A NOVEL ANDROGEN RECEPTOR GENE MUTATION IN TWO PATIENTS WITH A 46,XY DISORDER OF SEX DEVELOPMENT

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Background:

✓Androgen insensitivity syndrome in its complete form (CAIS) is a disorder of hormone resistance characterized by a female phenotype in an individual with an XY karyotype and testes producing age-appropriated normal concentrations of androgens.

✓Pathogenesis is the result of mutations in the X-linked androgen receptor *(AR)* gene, which encodes for the ligand-activated androgen receptor.

✓We report the clinical, biochemical and molecular features of two affected sisters in whom a novel mutation has been detected.

Cases:

A 17-year-old woman (patient 1) and her 15-year-old sister (patient 2) were referred presenting primary amenorrhea.

❖**Physical exploration:**

- Patient 1: Weight: 62.7 kg (+1.36 SDS), height: 169.5 cm (+1.55 SDS)
- Patient 2: Weight: 48.2 kg (-0.52 SDS), height: 169 cm (+1.76 SDS)
- Both exceeded its target size: 164 cm (+0.48 SDS)
- They presented female phenotype and external genitalia, normal breast development (Tanner V) and absent axillary and pubic hair.

Analysis of *AR*

A point mutation in intron 5, two nucleotides preceding exon 6: c.2319-2A>G in both.
This nucleotide is located in the splice site regulatory transcription region (AG/GT).
It can, therefore, be predicted that this mutation gives rise to an anomalous and inactive protein.

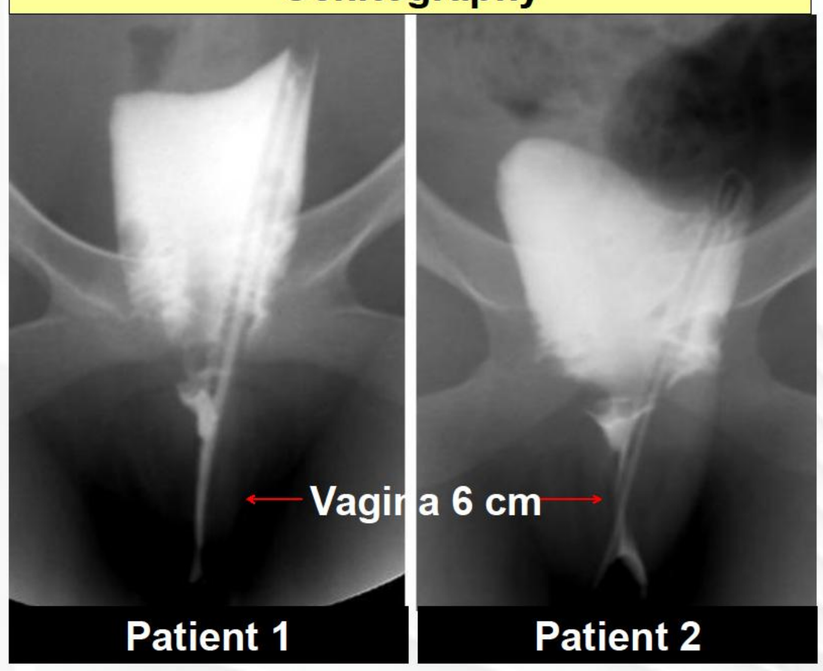
❖**Additional tests:**

- Karyotype was 46, XY
- Transabdominal pelvic ultrasonography showed internal gonads and absence of uterus.
- The endocrine profile revealed elevated testosterone and abnormally high LH.

Hormonal study

Hormones (VN)	Patient 1	Patient 2
Testosterone (µg/l) (♂: 2.7-8.3, ♀: 0.1-0.8)	5,1	2,7
Free testosterone (ng/dl) (♂: 6.6-30, ♀: 0.1-3.1)	11	5,1
Oestradiol (ng/l) (♂: 20-45, ♀: 20-220)	14	12
LH (UI/l) (♂: 2-9, ♀:2-14)	30	36
FSH (UI/l) (♂: 2-10, ♀:2-10)	8	7

Genitography



At present, gonadectomy has been deferred to complete pubertal development and optimize bone density, although it will be recommended from the second decade of age to prevent the risk of gonadal tumours.

Conclusions:

❖<u>This mutation had not been previously reported</u>.

❖*AR* gene mutation is the most frequent cause of 46, XY disorder of sex development, with a clearly higher frequency in the complete phenotype. Loss of function mutations can be found in most women with suspected CAIS, but only in about 15-20% of subjects with suspected partial androgen insensitivity syndrome (PAIS).

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