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21-Hydroxylase-Deficient Congenital Adrenal Hyperplasia

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Summary

Disease characteristics. 21-hydroxylase deficiency (21-OHD) is the most common cause of congenital adrenal hyperplasia (CAH), a family of autosomal recessive disorders involving impaired synthesis of cortisol from cholesterol by the adrenal cortex. In 21-OHD CAH, excessive adrenal androgen biosynthesis results in virilization in all individuals and salt wasting in some individuals. A classic form with severe enzyme deficiency and prenatal onset is distinguished from a nonclassic form with moderate enzyme deficiency and postnatal onset. The classic form is further divided into the simple virilizing form (~25% of affected individuals) and the salt-wasting form,f in which aldosterone production is inadequate (>75% of individuals). Newborns with salt-wasting 21-OHD CAH are at risk for life-threatening salt-wasting crises. Individuals with the nonclassic form of 21-OHD CAH have only moderate enzyme deficiency and present postnatally with signs of hyperandrogenism; females with the nonclassic form are not virilized at birth.

Diagnosis/testing. The diagnosis of 21-OHD CAH is suspected in: females who are virilized at birth, who become virilized postnatally, or who have precocious puberty or adrenarche; males with virilization in childhood; and infants of either sex with a salt-wasting crisis in the first four weeks of life. The diagnosis of 21-OHD CAH is confirmed by biochemical findings. Molecular genetic testing of the *CYP21A2* gene for a panel of nine common mutations and gene deletions detects about 80%-98% of disease-causing alleles in affected individuals and carriers. Entire gene sequencing may detect rarer alleles in affected individuals in whom the mutations are not identified by targeted mutation analysis or deletion/duplication analysis. Molecular genetic testing can be used for diagnosis in newborns with equivocal biochemical testing but is primarily used in genetic counseling for carrier detection of at-risk relatives and for prenatal diagnosis.

Management. Treatment for classic 21-OHD CAH includes glucocorticoid replacement therapy, which needs to be increased during periods of stress. Individuals with the salt-wasting form of 21-OHD CAH require treatment with 9α-fludrohydrocortisone and often sodium chloride. Bilateral adrenalectomy may be indicated for individuals with severe 21-OHD CAH who are homozygous for two null mutations and who have a history of poor control with hormonal replacement therapy. Females who are virilized at birth may require feminizing genitoplasty. Precocious puberty is treated with analogs of luteinizing hormone-releasing

hormone (LHRH). Surveillance includes monitoring of glucocorticoid/mineralocorticoid replacement therapy every three to four months while children are actively growing and less often thereafter, and monitoring for testicular adrenal rest tumors in males every three to five years after onset of puberty.

Genetic counseling. 21-OHD CAH is inherited in an autosomal recessive manner. Most parents are heterozygotes with one normal allele and one mutated allele. Approximately 1% of mutations occur *de novo*; thus, 1% of probands have only one parent who is heterozygous. In some instances, a parent who was not previously known to be affected may be found to have the nonclassic form of 21-OHD CAH. If the parents of a proband are both obligate heterozygotes, each sib has a 25% chance of inheriting both altered alleles and being affected, a 50% chance of inheriting one altered allele and being an unaffected carrier, and a 25% chance of inheriting both normal alleles and being unaffected. Once an at-risk sib is known to be unaffected, the risk of his/her being a carrier is 2/3. Prenatal testing is available and is often used in conjunction with prenatal treatment with dexamethasone to reduce the virilization of affected females and thus to reduce their need for clitoroplasty and/or vaginoplasty.

Diagnosis

Clinical Diagnosis

21-hydroxylase-deficient congenital adrenal hyperplasia (21-OHD CAH) is suspected in the following:

- Females who are virilized at birth, or who become virilized postnatally, or who have precocious puberty or adrenarche
- Males with virilization in childhood (i.e., pseudoprecocious puberty)
- Any infant with a salt-losing crisis in the first four weeks of life

Testing

Affected Untreated Individuals —17-hydroxyprogesterone (17-OHP). The diagnosis of 21-OHD CAH is confirmed by biochemical findings, such as an unequivocally elevated serum concentration of 17-OHP; i.e., greater than 20,000 ng/dL for classic 21-OHD CAH and between 2,000 and 15,000 ng/dL for nonclassic 21-OHD CAH (see Figure 1).

Plasma renin

- Plasma renin activity (PRA) is markedly elevated in individuals with the salt-wasting form of 21-OHD CAH and can also be elevated in some individuals with the simple virilizing form of 21-OHD CAH.
- Direct measurement of active renin can also be used.

Other adrenal steroids

- Serum concentrations of Δ^4-androstenedione and progesterone are increased in males and females with 21-OHD CAH.
- Serum concentrations of testosterone and adrenal androgen precursors are increased in affected females and prepubertal males.

Note: In individuals with the salt-wasting form of 21-OHD CAH, the serum concentration of aldosterone is inappropriately low compared to the degree of PRA elevation.

ACTH stimulation test. The serum concentration of 17-hydroxyprogesterone and Δ^4-androstenedione measured at baseline and at 60 minutes after intravenous injection of a

standard 250-µg bolus of synthetic ACTH (Cortrosyn^{TM}) are plotted on the nomogram in Figure 1. Although the ACTH stimulation test provides far more reliable diagnosis of 21-OHD CAH than a test of baseline values alone, the results must be confirmed with molecular genetic testing of *CYP21A2*.

Electrolytes. Individuals with untreated or poorly controlled salt wasting may have a decreased serum concentration of sodium, chloride, and total carbon dioxide (CO_2), an increased serum concentration of potassium, and inappropriately increased urine concentration of sodium.

Karyotype. Females with 21-OHD CAH have a normal 46,XX karyotype; males with 21-OHD CAH have a normal 46,XY karyotype.

Carriers —Individuals with one normal allele and one mutant allele are carriers (heterozygotes) and are asymptomatic; following ACTH stimulation, however, they may have slightly higher serum concentrations of 17-OHP than individuals with two normal alleles (Figure 1). In addition, because overlap exists in serum concentration of 17-OHP between heterozygotes and non-carriers after ACTH stimulation, such testing is no longer the preferred method of carrier identification.

Newborn Screening —Newborn screening for 21-OHD CAH serves two purposes:

- To identify infants with the classic form of 21-OHD CAH who are at risk for life-threatening salt-wasting crises
- To expedite the diagnosis of females with ambiguous genitalia

Newborn screening can also detect some (though not all) individuals with the nonclassic form of 21-OHD CAH.

States with mandated newborn screening for 21-OHD CAH are identified in the National Newborn Screening Status Report (pdf). The concentration of 17-OHP is measured on a filter paper blood spot sample obtained by the heel-stick technique as used for newborn screening for other disorders [Pang & Shook 1997].

- The majority of screening programs use a single screening test without retesting of samples with questionable 17-OHP concentrations (see Published Statements and Policies Regarding Genetic Testing).
- To improve efficacy of screening, a small number of screening programs re-evaluate samples with borderline first-tier test results with a second tier test. For example, because of the high false-positive rate of immunoassay methods, some programs measure the concentration of different hormones (17-OHP, Δ^4-androstenedione, and cortisol) by liquid-chromatography-tandem mass spectrometry as a second-tier test on samples with a positive first-tier test [Minutti et al 2004].

Note: (1) Samples taken in the first 24 hours of life are elevated in all infants and may give false-positive results [Allen et al 1997, Therrell et al 1998]. (2) False-positive results may also be observed in low birth-weight infants [Allen et al 1997] or premature infants [al Saedi et al 1996]. (3) False-negative results may be observed in neonates receiving dexamethasone for management of unrelated problems [Rohrer et al 2003].

Molecular Genetic Testing

GeneReviews designates a molecular genetic test as clinically available only if the test is listed in the GeneTests Laboratory Directory *by either a US CLIA-licensed laboratory or a non-US clinical laboratory. GeneTests does not verify laboratory-submitted information or warrant*

any aspect of a laboratory's licensure or performance. Clinicians must communicate directly with the laboratories to verify information.—ED.

Molecular Genetic Testing—Gene. *CYP21A2* is the only gene associated with 21-OHD CAH.

Clinical uses

- Confirmatory diagnostic testing
- Carrier testing
- Prenatal diagnosis
- Genotype/phenotype correlation for management (If a genotype associated with salt wasting is identified, administration of salt-retaining hormone [9α-fludrohydrocortisone] and salt supplementation may avert a salt-wasting crisis.)
- Preimplantation genetic diagnosis

Clinical testing

- **Targeted mutation analysis.** Molecular genetic testing of the *CYP21A2* gene for a panel of common mutations and gene deletions detects 80%-98% of disease-causing alleles in affected individuals. This set of mutations arises as a result of gene conversion (replacement of the *CYP21A2* gene by its adjacent pseudogene *CYP21A1P*, which contains multiple deleterious mutations) or unequal crossing over between *CYP21A2* and *CYP21A1P* [Wedell 1998]. The majority of individuals from heterogeneous populations with 21-OHD CAH are compound heterozygotes [Krone et al 2000].
- **Deletion/duplication analysis.** About 20% of mutant alleles are meiotic recombinations deleting a 30-kb gene segment that encompasses the 3' end of the *CYP21A1P* pseudogene, all of the adjacent *C4B* complement gene, and the 5' end of *CYP21A2*, producing a nonfunctional chimeric pseudogene [White et al 1988]. Methods such as Southern blot analysis, homozygosity testing for single nucleotide polymorphisms (SNPs), and multi-ligation probe analysis (MLPA) can be used to detect large deletions, including this 30-kb deletion.
- **Sequence analysis.** Entire gene sequencing may detect rarer alleles in affected individuals in whom mutations are not identified by targeted mutation analysis or deletion/duplication analysis.

Table 1 summarizes molecular genetic testing for this disorder.

Table 1. Molecular Genetic Testing Used in 21-OHD CAH

Test Methods	Mutations Detected	Mutation Detection Rate [1]	Test Availability
Targeted mutation analysis	A/C659G (intron 2 splice mutation), deletions, including complete deletion and 8-bp deletion in exon 3, P30L, I172N, exon 6 cluster mutation V281L, F306+t, Q318X, R356W, P453S [2]	~80%-98%	Clinical Testing
Deletion/duplication analysis	Complete deletion of *CYP21A2*		
Sequence analysis	*CYP21A2* sequence alterations	>80%-98%	

1. % of disease-causing alleles in affected individuals

2. Mutation panels may vary by laboratory.

Interpretation of test results

- **Sequence analysis.** For issues to consider in interpretation of sequence analysis results, click here.
- **Targeted mutation analysis.** Issues to consider in interpretation of targeted mutation analysis:
  - A large-scale gene conversion can transfer sequence containing more than one mutation from the pseudogene to the active gene [Mao et al 2002]. Thus, when targeted mutation analysis detects multiple mutations, it is possible that the mutations are either in *trans* configuration (i.e., are on separate chromosomes) or in *cis* configuration (i.e., are on the same chromosome and thus represent only one mutant allele rather than two). To avoid diagnostic errors, studying both parents as well as the proband is recommended to confirm the mutations and to determine if they are in *cis* configuration or *trans* configuration.
  - Another potential cause of misdiagnosis is duplication of the *CYP21A2* gene [Koppens et al 2002]. This could affect the screening of individuals who are not known carriers. A person carrying a functional gene and a copy with a mutation on the same chromosome may be incorrectly labeled a carrier.

Testing Strategy for a Proband with Classic 21-OHD CAH

For newborns (after the first day of life) and infants who have ambiguous genitalia or are at risk for 21-OHD CAH, the following are indicated:

- Complete history
- Complete physical examination
- Ultrasound examination of the pelvis and adrenal glands
- Karyotype or FISH for X and Y chromosome detection
- Measurement of serum concentration of 17-OHP and adrenal androgens
- In newborns with slight to moderate elevations of 17-OHP concentration, 60-minute ACTH stimulation test and molecular genetic testing of *CYP21A2* to confirm or exclude the diagnosis of 21-OHD CAH
- Measurement of PRA and serum electrolytes while monitoring the affected individual for symptoms and signs of adrenal crisis

Testing Strategy for a Proband with Nonclassic 21-OHD CAH

- A 60-minute ACTH stimulation test

  OR
- A single early-morning (before 8am) measurement of plasma 17-OHP concentration (Baseline values in affected individuals are not always elevated.)
- Molecular genetic testing of *CYP21A2*

Genetically Related (Allelic) Disorders

No other phenotypes are known to be associated with mutations in *CYP21A2*.

A contiguous gene syndrome involving *CYP21A2* and *TNX* led to a combination of Ehler-Danlos syndrome, hypermobility type and 21-OHD CAH [Burch et al 1997, Schalkwijk et al 2001].

Clinical Description

Natural History

21-hydroxylase-deficient congenital adrenal hyperplasia (21-OHD CAH) occurs in a classic form and a nonclassic form (Table 2).

In classic 21-OHD CAH, prenatal exposure to potent androgens such as testosterone and Δ^4-androstenedione at critical stages of sexual differentiation virilizes the external genitalia of genetic females, often resulting in genital ambiguity at birth. The classic form is further divided into the simple virilizing form (~25% of individuals) and the salt-wasting form, in which aldosterone production is inadequate (≥75% of individuals). Newborns with salt-wasting CAH caused by 21-OHD CAH are at risk for life-threatening salt-wasting crises.

Individuals with the nonclassic form of 21-OHD CAH have only moderate enzyme deficiency and present postnatally with signs of hyperandrogenism; females with the nonclassic form are not virilized at birth.

Table 2. Clinical Features in Individuals with Classic and Nonclassic 21-OHD CAH

Feature	Classic 21-OHD CAH	Nonclassic 21-OHD CAH
Prenatal virilization	Present in females	Absent
Postnatal virilization	Males and females	Variable
Salt wasting	~75% of all individuals	Absent
Cortisol deficiency	~100%	Rare

Classic Simple Virilizing 21-OHD CAH—Excess adrenal androgen production in utero results in genital virilization at birth in 46,XX females. In affected females, the excess androgens result in varying degrees of enlargement of the clitoris, fusion of the labioscrotal folds, and formation of a urogenital sinus. Because anti-müllerian hormone (AMH) is not secreted, the müllerian ducts develop normally into a uterus and fallopian tubes in affected females. It is not possible to distinguish between simple virilizing classic 21-OHD CAH and salt-wasting classic 21-OHD CAH based solely on the degree of virilization of an affected female at birth.

After birth, both females and males with classic simple virilizing 21-OHD CAH who do not receive glucocorticoid replacement therapy develop signs of androgen excess such as precocious development of pubic and axillary hair, acne, rapid linear growth, and advanced bone age. Untreated males have progressive penile enlargement and small testes. Untreated females have clitoral enlargement, hirsutism, male pattern baldness, menstrual abnormalities, and reduced fertility.

The initial growth in the young child with untreated 21-OHD CAH is rapid; however, potential height is reduced and short adult stature results from premature epiphyseal fusion. Even if treatment with cortisol replacement therapy begins at an early age and secretion of excess adrenal androgens is controlled, individuals do not generally achieve the expected adult height. Bone age remains advanced compared to chronologic age.

Pubertal development. In boys and girls with proper glucocorticoid therapy and suppression of excessive adrenal androgen production, onset of puberty usually occurs at the appropriate chronological age. However, exceptions occur even among individuals in whom the disease is well controlled.

It should be noted that in some previously untreated children, the start of glucocorticoid replacement therapy triggers true precocious puberty. This central precocious puberty may occur when glucocorticoid treatment releases the hypothalamic pituitary axis from inhibition by estrogens derived from excess adrenal androgen secretion.

Fertility. For most females who are adequately treated, menses are normal after menarche and pregnancy is possible [Lo et al 1999]. Overall fertility rates, however, are reported to be low. Reported reasons include inadequate vaginal introitus leading to unsatisfactory intercourse, elevated androgens leading to ovarian dysfunction and psychosexual behaviors around gender identity and selection of sexual partner(s).

Males. In males, the main cause of subfertility is the presence of testicular adrenal rest tumors, which are thought to originate from aberrant adrenal tissue and to respond to treatment with glucocorticoids. Further, gonadotropic hypogonadism may result from suppression of LH secretion by the pituitary by excessive adrenal androgens and their aromatization product [Ogilvie et al 2006].

Adrenal medulla. In individuals with classic 21-OHD CAH, deficiency of cortisol also affects the development and functioning of the adrenal medulla, resulting in lower epinephrine and metanephrine concentrations than those found in unaffected individuals [Merke et al 2000].

Classic salt-wasting 21-OHD CAH. When the loss of 21-hydroxylase function is severe, adrenal aldosterone secretion is insufficient for sodium reabsorption by the distal renal tubules, resulting in salt wasting as well as cortisol deficiency and androgen excess. Infants with renal salt wasting have poor feeding, weight loss, failure to thrive, vomiting, dehydration, hypotension, hyponatremia, and hyperkalemic metabolic acidosis progressing to adrenal crisis (azotemia, vascular collapse, shock, and death). Adrenal crisis can occur as early as age one to four weeks.

Affected males who are not detected in a newborn screening program are at high risk for a salt-wasting adrenal crisis because their normal male genitalia do not alert medical professionals to their condition; they are often discharged from the hospital after birth without diagnosis and experience a salt-wasting crisis at home. Conversely, the ambiguous genitalia of females with the salt-wasting form usually prompts early diagnosis and treatment.

Nonclassic 21-OHD CAH. Nonclassic 21-OHD CAH may present at any time postnatally, with symptoms of androgen excess including acne, premature development of pubic hair, accelerated growth, advanced bone age, and as in classic 21-OHD CAH, reduced adult stature as a result of premature epiphyseal fusion.

Females with nonclassic 21-OHD CAH are born with normal genitalia; postnatal symptoms may include hirsutism, temporal baldness, delayed menarche, menstrual irregularities, and infertility. Among adult females with nonclassic 21-OHD CAH, about 60% present with hirsutism only, about 10% with hirsutism and menstrual disorder, and about 10% with menstrual disorder only. The fertility rate among untreated females is reported to be 50% [Pang 1997]. Many females with nonclassic 21-OHD CAH develop polycystic ovaries.

Males with nonclassic 21-OHD CAH may have early beard growth and an enlarged phallus with relatively small testes.

Mildly reduced synthesis of cortisol is not clinically significant in individuals with nonclassic 21-OHD CAH.

Gender role behavior. Prenatal androgen exposure in females with classic forms of 21-OHD CAH has a virilizing effect on the external genitalia and childhood behavior. Prenatal androgen exposure correlates with a decrease in self-reported femininity by adult females, but not an increase in self-reported masculinity by adult females [Long et al 2004].

Changes in childhood play behavior correlated with reduced female gender satisfaction and reduced heterosexual interest in adulthood. Affected adult females are more likely to have gender dysphoria, and experience less heterosexual interest and reduced satisfaction with the assignment to the female sex. In contrast, males with 21-OHD CAH do not show a general alteration in childhood play behavior, core gender identity, or sexual orientation [Hines et al 2004].

Pathogenesis. When the function of 21-hydroxylating cytochrome 450 is inadequate, the cortisol production pathway is blocked, leading to the accumulation of 17-hydroxyprogesterone (17-OHP). The excess 17-OHP is shunted into the intact androgen pathway, where the 17,20-lyase enzyme converts the 17-OHP to Δ^4-androstenedione, which is converted into androgens. Since the mineralocorticoid pathway requires minimal 21-hydroxylase activity, mineralocorticoid deficiency (salt wasting) is a feature of the most severe form of the disease.

The lack of the steroid product impairs the negative feedback control of adrenocorticotropin (ACTH) secretion from the pituitary, leading to chronic stimulation of the adrenal cortex by ACTH, resulting in adrenal hyperplasia.

Genotype-Phenotype Correlations

Alleles can be grouped as severe or mild, based on residual enzyme activity (Table 3). An individual's phenotype generally results from the degree of enzyme activity of the least affected allele. A strong correlation between the severity of the clinical disease and the mutations is generally observed. However, for reasons that are not understood, genotype does not always predict phenotype within mutation-identical groups [Krone et al 2000], or even within the same family.

Classic 21-OHD CAH. The genotype for the classic form of 21-OHD CAH is predicted to be a severe mutation on both alleles, with completely abolished enzyme activity determined by in vitro expression studies. The point mutation A (or C) to G near the end of intron 2, one of the most frequent mutations in classic 21-OHD CAH, causes premature splicing of the intron and a shift in the translational reading frame. Although most individuals who are homozygous for this mutation have salt-wasting 21-OHD CAH, variation in severity of salt wasting is observed. This genotype-phenotype nonconcordance can be explained by increased alternate splicing that can occur when the normal splicing is abolished by the splice site mutation, allowing some protein production but with variable activity [Higashi et al 1988].

Nonclassic 21-OHD CAH. Individuals with nonclassic CAH are predicted to have two mild mutations or one severe and one mild mutation (i.e., to be compound heterozygotes). Approximately two-thirds of individuals with nonclassic 21-OHD CAH are compound heterozygotes. Missense mutations in exon 1 (P30L) and exon 7 (V281L) reduce enzyme activity and are generally associated with this form of the disease.

Table 3. Grouping of Common *CYP21A2* Mutations by Residual Enzyme Activity

Enzyme Activity	Phenotype	Mutation
0%	Severe (classic)	Whole gene deletion (null mutation) Large gene conversion 8-bp deletion in exon 3 Exon 6 cluster F306+t Q318X R356W
Minimal residual activity (<1%)		A/C 659G (intron 2 splice site mutation) (I2G)
2-11%		I172N
~20-50%	Mild (nonclassic)	P30L V281L P453S

From Krone et al 2000

Nomenclature

Congenital adrenal hyperplasia (or its common abbreviation, CAH) preceded by the description of the specific enzyme defect (e.g., 21-hydroxylase deficiency) is the current and preferable term.

Terms used in the past for 21-OHD CAH include: adrenogenital syndrome (AG syndrome), C-21-hydroxylase deficiency, and congenital adrenocortical hyperplasia.

The nonclassic form of 21-OHD CAH was previously referred to as the "attenuated" or "late-onset" form.

The salt-wasting form of 21-OHD CAH has also been called "salt-losing CAH."

Prevalence

Classic 21-OHD CAH. Analysis of data from almost 6.5 million newborns screened in different populations worldwide have demonstrated an overall incidence of 1:15,000 live births for the classic form of 21-OHD [Pang & Shook 1997].

Prevalence in specific populations:

- 1:300 in Yupik Eskimos of Alaska
- 1:5,000 in Saudi Arabia
- 1:10,000-1:16,000 in Europe and North America
- 1:21,000 in Japan
- 1:23,000 in New Zealand

Nonclassic 21-OHD CAH. The prevalence of nonclassic 21-OHD CAH in the general heterogeneous population of New York City was estimated to be 1/100. The highest ethnic-specific nonclassic disease prevalence (1/27) is found among Ashkenazi Jews. Other ethnic groups exhibiting high nonclassic disease prevalence are: Hispanics (1/40), Slavs (1/50), and Italians (1/300).

Differential Diagnosis

For current information on availability of genetic testing for disorders included in this section, see GeneTests Laboratory Directory. —ED.

The production of cortisol in the *zona fasciculata* of the adrenal cortex occurs in five major enzyme-mediated steps. Congenital adrenal hyperplasia (CAH) results from deficiency in any one of these enzymes; impaired cortisol synthesis leads to chronic elevations of ACTH and overstimulation of the adrenal cortex resulting in hyperplasia. The five forms of CAH are summarized in Table 4. Impaired enzyme function at each step of adrenal cortisol biosynthesis leads to a unique combination of retained precursors and deficient products. The most common enzyme deficiency, accounting for more than 90% of all CAH, is 21-hydroxylase deficiency (21-OHD).

Table 4. Enzyme Deficiencies Resulting in CAH

% of CAH	Deficient Enzyme	Substrate	Product	Androgen	Mineralo-corticoid
	Steroidogenic acute regulatory protein (STAR)	--	Mediates cholesterol transport across mitochondrial membrane	Deficiency [1]	Deficiency [2]
	3β-hydroxysteroid dehydrogenase (3β-HSD)	Pregnenolone, 17-OH pregnenolone, DHEA	Progesterone, 17-OHP, Δ^4-androstenedione	Deficiency [1]	Deficiency [2]
	17α-hydroxylase	Pregnenolone	17-OH pregnenolone	Deficiency [1]	Excess [3]
		Progesterone	17-OH (17-OHP)		
>90%	21-hydroxylase	Progesterone	Deoxycorticosterone (DOC)	Excess [4]	Deficiency [2]
		17-hydroxy progesterone	11-deoxycortisol		
5%	11β-hydroxylase	Deoxycorticosterone	Corticosterone	Excess [4]	Excess [3]

1. Males undervirilized at birth
2. Associated with salt wasting
3. Associated with hypertension
4. Females virilized at birth or later

Nonclassic 21-OHD CAH. Nonclassic 21-OHD CAH should be considered in females who present with any of variable hyperandrogenic symptoms. A general occurrence rate of 1%-3% is reported in females with hyperandrogenism, but in certain populations the prevalence is much higher.

Cytochrome P450 oxidoreductase deficiency. A rare form of CAH not included in Table 4 is cytochrome P450 oxidoreductase deficiency, caused by mutations in *POR*. Urinary steroid excretion indicates an apparent combined partial deficiency of the two steroidogenic enzymes P450C17 (17-hydroxylase) and P450C21 (21-hydroxylase). Of note, cytochrome P450 oxidoreductase is important in the electron transfer from NADPH to both enzymes.

The phenotypic spectrum of cytochrome P450 oxidoreductase deficiency ranges from isolated steroid abnormalities to classic Antley-Bixler syndrome (ABS). Individuals with POR deficiency have cortisol deficiency, ranging from clinically insignificant to life threatening. Newborn males have ambiguous genitalia, including small penis and undescended testes; newborn females have vaginal atresia, fused labia minora, hypoplastic labia majora, and/or large clitoris. Craniofacial features of ABS, at the most severe end of the POR spectrum, can include craniosynostosis, choanal stenosis or atresia, stenotic external auditory canals, and hydrocephalus. Skeletal anomalies can include radiohumeral synostosis, neonatal fractures,

congenital bowing of the long bones, camptodactyly, joint contractures, arachnodactyly, and clubfeet.

Inheritance is autosomal recessive.

Management

Evaluations at Initial Diagnosis to Establish the Extent of Disease

To assess for salt wasting:

- Plasma renin activity (PRA) or direct renin assay
- Serum electrolytes

To distinguish classic and nonclassic forms of 21-hydroxylase-deficient congenital adrenal hyperplasia (21-OHD CAH):

- Baseline 17-OHP, Δ^4-androstenedione, cortisol, and aldosterone
- ACTH stimulation test to compare stimulated concentration of 17-OHP to the baseline level

To assess the degree of prenatal virilization in females:

- Careful physical examination of the external genitalia and its orifices
- Vaginogram to assess the anatomy of urethra and vagina

To assess the degree of postnatal virilization in both males and females:

- Bone maturation assessment by bone age
- Serum concentration of adrenal androgens (unconjugated dehydroepiandrosterone [DHEA], Δ^4-androstenedione, and testosterone)

Treatment of Manifestations

It is imperative to make the diagnosis of 21-OHD CAH as quickly as possible in order to initiate therapy and arrest the effects of cortisol deficiency and mineralocorticoid deficiency, if present.

A multidisciplinary team of specialists in pediatric endocrinology, pediatric urology/surgery, medical genetics, and psychology is essential for the diagnosis and management of the individual with ambiguous genitalia [Hughes et al 2006].

Classic 21-OHD CAH —Glucocorticoid replacement therapy. The goal of glucocorticoid replacement therapy is to replace deficient steroids, minimize adrenal sex hormone and glucocorticoid excess, prevent virilization, optimize growth, and promote fertility [Clayton et al 2002].

Treatment for CAH principally involves glucocorticoid replacement therapy, usually in the form of hydrocortisone (10-20 mg/m^2 per 24 hours) given orally in two or three daily divided doses. Glucocorticoid therapy for children involves balancing suppression of adrenal androgen secretion against iatrogenic Cushing's syndrome in order to maintain a normal linear growth rate and normal bone maturation.

Overtreatment with glucocorticosteroids can result in Cushingoid features and should be avoided. It often occurs when serum concentration of 17-OHP is reduced to the physiologic range for age. An acceptable range for serum concentration of 17-OHP in the treated individual

is higher (100-1,000 ng/dL) than normal, providing androgens are maintained in an appropriate range for gender and pubertal status.

During periods of stress (e.g., surgery, febrile illness, shock), all individuals with classic 21-OHD CAH require increased amounts of glucocorticoid. Typically, two to three times the normal dose is administered orally or by intramuscular injection when oral intake is not tolerated.

Affected individuals should carry medical information regarding emergency steroid dosing.

Individuals with classic 21-OHD CAH require lifelong administration of glucocorticoids. After linear growth is complete, more potent glucocorticoids (such as prednisone and dexamethasone) that tend to suppress growth in childhood can be used.

Mineralocorticoid replacement therapy. Treatment with 9α-fludrohydrocortisone (Florinef®) (0.05-0.3 mg/day orally) and sodium chloride (1-3 g/day added to formula or foods) is necessary in individuals with the salt-wasting form of 21-OHD CAH.

Sodium chloride supplementation may not be necessary after infancy; the amount of mineralocorticoid required daily may likewise decrease with age.

Adrenalectomy. Bilateral adrenalectomy has been reported as a treatment of individuals with severe 21-OHD CAH who are homozygous for two null mutations and who have a history of poor control with hormonal replacement therapy [Van Wyk et al 1996, Meyers & Grua 2000]. It is thought that they may be more successfully treated as individuals with Addison disease.

It is important to note that recurrence of increased serum concentration of adrenal steroid hormones has been observed in some females with 21-OHD CAH undergoing adrenalectomy. The elevated serum concentration of adrenal steroids is thought to result from the presence of ectopic adrenal rests in the ovaries. More long-term data are needed to determine the significance and frequency of the rests in these women.

Feminizing genitoplasty. In females with classic 21-OHD CAH who are virilized at birth, feminizing genitoplasty may be performed to remove the redundant erectile tissue while preserving the sexually sensitive glans clitoris and to provide a normal vaginal orifice that functions adequately for menstruation, intromission, and delivery. Clitoroplasty is typically performed in early childhood (preferably at age 6-18 months). When necessary, vaginoplasty is usually performed in late adolescence because routine vaginal dilation is required to maintain a patent vagina.

Precocious puberty. The true precocious puberty that may occur in 21-OHD CAH can be treated with analogs of luteinizing hormone-releasing hormone (LHRH).

Transition from adolescence to adulthood. Improved care for individuals with 21-OHD CAH has resulted in a good prognosis and normal life expectancy. In adults the goals of treatment shift away from preservation of normal growth, the main concern in children, to the preservation of fertility, healthy sexual function, and maintenance of general well being including bone health and the assessment of and management for risk of cardiovascular diseases. Optimal treatment of adults with CAH requires a multidisciplinary approach, including psychological support by specialists [Ogilvie et al 2006]. At present, evidence-based treatment protocols for adults are lacking [Kruse et al 2004].

Nonclassic 21-OHD CAH—Individuals with nonclassic 21-OHD CAH do not always require treatment. Many are asymptomatic throughout their lives, or symptoms may develop during puberty, after puberty, or postpartum.

Traditionally, individuals with nonclassic 21-OHD CAH have been treated with lower amounts of glucocorticoid than those required for individuals with classic 21-OHD CAH. Indications for treatment include bone age advancement, severe acne [Degitz et al 2003], hirsutism, menstrual irregularity, testicular masses, and infertility.

Prevention of Primary Manifestations

Salt-wasting crisis. Newborn screening programs aim to identify infants with classic 21-OHD CAH and to initiate treatment prior to a potentially life-threatening salt-wasting crisis.

Female genital ambiguity. Through molecular genetic testing of fetal DNA, defects in 21-OHD CAH synthesis can be diagnosed in utero. Genital ambiguity in female fetuses can be reduced or eliminated by suppressing fetal androgen production through administration of dexamethasone to the mother beginning early in gestation and continuing until delivery.

See Treatment of Manifestations: Glucocorticoid replacement therapy and Mineralocorticoid replacement therapy.

Prevention of Secondary Complications

Short stature. Short stature may result from glucocorticoid-induced growth suppression caused by over-treatment with glucocorticoids or from advanced skeletal maturation caused by inadequate glucocorticoid treatment. Injections of human growth hormone alone or in combination with gonadotropin-releasing hormone (GnRH) may be used both to improve linear growth in individuals with 21-OHD CAH who have significant growth failure [Quintos et al 2001] and to improve final height [Lin-Su et al 2005].

Surveillance

The following evaluations should be performed every three to four months when children are actively growing. Evaluation may be less often thereafter. The frequency of evaluation should vary depending on individual needs.

Efficacy of glucocorticoid replacement therapy is monitored by measurement of the following:

- Early-morning serum concentrations of 17-OHP, Δ^4-androstenedione, and testosterone approximately every three months during infancy and every three to six months thereafter. (In some instances, measurement of urinary pregnantriols and 17 ketosteroids in a 24-hour urine sample may help assess hormonal control. However, the process of urine collection makes it less practical than a simple blood draw.)
- Linear growth, weight gain, pubertal development, and clinical signs of cortisol and androgen excess
- Bone age to assess osseous maturation (at 6-12 month intervals)

Efficacy mineralocorticoid replacement therapy is monitored by measurement of the following:

- Blood pressure
- Early morning plasma renin activity or direct renin assay in a controlled position (usually upright)

Monitoring for testicular abnormalities in males. Periodic imaging of the testes either by ultrasonography or MRI should begin after puberty and be repeated every three to five years.

Testing of Relatives at Risk

If prenatal testing for 21-OHD CAH has not been performed, it is appropriate to measure 17-OHP from newborn screening blood samples of at-risk sibs to facilitate early diagnosis and treatment.

Therapies Under Investigation

Search ClinicalTrials.gov for access to information on clinical studies for a wide range of diseases and conditions.

Other

Pregnant females with classic 21-OHD CAH. Pregnant females who have classic salt-wasting 21-OHD CAH need to be monitored closely by an endocrinologist. Maintenance doses of glucocorticoid and mineralocorticoid usually need to be increased because adrenal androgens tend to increase during pregnancy. Despite excess production of maternal adrenal androgens, the genitalia of their female fetuses may not be virilized [Lo et al 1999].

Genetics clinics are a source of information for individuals and families regarding the natural history, treatment, mode of inheritance, and genetic risks to other family members as well as information about available consumer-oriented resources. See the GeneTests Clinic Directory.

Support groups have been established for individuals and families to provide information, support, and contact with other affected individuals. The Resources section (below) may include disease-specific and/or umbrella support organizations.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members. This section is not meant to address all personal, cultural, or ethical issues that individuals may face or to substitute for consultation with a genetics professional. To find a genetics or prenatal diagnosis clinic, see the GeneTests Clinic Directory.

Mode of Inheritance

21-hydroxylase-deficient congenital adrenal hyperplasia (21-OHD CAH) is inherited in an autosomal recessive manner.

Risk to Family Members

Parents of a proband

- Most parents are heterozygotes with one normal allele and one mutated allele.
- Heterozygotes are asymptomatic but may have slightly elevated 17-OHP levels when stimulated with ACTH, as compared to individuals with two normal alleles (see Carrier Detection).
- Approximately 1% of mutations occur *de novo* and thus, 1% of probands have only one parent who is heterozygous [Krone et al 2000].

- In some instances, a parent who was previously not known to be affected may be found to have the nonclassic form of 21-OHD CAH. It is appropriate to evaluate both parents of a proband with molecular genetic testing and hormonal profiling to determine if either has nonclassic 21-OHD CAH.

Sibs of a proband

- If the parents of a proband are both obligate heterozygotes, each sib has a 25% chance of inheriting both altered alleles and being affected, a 50% chance of inheriting one altered allele and being an unaffected carrier, and a 25% chance of inheriting both normal alleles and being unaffected.
- Once an at-risk sib is known to be unaffected, the risk of his/her being a carrier is 2/3.
- If one parent of a proband is heterozygous and the other has 21-OHD CAH, each sib has a 50% chance of inheriting both mutated alleles and being affected and a 50% chance of inheriting one mutated allele and being a carrier.

Offspring of a proband

- An affected individual transmits one disease-causing allele to each child.
- Given the high carrier rate for 21-OHD CAH, it is appropriate to offer molecular genetic testing of the *CYP21A2* gene to the reproductive partner of a proband.
  - If the reproductive partner is determined not to be a carrier, the child is at significantly decreased risk of having 21-OHD. (Since targeted mutation analysis does not detect 100% of altered alleles, there is a slight residual risk that the reproductive partner may carry a mutant allele that might be detected if the entire gene were sequenced.)
  - If the reproductive partner is determined to be heterozygous for an identified mutation, the risk to each child of being affected is 50%. The ability to predict the phenotype based on genotype is imperfect (see Genotype-Phenotype Correlations).

Other family members. Sibs of the proband's obligate heterozygous parents are at 50% risk of also being carriers.

Carrier Detection

Molecular genetic testing. Carrier testing using molecular genetic testing of the *CYP21A2* gene is available to at-risk relatives when one or both disease-causing mutations have been identified in the proband.

Hormonal testing. Although carriers may have slightly higher serum concentration of 17-OHP than non-carriers when stimulated with ACTH, overlap exists between heterozygotes and non-carriers. Thus, molecular genetic testing is the preferred method of carrier testing.

Related Genetic Counseling Issues

Genotype-phenotype correlations. In most individuals with 21-OHD CAH, genotype can be used to predict disease severity. As with autosomal recessive disorders, the expressed phenotype reflects the less severe mutation of an individual's alleles. The severity of each mutation is characterized by the percentage of the remaining enzyme activity from in vitro expression studies. Table 3 describes the common mutations and the phenotypes. Individuals with the salt-wasting form usually have the most severe mutations (homozygous deletions), while those with nonclassic 21-OHD CAH usually have the milder V281L mutation [Wilson et al 1995]. However, a considerable degree of divergence is observed within mutation groups

with intermediate severity [Krone et al 2000]. Genotype-phenotype nonconcordance occurs, although infrequently, with less severe allelic mutations such as V281L, P30L, and I172N. In addition, the splice mutation in intron 2 is commonly associated with phenotypic variation of salt-wasting severity, which can be explained by variable splicing. In the context of prenatal diagnosis, it is important to distinguish classic and nonclassic genotypes in order to determine the necessity of prenatal treatment. Rare exceptions have occurred: in a small number (<3%) of affected individuals with the V281L or P30L mutations, the mutations conferred the classic phenotype when a nonclassic phenotype was expected; Stikkelbroeck et al (2003) demonstrated that a very small percentage of people who had I172N and another severe mutation presented with a nonclassic phenotype when a classic phenotype was expected.

In families where the proband is a virilized female, predicting the risk of genital virilization in subsequent female fetuses is feasible. If the proband is a male, prediction of phenotype based on genotype is not possible and the subsequent affected female fetus must be treated until term to avoid genital ambiguity.

Family planning. The optimal time for determination of genetic risk, clarification of carrier status, and discussion of the availability of prenatal testing and treatment is before pregnancy.

DNA banking. DNA banking is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methodology and our understanding of genes, mutations, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals. DNA banking is particularly relevant in situations in which the sensitivity of currently available testing is less than 100%. See DNA Banking for a list of laboratories offering this service.

Prenatal Testing and Treatment

High-risk pregnancies. Prenatal diagnosis in pregnancies at risk for classic 21-OHD CAH has been performed for several decades, and prenatal treatment with dexamethasone to reduce the virilization of affected females [New et al 2003] and thus to reduce their need for clitoroplasty and/or vaginoplasty has been used successfully since 1984. A prenatal treatment program should include the following components (see Figure 2):

- Pre-pregnancy genetic counseling
- Pre-pregnancy molecular genetic testing of the proband and both parents to identify the two disease-causing *CYP21A2* mutations and to confirm that both parents are carriers
- Once pregnancy is confirmed, but after nine weeks' gestation and prior to any prenatal testing, daily administration to the pregnant mother of oral dexamethasone (20 µg/kg/day, using pre-pregnant weight for calculation) in three divided doses to suppress excess fetal adrenal androgen secretion and to prevent virilization of an affected female
- Determination of fetal sex through cytogenetic analysis or use of Y-chromosome probes performed on fetal cells obtained by chorionic villus sampling (CVS) at about ten to 12 weeks' gestation or by amniocentesis usually performed at about 15-18 weeks' gestation (Because management decisions depend upon the results of prenatal testing, it is advantageous to have results as early in the pregnancy as possible. Therefore, prenatal diagnosis by CVS at about ten to 12 weeks' gestation is preferred.)
- If the fetus is a female and if the two *CYP21A2* disease-causing mutations have been identified in the proband, molecular genetic testing of *CYP21A2* in fetal DNA to determine if the fetus has inherited both disease-causing alleles

- If the fetus is determined by cytogenetic analysis or use of Y-chromosome specific probes to be a male, or by DNA analysis to be an unaffected female, cessation of dexamethasone treatment
- If the fetus is a female and either is determined by DNA analysis to have classic 21-OHD CAH or is of indeterminate status, continutation to term of dexamethasone treatment

Note: (1) Prenatal treatment has no effect on the need for hormone replacement therapy in infancy or any time thereafter. (2) In general, prenatal treatment for fetuses at risk for nonclassic 21-OHD CAH is not indicated [Clayton 2002]; however, rare exceptions of genotype-phenotype nonconcordance need to be considered (see discussion in Related Genetic Counseling Issues). (3) Prenatal testing by measurement of amniotic fluid concentration of 17-OHP or HLA typing of amniocytes for linkage analysis has been superseded by molecular genetic analysis of *CYP21A2*.

Note: Gestational age is expressed as menstrual weeks calculated either from the first day of the last normal menstrual period or by ultrasound measurements.

When properly administered, dexamethasone is effective in preventing virilization of the genitalia an affected female fetus. Prenatal treatment with dexamethasone is generally well tolerated by both the mother and the fetus [New et al 2003]; however, statistically greater weight gain striae and edema are reported in dexamethasone-treated mothers. The largest studies have shown no increased risk for congenital abnormalities and no effect on birth weight, birth length, or head circumference compared to controls, provided that the mother and physician adhere to the recommended therapeutic protocol [Forest et al 1989, Lajic et al 1998, New et al 2001]. In addition, follow-up studies demonstrate that growth and development is normal in girls who were treated prenatally [Trautman et al 1995, Forest 1998, Lajic et al 1998]. However, long-term follow-up of children who have been treated with dexamethasone during either part or all of the pregnancy continues to be warranted.

Low-risk pregnancies. With the increase in use and improved resolution of prenatal ultrasonography, fetal genital and/or adrenal abnormalities may be detected more frequently than in the past [Saada et al 2004]. Pinhas-Hamiel et al (2002) detected genital ambiguity in 16 fetuses out of 10,000 who underwent prenatal ultrasound examination. Three of the 16 were ultimately diagnosed with 21-OHD CAH.

If ambiguous external genitalia are noted on routine ultrasound examination, a fetal karyotype, FISH for SRY, and ultrasound evaluation for müllerian structures should be obtained. A 46,XX karyotype in an SRY-negative fetus with a normal-appearing uterus should raise consideration of classic 21-OHD CAH. Amniocentesis to measure 17-hydroxyprogesterone (17-OHP) concentration in the amniotic fluid and/or molecular genetic testing of *CYP21A2* may be appropriate.

Although the diagnosis of an affected fetus in a low-risk pregnancy would likely not occur in time for prenatal treatment, the prenatal diagnosis of 21-OHD CAH can be valuable in the medical management of the newborn and in preparation of the family for the related medical and social issues of 21-OHD CAH.

Preimplantation genetic diagnosis (PGD) may be available for families in which the disease-causing mutations have been identified in an affected family member. For laboratories offering PGD, see Testing.

Molecular Genetics

Information in the Molecular Genetics tables is current as of initial posting or most recent update. —ED.

Table A. Molecular Genetics of 21-Hydroxylase-Deficient Congenital Adrenal Hyperplasia

Gene Symbol	Chromosomal Locus	Protein Name
CYP21A2	6p21.3	Cytochrome P450 XXI

Data are compiled from the following standard references: gene symbol from HUGO; chromosomal locus, locus name, critical region, complementation group from OMIM; protein name from Swiss-Prot.

Table B. OMIM Entries for 21-Hydroxylase-Deficient Congenital Adrenal Hyperplasia

201910	ADRENAL HYPERPLASIA, CONGENITAL, DUE TO 21-HYDROXYLASE DEFICIENCY

Table C. Genomic Databases for 21-Hydroxylase-Deficient Congenital Adrenal Hyperplasia

Gene Symbol	Entrez Gene	HGMD
CYP21A2	1589 (MIM No. 201910)	CYP21A2

For a description of the genomic databases listed, click here.

Note: HGMD requires registration.

Normal allelic variants: The functional gene for adrenal 21-hydroxylase, *CYP21A2,* is located about 30 kb from a nonfunctional pseudogene, *CYP21A2P*, on chromosome 6p in the human leukocyte antigen (HLA) gene cluster. *CYP21A2* and *CYP21A2P* consist of ten exons. The gene *CYP21A2* has five normal variants (655C>A, insL9, K102R, D183E, S268T, and N493S).

Pathologic allelic variants: The high degree of sequence similarity (96%-98%) between *CYP21A2* and *CYP21A2P* apparently permits two types of recombination events: (1) unequal crossing over during meiosis, which results in complementary deletions/duplications of *CYP21A2*; and (2) conversion events between *CYP21A2* and *CYP21A2P* such that inactivating mutations are transferred from *CYP21A2P* to *CYP21A2* [Tusie-Luna et al 1995, Higashi et al 1988, Wedell 1998]. Nine disease-causing mutations in the nonfunctional pseudogene inactivate the functional gene when transferred from *CYP21A2P* to *CYP21A2* [Wedell 1998]. These nine mutations, together with *CYP21A2* deletion and apparent large gene conversion, account for about 95% of all disease-causing *CYP21* alleles [Wedell 1998].

More than 100 mutations, including point mutations, small deletions, small insertions, and complex rearrangements of the gene, have been described to date. (For more information, see Genomic Databases table.)

Normal gene product: The encoded protein is predicted to contain 494 amino acids with a molecular weight of 55 kd. The enzyme is at most 28% homologous to other cytochrome P450 enzymes.

Abnormal gene product: Aberration of the product depends on the specific mutation. About 20% of the mutations are meiotic recombinations deleting a 30-kb gene segment that encompasses the 3' end of the *CYP21A1P* pseudogene, all of the adjacent *C4B* complement gene, and the 5' end of *CYP21A2*, producing a nonfunctional chimeric pseudogene. Another common mutation is the intron 2 splice mutation (656 A/C to G), occurring with a frequency of 20%-30%, leading to aberrant splicing and truncated small or unusual protein [Higashi et al 1988].

Resources

GeneReviews provides information about selected national organizations and resources for the benefit of the reader. GeneReviews is not responsible for information provided by other organizations. Information that appears in the Resources section of a GeneReview is current as of initial posting or most recent update of the GeneReview. Search GeneTests*for this disorder and select* Resources *for the most up-to-date Resources information.*—ED.

CARES (Congenital Adrenal Hyperplasia Research, Education and Support) Foundation, Inc.
189 Main Street
Millburn NJ 07041
Phone: 866-227-3737; 973-912-3895 (in New Jersey)
Email: Kelly@caresfoundation.org
www.caresfoundation.org

Congenital Adrenal Hyperplasia Due to 21-Hydroxylase Deficiency: A guide for patients and their families
CAH printable booklet

National Library of Medicine Genetics Home Reference
21-hydroxylase deficiency

NCBI Genes and Disease
Congenital Adrenal Hyperplasia

Rare Genetic Steroid Disorders Consortium Registry
The Mount Sinai School of Medicine
One Gustave L. Levy Place Box 1198
New York NY 10029-6574
Email: maria.new@mssm.edu
Rare Genetic Steroid Disorders Consortium Registry

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Medical Genetic Searches: A specialized PubMed search designed for clinicians that is located on the PubMed Clinical Queries page. PubMed

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Chapter Notes

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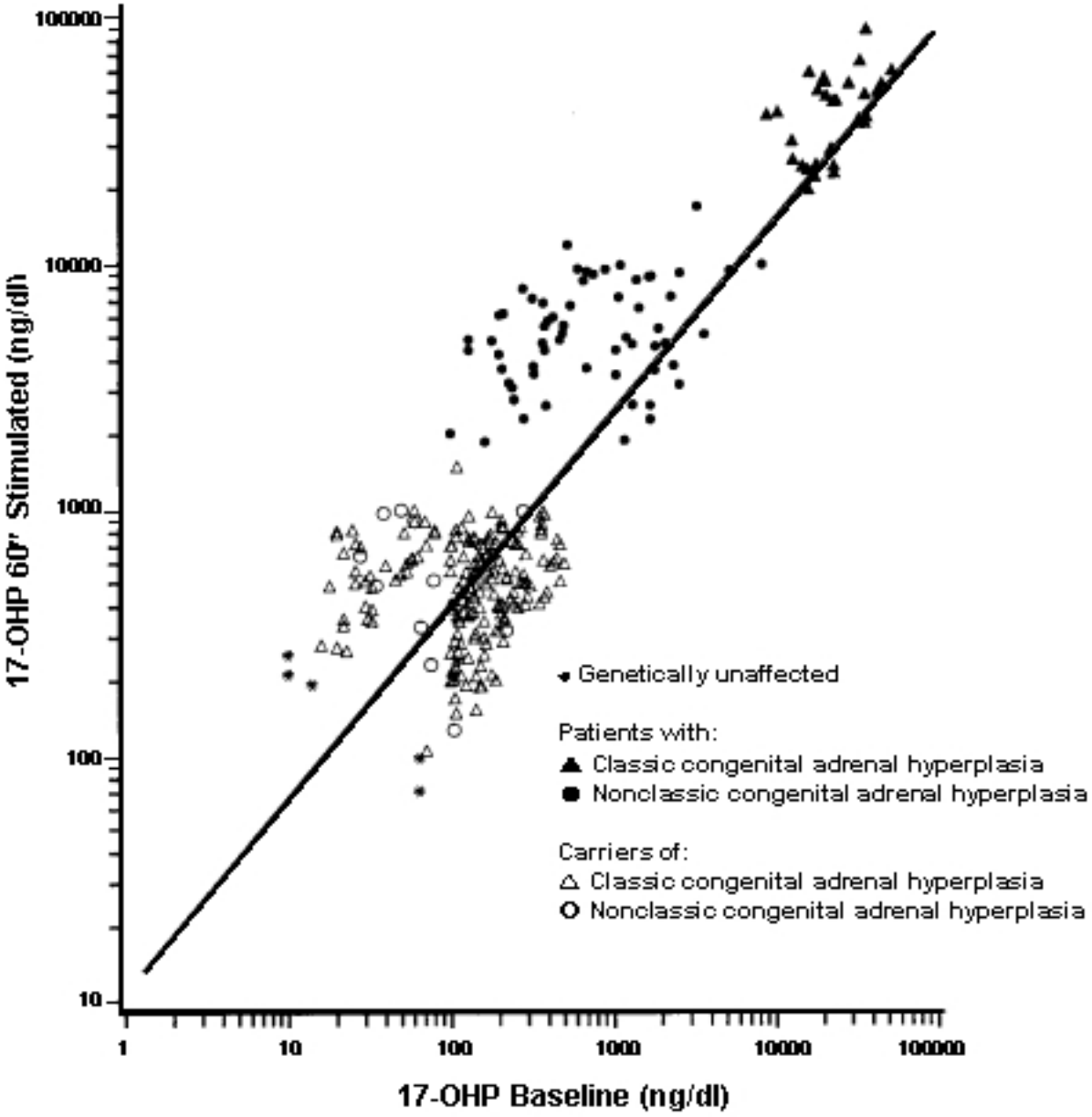

Figure 1. 17-OHP Nomogram for the diagnosis of steroid 21-hydroxylase deficiency (60-minute cotrosyn stimulation test). The data for this nomogram was collected between 1982 and 1991 at the Department of Pediatrics, the New York Hospital-Cornell Medical Center, New York.

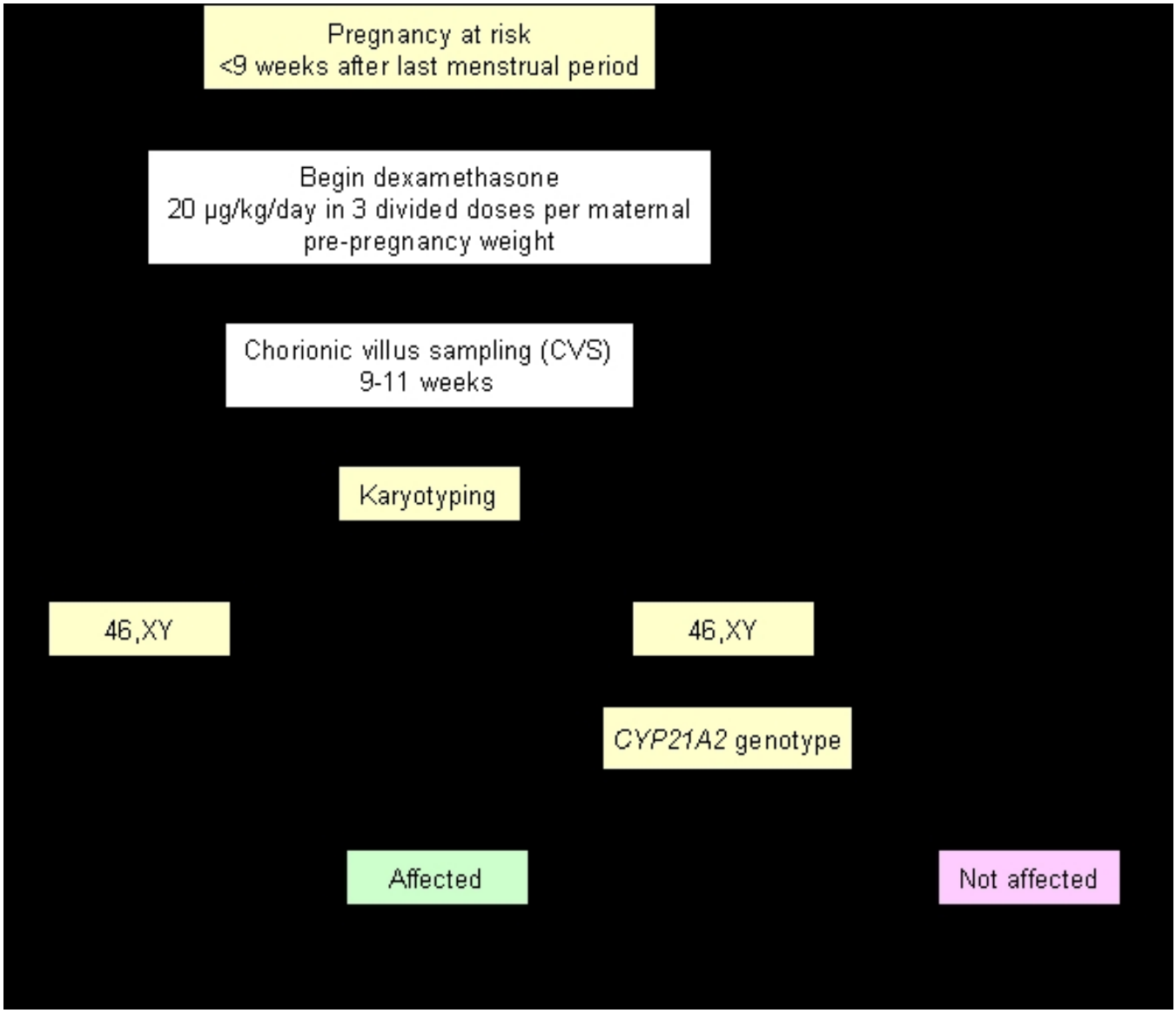

Figure 2. Prenatal diagnosis and treatment for fetuses at risk for classic 21-OHD CAH