5α-Steroid Reductase 2 Deficiency in a Large Family

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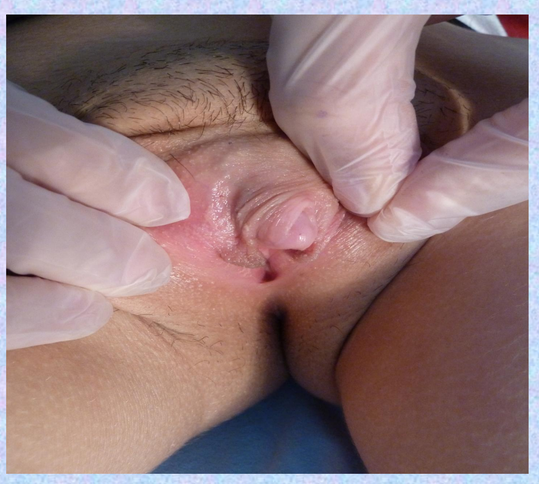
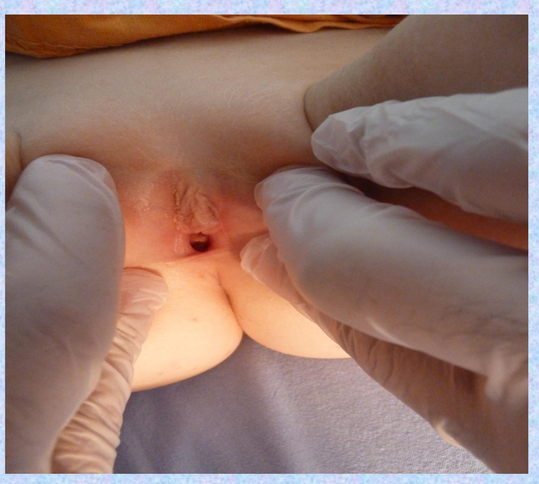
Background: 5α-Reductase is an enzyme that converts testosterone to dihydrotestosterone (DHT) in peripheral tissues. DHT is responsible for the differentiation of male external genitalia. Mutations in the 5alpha-steroid reductase type 2 gene (*SRD5A2*) result in incomplete masculinisation of the external genitalia in subjects with a 46,XY karyotype. The clinical spectrum of a 46,XY individual with 5α-reductase deficiency at birth can range from complete female appearance of the external genitalia to nearly complete male phenotype.

Aim: Our aim is to report the molecular and clinical characteristics of a Turkish family with 5α-reductase deficiency who had a homozygote mutation of *SRD5A2* gene.

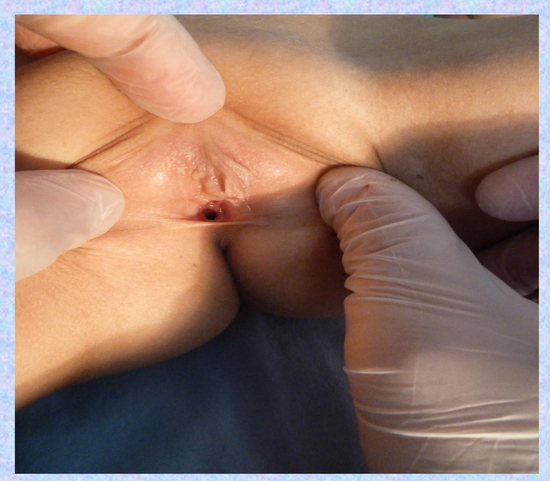
Patients and Methods: A 14-year-old girl presented with primary amenorrhea and lack of breast development. She had a history of inguinal hernia surgery. Her parents are healthy cousins. Physical examination of the patient identified a predominantly female phenotype except clitoris-like phallus (2 cm) and bilateral inguinal masses. Genital ambiguity was stage 4b according to Sinnecker's classification. Her breast, pubic hair and axillary hair were at Tanner stage 1, 4 and 1, respectively. A chromosome analysis revealed a 46,XY karyotype. Pelvic ultrasonography confirmed absence of müllerian structures and the presence of both gonads with features of normal testes in the inguinal canal. A Testosterone/DHT ratio was 9,7 and further increased to 14,5 after stimulation with hCG.



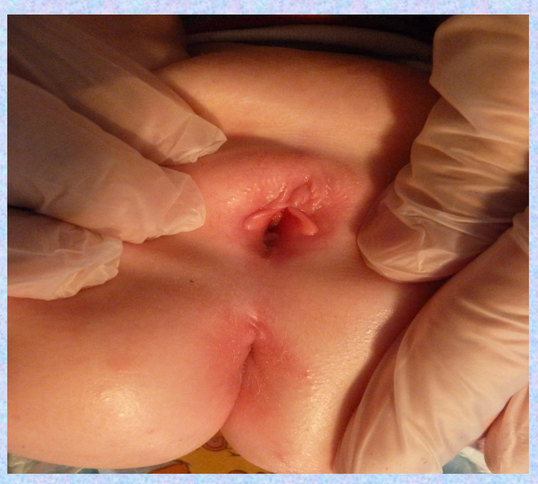
Patient 1



Patient 2



Patient 3



Patient 4

Results: A previously reported homozygous missense mutation (p.A65P) was detected in the *SRD5A2* gene. After the diagnosis, her eight sisters were screened. Three of her siblings were also found to be homozygous for the same mutation.

Lab test results

hCG Stimulation Test

	Patient 1		Patient 2		Patient 3		Patient 4 (6-month-old)	
	Before	After	Before	After	Before	After	Before	After
T.Testosteron (ng/dl)	342	1165	8	28	<0.1	26	<0.1	212
Progesteron (ng/ml)	0.31	0.71	0.32	0.53	0.65	0.44	0.24	0.71
LH (mIU/ml)	3.48	1.95	0.02	0.0	0.09	0.09	0.72	0.81
FSH (mIU/ml)	8.25	3.65	1.23	0.46	0.46	0.21	1.03	0.58
Androstenedion (ng/ml)	1.41	2.45	0.502	0.436	< 0.30	< 0.30	< 0.30	0.369
DHT (pg/ml)	349.3	802.7	139.7	132.2	76.0	72.6	0.1	113.9
T/DHT	9.7	14.5	0.5	2.1		3.6		18.7

Conclusion: Although rare, *SRD5A2* gene defect should be suspected in any girl presenting with primary amenorrhea and virilisation at puberty. It is important that siblings of the diagnosed cases be screened with genital system examination, as well as chromosomal and, if necessary mutational analysis.