21-Hydroxylase-Deficient Congenital Adrenal Hyperplasia

Genetics

-CYP21A2 (6p21.3)

-AR

Clinical findings/Dysmorphic features

-Adrenal glands produce excess androgens (male sex hormones) --> virialized female or childhood virilization in males; precocious puberty or adrenarche (early); ambiguous genitalia

-Infant with Na+ losing crisis at birth, life-threatening (adrenal glands make too little aldosterone --> body unable to retain enough Na+ --> lost in urine)

-Non-classic form: moderate enzyme deficiency with variable postnatal virilization, no salt wasting, but rare cortisol deficiency

Etiology

-Overall incidence of 1:15,000 live births for the classic form of 21-OHD

-Non-classic 21-OHD CAH: 1:100

Pathogenesis

-Deficient function of 21-hydroxylating cytochrome 450 --> cortisol production pathway is blocked --> accumulation of 17-hydroxyprogesterone (17-OHP) --> 17-OHP is shunted into the intact androgen pathway --> 17,20-lyase enzyme converts the 17-OHP to Δ4-androstenedione --> converted to androgens

Genetic testing/diagnosis

-Classic 21-OHD CAH: clinical features + elevated serum 17-OHP + elevated adrenal androgens

-Non-classic 21-OHD CAH: comparison of baseline serum 17-OHP and ACTH-stimulated serum 17-OHP or early morning elevated 17-OHP

-Sequencing: ~70-80%, Deletion/Duplication: ~20-30%

Others:

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

--> identify infants with classic form of 21-OHD CAH --> risk for life-threatening salt-wasting

--> expedite diagnosis of females with ambiguous genitalia

-NBS rarely detects individuals with non-classic form of 21-OHD CAH