New Horizons: Molecular Basis and Novel Therapeutics in Congenital Adrenal Hyperplasia

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Congenital Adrenal Hyperplasia (CAH, OMIM + 201910) is an inborn error of metabolism which represents a group of autosomal recessive disorders. These disorders are owing to defects in steroidogenic pathway involved in biosynthesis of mineral-corticoids (aldosterones), glucocorticoids (cortisol) and sex-steroids (androgens). A wide range of clinical severity exists in the individuals with CAH, depending on the extent of enzyme impairment. There are three recognized clinical forms of CAH: salt wasting (SW), simple virilizing (SV) and non-classical (NC). Five different enzymes are involved in this pathway. More than 95% of CAH cases are due to impaired function of 21-OHase enzyme (EC1.14.99.10) which are linked to mutations in 21-OHase encoding gene (CYP21A2) [1]. The worldwide prevalence of classical CAH is around in 15,000–20,000 live births whereas the non-classical CAH is more frequent with 1 in 100 individuals in the general Caucasian population [2]. CYP21A2 gene is located on the chromosome 6 (6p21.3). The CYP21A2 gene is a component of a complicated structure, referred to as the RCCX module, having bi-modular form (RCCX-RCCX). It consists of two sets of genes arranged in tandem: RP1-C4A-CYP21A1P-TNXA-RP2-C4B-CYP21A2-TNBX. The CYP21A1P (pseudogene) gene has been manifested as non-functional due to presence of deletion, conversions, missense, non-sense and frameshift mutations. Majority of disease causing known mutations in the functional gene (CYP21A2) arise from the pseudogene (CYP21A1P) derived sequences, which are transferred by misalignment

followed by unequal crossing over and non-homologous recombination [3]. More than 180 sequence variations in CYP21A2 gene have been reported (<http://www.cypalleles.k.se/cyp21.htm>) worldwide. Notwithstanding, few studies have been reported the spectrum and frequency of CYP21A2 gene mutations in Indian CAH population [4–6]. The i2g mutation was found as the most common in North Indian population [5]. The functional characterization of novel mutations in CAG gene has demonstrated good association between the degree of enzymatic impairment in vitro and in silico with the clinical disease presentation [6]. Interestingly, the phenotype of the patient and the parameters obtained on the functional characterization were found in the concomitance with protein structure as well as characteristic of the non-classical phenotype.

In the classical forms, congenital adrenal hyperplasia has been traditionally treated with daily oral doses of glucocorticoids and mineral corticoids supplements. However, the short half-life of hydrocortisone minimizes growth suppression along with other side effects of longer acting, more potent glucocorticoids such as prednisone and dexamethasone [7]. Abiraterone acetate is an orally active, potent 17 α -HSD inhibitor normalized the pre-dose serum androstenedione in women with poorly controlled classic CAH [8]. A clinical trial is underway in pre-pubertal children with CAH (Clinical Trials, gov identifier: NCT02574910) with the goal of minimizing exogenous GC and endogenous adrenal sex steroid hormone exposure in order to normalize growth and pubertal development. Other medical strategy is in reduction of adrenocorticotrophic hormone (ACTH) production by minimizing adrenal androgen excess using corticotrophin-releasing hormone receptor type 1 antagonist, NBI-77860 in addition to conventional therapy [9]. In two decades, since the initial report that adenoviral gene therapy transiently restored

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enzyme activity in a mouse model of 21-hydroxylase deficiency, animal research is under study using intravenous injection of an adenovirus-cyp21a1 vector to achieve functional enzyme expression. Permanent correction of mutations causing CAH with gene therapy directed at a patient's own adrenal stem cells would theoretically cure CAH. Cell based therapies and gene editing technology now in development may be options for disease cure in the future [10]. Recently, to rescue from underlying molecular defects in CYP21A1 gene using novel molecules viz, potentiators are also in progress.

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