Heterozygous *CYP11A1* mutation associated with 46XY Disorder of Sex Differentiation and mild Adrenal Insufficiency

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CYP11A1 gene

- Encodes the P450 side chain cleavage(scc) enzyme
- This protein localises to the mitochondrial inner membrane
- It catalyses the conversion of cholesterol to pregnenolone
- The first and rate-limiting step in the synthesis of all steroid hormones

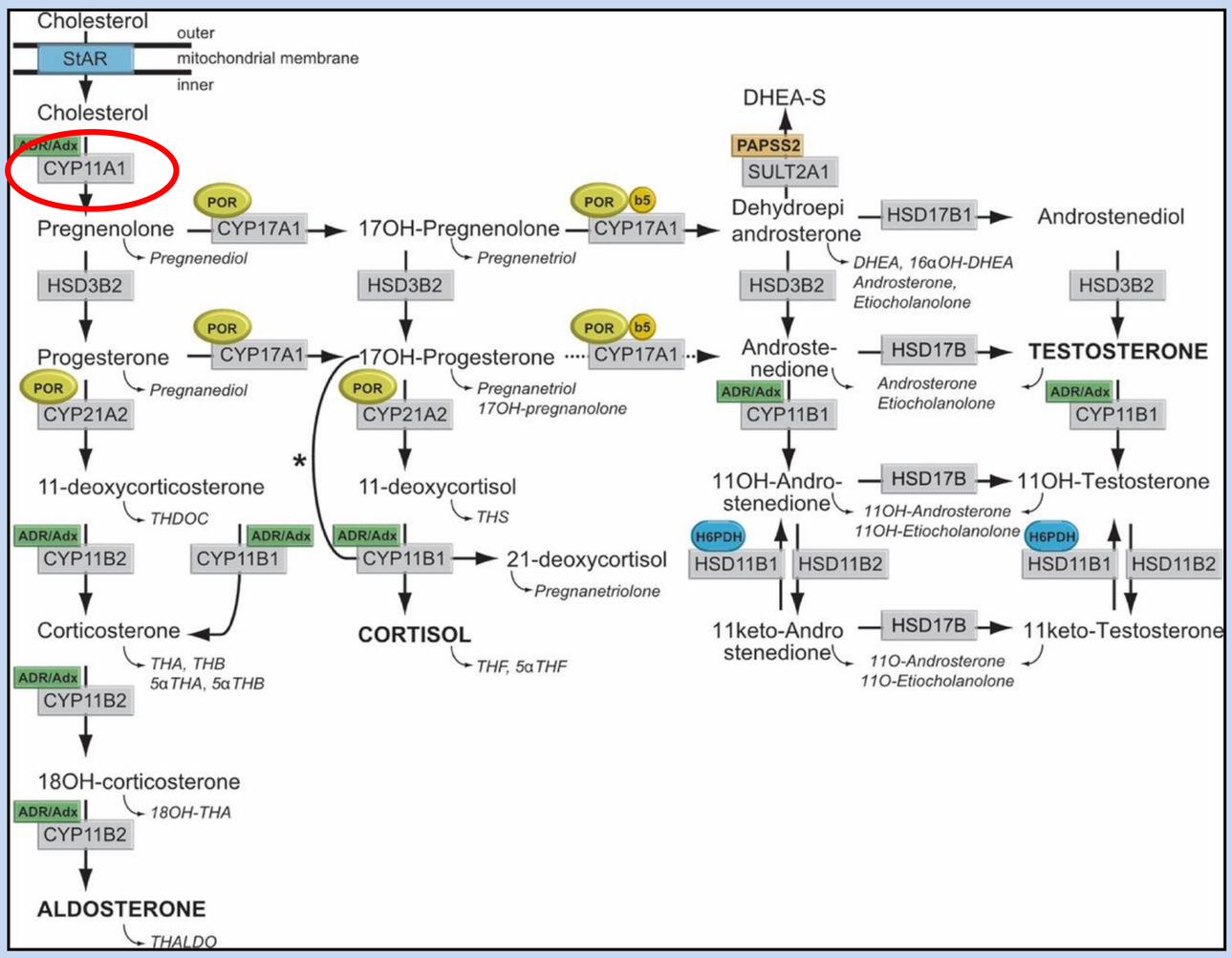

Figure 1: Diagram of adrenal steroid biosynthesis[1]
The red oval depicts where the *CYP11A1* gene, that encodes the P450 side chain cleavage enzyme, acts to convert cholesterol to pregnenolone

P450scc enzyme deficiency

- Is a rare disorder
- Presents as primary adrenal insufficiency with varying degrees of DSD in 46XY individuals
- Genetics: typically due to biallelic loss of function variants in *CYP11A1*, either homozygous or compound heterozygous mutations

Clinical case

- Preterm infant (36 weeks gestation)
- Birthweight 2.9 kg
- Non-consanguineous parents
- Hypoglycaemia on day 1 of life that quickly resolved
- Atypical genitalia noted at birth, raising concerns of a possible disorder of sex development; perineal hypospadias, chordee and cryptorchidism

Table 1: Initial investigations from clinical case

Investigation	Result
Karyotype	46XY
USS Pelvis	No mullerian structures Testes in inguinal canal bilaterally
Electrolytes	Stable
Hypoglycaemia screen	Inappropriately raised plasma insulin level at time of hypoglycaemia
17 Hydroxy progesterone	Normal
Aldosterone	Normal
Renin	Normal
Short synacthen test	Suboptimal (peak cortisol 397nmol/l)

46XY DSD gene panel

- Heterozygous frameshift mutation in *CYP11A1* c.835delA p.(Ile279Tyrfs*1)
- Classified as a pathogenic variant
- Recessive state typically causes severe adrenal insufficiency and 46XY sex reversal and have been widely reported
- Heterozygous *CYP11A1* mutation contributing to the phenotype are extremely unusual and rare
- In the absence of other explanation, it is possible that the heterozygous *CYP11A1* mutation in our patient is contributing to the phenotype of mild adrenal insufficiency and undervirilisation

Conclusion

- Recessive (homozygous and compound heterozygous) *CYP11A1* mutations are known to result in severe adrenal insufficiency and DSD in 46XY infants.
- Heterozygous loss of function mutations in *CYP11A1,* such as that in our patient, can cause mild adrenal insufficiency and undervirilisation in 46XY.individuals
- Due to the rarity of such descriptions in the literature, more reported cases and molecular studies might add to the body of evidence

Reference

1. Bacila I, Elder C, Krone N, Update on adrenal steroid hormone biosynthesis and clinical implications, *Archives of Disease in Childhood* 2019/archdischild-2017-31387