SURPRISING X CHROMOSOMES: UNUSUAL MOSAICISM

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INTRODUCTION

Among 46,XY individuals, androgen insensitivity syndrome (AIS) due to deleterious genetic variants of the androgen receptor (*AR*) gene can cause a difference of sexual development (DSD).

Typically, individuals with complete androgen insensitivity syndrome (CAIS) present with female external genitalia and palpable labial masses.

Whereas most patients with CAIS carry germline variants inherited in an X-linked manner, approximately 30% of patients manifest *de novo* variants.

AIM

We describe an infant with phenotype-genotype incongruity associated with a genetic variant in *AR*.

CASE PRESENTATION

This patient was referred to endocrinology at the age of 3 weeks for evaluation of atypical genitalia. He was born at 35 weeks with a birth weight 2.94 kg and was the product of a twin pregnancy.

The exam was normal apart from bifid scrotum, bilateral descended testes, scrotal hypospadias with chordee, and 1 cm phallus. Initial lab studies showed normal random growth hormone, cortisol, and 17-hydroxyprogesterone levels.

A pelvic ultrasound revealed absence of any Mullerian structures. No apparent gonads were seen in the pelvic area.

Chromosome analysis showed 46,XY karyotype.

FISH confirmed presence of the SRY gene. Studies obtained at 2 months of life are:

LH	FSH	Testo-sterone	DHT
1.78 IU/L	0.45 IU/L	282 ng/dl (9.8 nmol/L)	65 ng/dl (2.2 nmol/L)

Table 1: showing lab results at 2 months of life. LH: Lutenizing hormone, FSH: Follicle-stimulation hormone, DHT: Dihydrotestosterone

Due to the infant's undervirilization, whole exome sequencing was performed.

A rare pathogenic variant in the *AR* gene, c2104C>T, predicted to result in amino acid substitution p.Leu702Phe (rs1555995851) was detected in 48% of the sequence reads. This finding is consistent with somatic mosaicism.

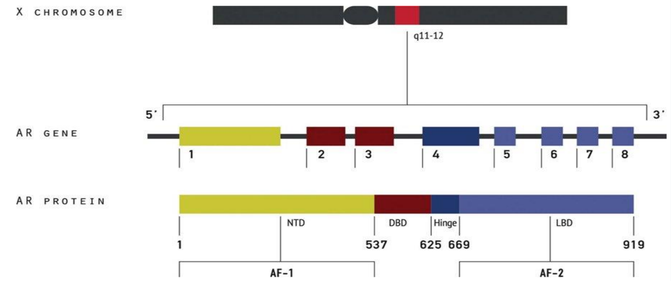

Fig 1: Schematic of the Androgen Receptor gene and protein.

DISCUSSION

The initial evaluation of this patient excluded hypopituitarism and defects in steroidogenesis from consideration.

This *AR* gene sequence variant has been previously confirmed to be associated with CAIS.

In this patient, somatic mosaicism for a pathogenic *AR* variant likely explains the inconsistency between his partially virilized phenotype and the sequence variant predicted to cause CAIS.

Somatic mosaicism for a DNA sequence variant, resulting from post-zygotic changes during the early stages of embryo development, is emerging as a significant contributor to DSD and other genetic disorders.

CONCLUSION

Identification of mosaicism is important for management and will help the medical team and the family discuss sex of rearing.

For patients with mosaicism for a disease-causing variant, the proportion of cells with a wild type *AR* is likely variable and may ultimately influence androgen responsiveness and the patient's phenotype during adolescence and adulthood. Virilization at puberty has been reported in males with somatic mosaicism of *AR* (JCEM 2005; 90:106).

CONCLUSION-CTD

Our patient showed some response to a testosterone trial and will receive another trial course of higher dose testosterone.

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