Chapter 1
Congenital Adrenal Hyperplasia Owing to 17α-Hydroxylase/17,20 Lyase and P450 Oxidoreductase Deficiencies

Christa E. Flück

Congenital adrenal hyperplasia (CAH) due to genetic mutations in the genes for *CYP17A1* (*MIM 609300*) and *CYP OR* (*MIM 124015*) are rare and may cause disordered sexual development (DSD).

The CYP17A1 enzyme catalyzes two distinct reactions in the steroid pathway; its 17α-hydroxylase (17OHase) activity is essential to produce 17-hydroxypregnenolone (17OHPreg) and 17-hydroxyprogesterone precursors of cortisol, and its 17,20 lyase activity is needed for the production of C19 precursors of sex steroids. As a consequence, lack of 17OHase activity causes glucocorticoid (GC) and sex steroid deficiency. However, compensatory overproduction of corticosterone and deoxycorticosterone with weak GC and significant mineralocorticoid action results in subclinical hypocortisolism but severe hypertension and hypokalemia. By contrast, lyase deficiency causes a lack of sex steroids leading to 46,XY DSD with severe undervirilization in 'male' newborns, and absent or incomplete pubertal development in both sexes. While the first clinical and biochemical description of patients with 17OHase deficiency is dated 1966 [1] and 1970 [2], it was not until 1988 that the underlying genetic defect was found [3]. Over the last two decades numerous point mutations, deletions/insertions, and splicing mutations have been reported for the CYP17A1 gene. Generally, mutations affecting the steroid-binding domain of CYP17A1 or disturbing the interaction with P450 oxidoreductase (OR) for electron transfer cause combined 17OHase and lyase deficiency. Although there seems no 'hot spot' in the gene for mutations, CYP17A1 mutations W406R and R362C predominate in a larger cohort of Brazilians originating from Spain or Portugal suggesting a founder effect [4]. By contrast, only four CP17A1 point mutations (E305G, R347C/H, and R358Q) are reported to cause isolated lyase deficiency [5–7], first described in 1997 [5]. These mutations are thought to interfere with either cofactor cytochrome b5 in the specific electron transfer from

C.E. Flück (✉)
Pediatric Endocrinology and Diabetology, University Children's Hospital, University of Bern, 3010 Bern, Switzerland
e-mail: christa.flueck@dkf.unibe.ch

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OR to CYP17A1 during the lyase reaction [8] or to alter substrate binding for 17OHPreg specifically [6].

OR is the obligate electron donor to the steroidogenic enzymes CYP17A1, CYP21A2, and CYP19A1. Therefore, patients with OR deficiency have a complex pattern of disordered steroidogenesis that was initially described as apparent combined 21OHase and 17OHase deficiency in 1985 [9]. Usually mineralocorticoid production remains normal while cortisol and sex steroid production are impaired to variable degrees with different OR mutations. Because of affected CYP17A1 and CYP19A1 activities leading to impaired testosterone and estrogen production, *OR* mutations may cause severe sexual ambiguity in both sexes (46,XY DSD or 46,XX DSD). Affected girls may present with different degrees of virilization at birth suggesting prenatal androgen exposure (Prader III–V). Affected boys present with varying degrees of undervirilization ranging from micropenis to severe hypospadias. In addition, patients with 'severe' OR mutations may present with skeletal malformations previously described as Antley Bixler craniosynostosis syndrome (*MIM 207410*) with genital anomalies [10]. This is explained by the fact that OR interacts with all microsomal type II P450s including enzymes involved not only in steroidogenesis but also in bone development, cholesterol biosynthesis, drug metabolism, and more [11]. Since the first description in 2004 [12, 13], about 40 inactivating *OR* mutations have been described (http://www.cypalleles.ki.se/por.htm) in patients presenting with an extremely broad range in phenotype [11]. Several patients previously misdiagnosed for having 21OHase or 17OHase deficiency were identified. Genotype–phenotype correlation is currently being studied by several groups [14, 15]. Overall, OR A287P mutation appears to predominate in European patients while R457H is mostly found in Japanese patients [11]. Mutations destroying the FAD binding to OR such as R457H seem to inactivate all interacting P450s [13–16]. By contrast, mutations not directly involved in the electron transfer but involved in the direct interaction with partners or cofactors (e.g., A287P) seem to affect activity of partner proteins to different degrees [16, 17]. In addition, a large number of sequence variations have been identified in 842 healthy individuals of 4 ethnic groups and the missense mutation A503V was found on 27% of all alleles [18]. Further, (ongoing) studies focus on the impact of OR mutations on drug-metabolizing P450s [19, 20] to elucidate the impact of OR variants for pharmacogenomic aspects.

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