The role of a next generation sequencing panel in the diagnostic pathway in Disorders of Sex Development

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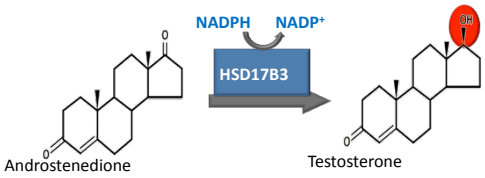
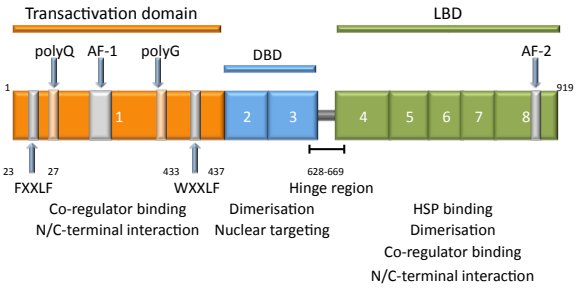
The clinical presentation of both CAIS and 17B-HSD3 deficiency can be similar and therefore difficult to differentiate.

17-ß-HSD3



- Most affected individuals female external genitalia at birth
- Few infants present with ambiguous genitalia
- Testes usually located in inguinal canal
- Often misdiagnosed with CAIS
- **Profound virilization at puberty**
- **Malignancy risk: 28%** (Hughes IA, et al. Arch Dis Child. 2006;91:554-562)

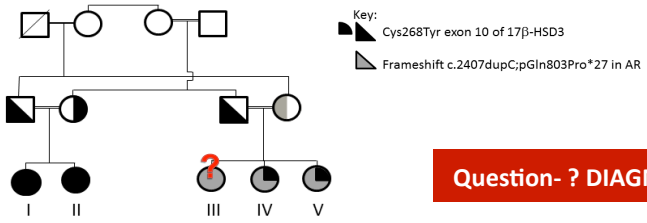
CAIS



- Female external genitalia at birth
- Bilateral inguinal or labial swellings
- **Malignancy risk: 2%**

PHENOTYPE

Patient	Age (years)	Karyotype	Genital appearance	USP	Basal T/A ratio	Day 5 T/A ratio (normal >0.8)	Gonadectomy
I	0	XY	Female, right labial swelling	Normal	<0.5/2.4	_	Yes
II	0	XY	Female, right inguinal hernia	Normal	<0.5/0.7	0.19 (1.4/7.4)	Yes
III	0	XY	Female, B/L inguinal hernia	Normal	0.7/1.4	3.27(3.6/1.1)	Yes
IV	7	XY	Female	Normal	1.1/1.1	2.45 (2.7/1.1)	No
V	4	XY	Female	Normal	1/0.9	3.08 (3.7/1.2)	No



Question- ? DIAGNOSIS IN PATIENT III

Patient III (presented after patients I & II):

- Mutation analysis identified a single base pair mutation (c.857G>A) in exon 10 of 17B-HSD3 gene.
- Her gonadal DNA was sequenced to determine if recombination had occurred causing this copy of the gene becoming homozygous. However both gonads were heterozygous for the mutation.
- Clonal sequencing was therefore performed using a custom designed TruSeq amplicon panel covering 32 genes associated with 46,XX and 46,XY DSD.
- A novel hemizygous frameshift mutation c.2407dupC; p.Gln803Pro*27 in the androgen receptor was identified in patients III-V.

CONCLUSION

- Accurate genetic diagnosis is essential in disorders of sex development (DSD), guiding medical management and enabling optimal personalized care delivery.
- These cases highlight the value of targeted sequencing panels in DSD.
- Biochemical tests can be equivocal, for example, performing a USP is not helpful in prepubertal children with 17β-HSD3 deficiency.
- Reaching the correct diagnosis in DSD is critical to subsequent management decisions, e.g. adult gonadectomy facilitates a more physiological transition through puberty in CAIS, whereas early gonadectomy or a block and replace regimen during puberty is required in patients with 17β-HSD3 mutations.