Severe 5 alpha reductase 2 deficiency with aphallia is caused by p.Y91H SRD5A2 mutation and is responsive to dihydrotestosterone administration during early childhood

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Disclosure Statement: The authors have nothing to disclosure.

Background:

5-alpha-reductase-2 (5α-RD2) deficiency:

- an autosomal recessive 46,XY DSD
- Neonatal presentation is male under-virilization with ambiguous genitalia.
- **Pubertal** rise in testosterone and 5α-RD1 isoenzyme activity results in pubertal virilization, which commonly leads to change in gender assignment[1].
- Early diagnosis and good prediction of the pubertal virilization related to the diagnosis is critical for early treatment and gender assignment.

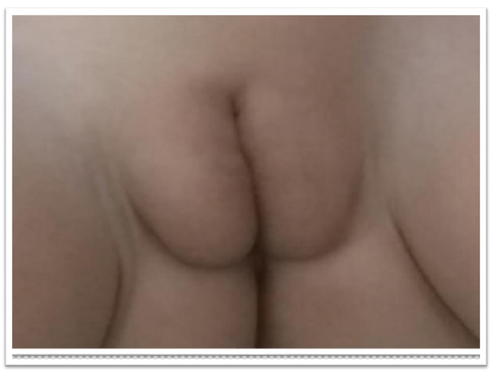
Objective:

To elucidate the genetic cause and the optimal treatment for a unique 46,XY DSD patient.

Methods and results:

Consanguineous Palestinian parents requested a change to male gender assignment in their 2.5y old phenotypical (external genitalia) girl following the finding of testis in labia (Figure 1).

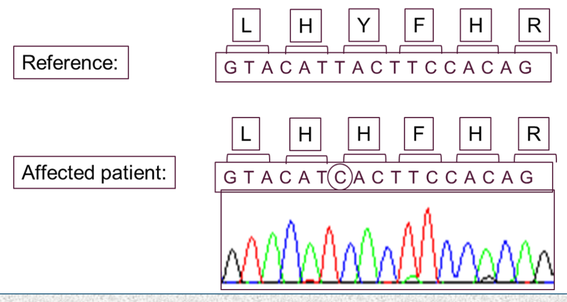
Figure 1- external genitalia before treatment.



normal appearing labia majora containing palpable testis.

hypoplastic labia minora with complete aphallia.
High anogenital ratio (o.78) (Male >0.5) -indicating testosterone responsive genitalia

Figure 2- Sequencing of the 5α RD2 gene - 271 T>C ,Y91H mutation.



Laboratory examinations :

- 46 XY karyotype,
- normal basal and ACTH stimulated glucocorticoids levels
- high HCG stimulated testosterone
- a testosterone/androstenedione ratio of 2.4
- XY karyotype + evidences to the presence of fetal testosterone such as descended testis =high probability for 5α-RD2 deficiency.
- SRD5A2 gene Sequencing :

271T>C, Y91H mutation, in 5α-RD2 transmembranal domain (figure 2).

Urinary steroid metabolites profile :

Severe dysfunction of the mutated 5α-RD2 [2].

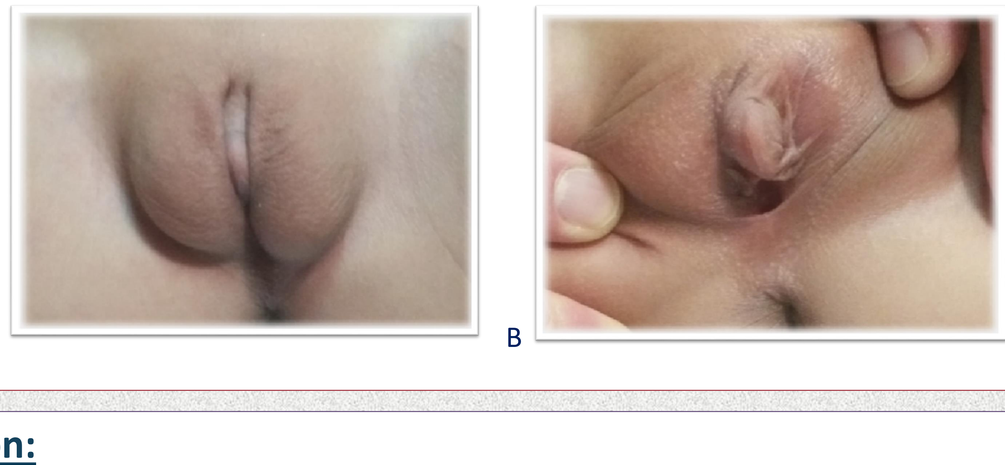
Metabolites	ratio	Normal ratio 3m-6y
aTHB/THB	0.22	1.88-4.68
aTHF/THF	0	1.01-3.33

Is the extreme low ratios explain the extreme undervirilization and aphallia?

The rare phenotype of absence of clitoromegaly and complete aphallia complicated the adherence to the parents' request for male gender assignment.
A 4 months trial of daily local dihydrotestosterone administration resulted in dramatic enlargement of the rudimentary clitoris to a phallus of >2cm length enabling reconstruction urological surgery (Figure 3).

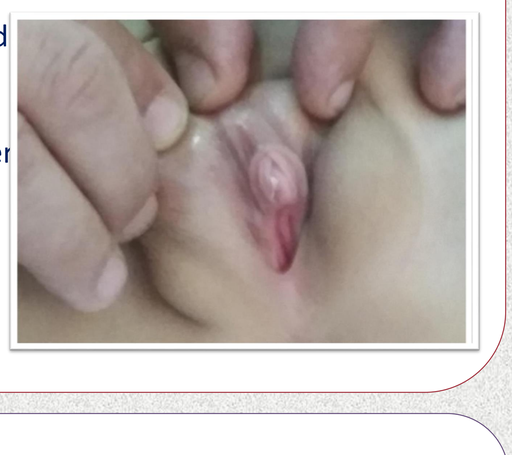
Figure 2- external genitalia after local Dihydrotestosterone jel treatment

A, B, C- enlarged clitoris with palpable corpus after 3 months treatment.



A B C

D- enlarged penile shaped clitoris after 4 months long treatment.



D

Conclusion:

- The new Y91H mutation in the SRD5A2 gene, causes severe 5α-RD2 enzymatic dysfunction as reflected in urine metabolites
- It results in a unique aphallic XY-DSD phenotype. The very low ratio of 5 alpha to 5 beta steroid metabolites may explain this severe neonatal phenotype.
- The prepubertal use of local dihydrotestosterone is efficient in developing a penis corpus even in “aphallia”.
- Further studies correlating quantitative 5α-RD2 enzymatic activity to genotype and phenotype may enable early and comprehensive gender assignment recommendations.

55ESPE 349--P1
Gonads & DSD
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DOI: 10.3252/pso.eu.55ESPE.2016
Poster presented at: ESPE 2016 PARIS