCR product. Results are interpreted, and a detailed result report is sent to the patient's physician.

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