



Adrenal Hyperplasia, Congenital, due to 21-Hydroxylase Deficiency

Alternative Names

Adrenal Hyperplasia III
21-@Hydroxylase Deficiency
CYP21 Deficiency
Congenital Adrenal Hyperplasia 1
CAH1
Cytochrome P450, Subfamily XXIA, Polypeptide 2
CYP21A2
Cytochrome P450, Subfamily XXI
CYP21
Steroid Cytochrome P450 21-Hydroxylase
P450c21
21-@Hydroxylase B, Included
CYP21B
CA21H
Cytochrome P450, Subfamily XXIA, Polypeptide 1
Pseudogene
CYP21A1P
CYP21P
CYP21A
Hyperandrogenism, Nonclassic Type, Due To 21-
Hydroxylase Deficiency

Record Category

Disease phenotype

WHO-ICD

Endocrine, nutritional and metabolic diseases >
Disorders of other endocrine glands

Incidence per 100,000 Live Births

11-50

OMIM Number

201910

Mode of Inheritance

Autosomal recessive

Gene Map Locus

6p21.3

Description

Congenital adrenal hyperplasia (CAH) is a genetic disorder resulting from total or partial deficiency of an enzyme involved in cortisol and aldosterone biosynthesis. In 95% of the cases of CAH, this enzyme is the 21-hydroxylase, which is responsible for the conversion of 17-hydroxyprogesterone to 11-deoxycorticosterone. The deficiency of this enzyme leads not only to loss of cortisol synthesis, but also to the accumulation of cortisol precursors, and increase in ACTH, and consequently, androgen levels. CAH has four different clinical forms, of which the salt wasting type (SW) is the most severe. This form is characterized by life threatening vomiting and dehydration, occurring within the first few weeks of life, due to severe salt imbalances. Excess exposure of the female fetus to androgen causes masculinization of the genital-urinary structures, leading to erroneous gender assignments. Adult women present with clitorimegaly, poorly developed vaginal labia, oligomenorrhea, and infertility. In boys, body growth is unusually fast, and puberty is premature. The other forms of the disease are the simple virilizing or SV type (characterized by virilization in prepubertal children), the non-classical CAH (a milder form portrayed by shortened stature, near syncope, premature development of pubic hair, hyperpigmentation, acne, menstrual disturbances in females, excess body hair and infertility), and the cryptic type (late onset, asymptomatic).

About 1 in 21,500 live births are affected by CAH. Prenatal diagnosis is now available for the disease. Diagnosis is made in the first trimester by chorionic villus sampling and in the second trimester by measuring hormones such as 17-hydroxyprogesterone in the amniotic fluid. Considering the lethal nature of the disease, neonatal screening is also performed by measuring the hormonal levels on heelstick blood. Treatment involves administering glucocorticoids, like hydrocortisone and prednisone, and mineralocorticoid analogues to improve the hormonal



balance. Genital reconstructive surgery is also available to reconstruct the vagina, and reduce the size of clitoris in females.

Molecular Genetics

The gene coding for 21-hydroxylase is located at 6p21.3. The functional gene, called CYP21 or CYP21B has 10 exons and codes for a protein with 494 amino acids (55.8KDa). A highly homologous pseudogene called CYP21P or CYP21A is also present, contiguous to the functional gene, rendering it easy for recombination events, and consequent mutations to occur.

Epidemiology in the Arab World

Egypt

Gad (2002) studied the CYP21 mutations in two Egyptian CAH patients. The first case was an infant girl, who presented with genital ambiguity. Her parents were first cousins, and two of her siblings, (a boy, and a girl with 'abnormal genitalia') had died in infancy. She had below normal serum sodium and greater than normal potassium levels. Her basal 17-hydroxyprogesterone level was highly increased (190 ng/ml). Ultrasonography of the internal genitalia was performed, showing intact Mullerian structures and ovaries. The second patient was a 5 day old infant. The boy's parents were double cousins, and they had three earlier children who died in infancy, as well as one twin miscarriage at 4 months gestation. The baby had an enlarged penis, and dark scrotal and genital skin. His serum sodium and potassium levels were abnormal too, although his basal 17-hydroxyprogesterone level was almost normal. PCR analysis of the patients' DNA using primers for four common Egyptian CYP21 mutations showed that both were homozygous for the I172N mutation. Their mothers were both heterozygous for the mutation. This mutation has been shown to have a wide spectrum of phenotypes, and is usually associated with the SV clinical form. However, both the cases that Gad (2002) studied belonged to the salt wasting type, indicating that this mutation can lead to the severe lethal phenotype too. Gad (2002) could not explain how the same mutation could lead to different biochemical phenotypes in relation to the basal hydroxyprogesterone levels in the two cases.

Jordan

Arnaout (1992) determined the frequency of non-classical adrenal hyperplasia due to deficiencies of 3 beta-hydroxy-delta 5-steroid dehydrogenase, 21-hydroxylase, and 11 beta-hydroxylase among 65 women with hirsutism. All enzyme defects were

identified by comparing the patients' hormonal responses to 0.25 mg intravenous bolus of alpha 1-24-ACTH with those of age-matched normal women. The hormones measured in plasma during the ACTH stimulation tests were progesterone, 17-hydroxypregnenolone, 17-hydroxyprogesterone, DHEA-sulfate, androstenedione, testosterone, 11-deoxycortisol, and cortisol. Similarly these hormones were measured after overnight 1 mg oral dexamethasone. Twelve women (18.5%) had 3 beta-hydroxy-delta 5-steroid dehydrogenase deficiency, 24 (37%) 21-hydroxylase deficiency, and 14 (21.5%) 11 beta-hydroxylase deficiency. Women with 21-hydroxylase deficiency also had evidence of a partial deficiency in 11 beta-hydroxylase activity (12 of the 24 patients). Similarly, most (11 of the 14) of the women with 11 beta-hydroxylase deficiency also had evidence of a deficiency in 3 beta-hydroxy-delta 5-steroid dehydrogenase activity. Among the 15 patients with no adrenal biosynthetic defect, eight had high plasma androgen concentrations, and seven had normal concentrations.

Ajlouni et al. (1996) reported three new patients with congenital adrenal hyperplasia due to a defect in 11-beta-hydroxylase enzyme with short fourth metatarsals. Gynecomastia was noted in one patient. Ajlouni et al. (1996) indicated that the relative rarity of 11-beta-hydroxylase deficiency and the association of skeletal abnormalities was suggestive for the possibility that this was more than a mere coincidental finding.

Taher et al. (2004) conducted a study aimed to display the spectrum of initial presentation and etiology among children with precocious puberty and to assess any association between the clinical features and the underlying cause of the condition. Forty-three girls and seven boys with precocious puberty were diagnosed at the Endocrine Clinic of Jordan University Hospital and at The National Center for Diabetes, Endocrinology and Genetics, Amman, Jordan, between the 1984 and 2003. Mean age for the girls with precocious puberty was 4.1 years +/- 2.5 SD and for the boys was 2.4 years +/- 1.9 SD. Congenital adrenal hyperplasia was diagnosed in four boys and four girls, and hypothyroidism in three girls.

Kuwait

Lubani et al. (1990) found 60 children with CAH diagnosed between 1978 and 1988, giving an estimated prevalence of 1 in 9,000 live births. In addition, there was presumptive evidence of CAH resulting in the death of 20 other children, giving a



prevalence figure of 1 in 7,000. In 54 patients (90%), 21-hydroxylase deficiency was diagnosed; in three patients each, the diagnosis was 3-beta-hydroxysteroid dehydrogenase deficiency and 11-beta-hydroxylase deficiency.

Oman

Soliman et al. (1997) reported six children with congenital adrenal hyperplasia (CAH) who had late initiation of corticosteroid treatment and/or poor compliance and developed true precocious puberty with early maturation of the hypothalamic-pituitary-gonadal axis. These patients were treated with standard-dose hydrocortisone and fludrocortisone. Administration of depot leuporelin (3.75 mg subcutaneously every 28 days) for 2 years or longer was effective in arresting the manifestations of puberty, decelerating the pretreatment growth velocity ([GV] 10.8 ± 1.5 v 3.65 ± 0.95 cm/yr), increasing the predicted adult height ([PAHT] 147.5 ± 7.8 v 153.4 ± 8.3 cm), and decreasing the bone age to statural age ratio (1.26 ± 0.13 v 1.16 ± 0.09). Analysis of auxanological data during the first 2 years of life showed that linear growth was significantly accelerated and bone age was advanced in patients who developed CPP compared with 11 age-matched patients. Soliman et al. (1997) indicated that proper glucocorticoid replacement to achieve adequate control of hyperandrogenemia during early life might prevent development of CPP in these patients. They also added that gonadotropin-releasing hormone agonist (GnRHa) therapy can improve the final adult height, bringing it closer to that expected from the genetic potential.

Rajab et al. (2005) undertook a study to estimate the prevalence of commonly diagnosed autosomal recessive diseases in Oman from a hospital-based register in years 1993 to 2002. The study revealed that congenital adrenal hyperplasia was diagnosed in 55 patients, with an observed incidence of 1 in 10,000 births. Similarly, Sawardekar (2005) conducted a study to establish the prevalence of major congenital malformations in children born during a 10-year period in Nizwa Hospital. Of the 21,988 total births in the hospital, four children were born with congenital adrenal hyperplasia (21 OH deficiency). Sawardekar (2005) hinted for a possible genetic contribution in these children.

Tunisia

The distribution of mutations in the CYP21 gene causing 21-OHD was reported for the first time in the Tunisian population by Kharrat et al. (2004). A total

of 51 unrelated Tunisian patients with CAH (10 males, 41 females) were selected for the study. Of these, 44 patients were diagnosed with the Salt Wasting (SW) form of the disease. At least 31 of the patients were from consanguineous families. PCR-RFLP was used to detect six point mutations in the CYP21 gene in these patients. In addition, non-selective amplification of exon 3 was also performed to detect large deletions, as was direct sequencing of the entire gene, to detect any uncommon mutations. Mutations in the CYP21 gene could be detected in 94.1% of the chromosomes. Of these, 36 patients had one of the mutations, nine patients were found to be heterozygous with two different mutations, whereas one patient was found to be homozygous for two different mutations. The most common mutation identified in the population was Q318X in exon 8 (35.3%), followed by large deletions of the gene (19.6%), IVS2-13A/C-G (17.6%), and I172N (10.8%). In fact, these four mutations accounted for 87% of the cases with the severe form of CAH. Kharrat et al. (2004) attributed the high frequency of the Q318X mutation in the Tunisian population to founder effect. They further went on to propose that this mutation be used for screening purposes in the Tunisian population. The Q318X mutation was also found to be linked to a 601 C-G polymorphism in the same gene. Novel mutations detected included W19X, frame shift mutation due to insertion of C in position 2699, R483W, and a small conversion DNA sequence from exon 5 to exon 8. All these new mutations were found in patients with the SW form of the disease, implying that the mutations completely destroyed the enzymatic activity.

United Arab Emirates

Gatee et al. (1996) studied 102 women of Arab and Asian origins with hirsutism, polycystic ovary syndrome was diagnosed in 93 patients (91%) including 26 cases with hirsutism and regular menstrual periods. Late onset congenital adrenal hyperplasia due to 21-hydroxylase deficiency was identified in two cases, thus forming a prevalence of 8% in those who underwent adrenocorticotropin stimulation.

References

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Related CTGA Records

Polycystic Ovary Syndrome 1

External Links

<http://www.congenitaladrenalpherplasia.org/>

<http://www.emedicine.com/PED/topic48.htm>

<http://www.genetests.org/profiles/cah>

<http://www.nlm.nih.gov/medlineplus/ency/article/000411.htm>

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