

## Chapter 2

# Congenital Adrenal Hyperplasia Owing to 11 $\beta$ -Hydroxylase Deficiency

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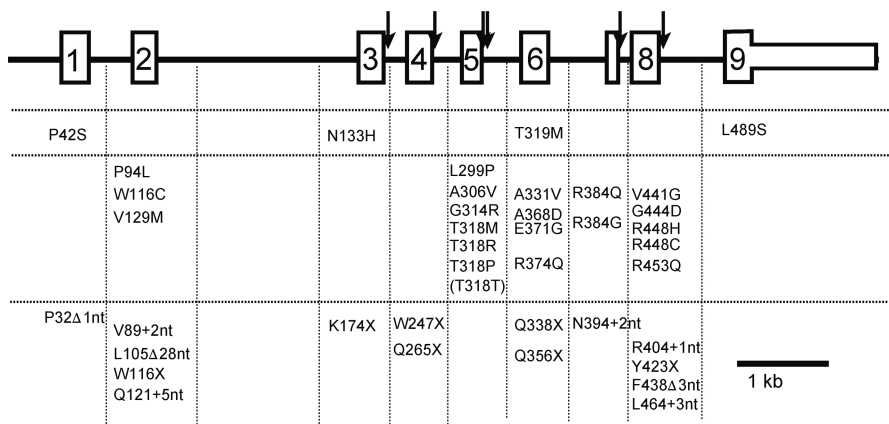
Humans have two isozymes with 11 $\beta$ -hydroxylase activity that are, respectively, required for cortisol and aldosterone synthesis. CYP11B1 (11 $\beta$ -hydroxylase) converts 11-deoxycortisol to cortisol and 11-deoxycorticosterone to corticosterone, is expressed at high levels, and is regulated by ACTH. CYP11B2 (aldosterone synthase) is normally expressed at low levels and is regulated mainly by angiotensin II and potassium levels. In addition to 11 $\beta$ -hydroxylase activity, the latter enzyme has 18-hydroxylase and 18-oxidase activities and thus can synthesize aldosterone from deoxycorticosterone. Mutations in the CYP11B1 gene cause steroid 11 $\beta$ -hydroxylase deficiency, a form of congenital adrenal hyperplasia. Mutations in CYP11B2 result in aldosterone synthase deficiency, which can cause hyponatremia, hyperkalemia, and hypovolemic shock in infancy. These are both recessive disorders. Unequal crossing over between the CYP11B genes can generate a duplicated chimeric gene with the transcriptional regulatory region of CYP11B1 but sufficient coding sequences from CYP11B2 so that the encoded enzyme has aldosterone synthase (i.e., 18-oxidase) activity. This results in glucocorticoid-suppressible hyperaldosteronism, a form of hypertension inherited in an autosomal dominant manner. This review concentrates on steroid 11 $\beta$ -hydroxylase deficiency.

Except in particular populations such as Moroccan Jews, this disorder comprises only a few percent of cases of congenital adrenal hyperplasia. Because 11-deoxycortisol can be converted to androstenedione, signs of androgen excess are prominent including virilization of affected females and rapid somatic growth, premature epiphyseal closure, and short adult stature in untreated males and females. These features are similar to those seen in patients with 21-hydroxylase deficiency. Additionally, 11 $\beta$ -hydroxylase deficiency patients have high levels of deoxycorticosterone and metabolites that are mineralocorticoids, causing sodium retention and hypertension in most patients. This contrasts with the salt wasting seen in many patients with 21-hydroxylase deficiency. Severely virilized females with

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**Fig. 2.1** Mutations causing 11β-hydroxylase deficiency. Exons are numbered and a 1 kb scale is shown. *Arrows* denote splice site mutations. The top line of mutations are those that yield partial enzymatic activity and are associated with nonclassic disease. The next group are more severe missense mutations, and the bottom group are nonsense and frameshift mutations that destroy enzymatic activity. For clarity, *vertical lines* group mutations by their locations within particular exons

11β-hydroxylase deficiency can thus sometimes survive for years without diagnosis and be raised as males. This previously occurred in up to half of affected females in the Moroccan Jewish population, but most females have been reared as girls in recent years.

Whereas many Moroccan Jewish patients carry a characteristic mutation, R448H, many other causative mutations have been identified (Fig. 2.1). Whereas most 21-hydroxylase deficiency mutations are caused by recombinations between the normally active gene and an adjacent pseudogene, there is no corresponding 11β-hydroxylase pseudogene to act as a donor of deleterious mutations. Thus most CYP11B1 deficiency alleles carry sporadic missense, nonsense, or splice site mutations. Gene deletions due to unequal crossing-over between CYP11B1 and CYP11B2 have been reported rarely. Mild, nonclassic 11β-hydroxylase deficiency is apparently unusual. Approximately two-thirds of classic patients are hypertensive regardless of genotype.

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