Three Siblings with Androgen Insensitivity Syndrome due to an *AR* mutation with Differing Phenotypes

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Background: Androgen insensitivity syndrome (AIS) is the most common cause of 46,XY sexual differentiation disorders. Genetically it is encountered in males as 1/20.400 - 1/99.000. It has X-dependent recessive inheritance. More than 400 mutations have been determined in androgen receptor (AR) gene on Xq11-12. There are *de novo* mutations in approximately 30% of cases. Clinical presentation is variable among cases with a range from a complete female to male external genitalia. There is a weak correlation between genotype and phenotype.

Aim: Our aim is to report clinical and molecular characteristics of siblings with AIS.

Patients And Methods: Two siblings newborns with ambiguous genitalia were examined. The parents were second-degree cousins. Both patients had a genital ambiguity stage 3a according to Sinnecker's classification. 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. Patient 3, who was reared as a girl, their 12 years and 6 months old sibling, who was reared as a girl, invited for screening. The physical examination revealed female phenotype, and bilateral inguinal masses. Genital ambiguity was stage 5 according to Sinnecker's classification. 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.

Lab test results

	Patient 1	Patient 2	Patient 3
T.Testosteron (ng/dl)	1477	619	<0.1
LH (mIU/ml)	3.6	7.2	0,08
FSH (mIU/ml)	0.33	3.8	3,8

Results: All three patients were found to have a hemizygotus mutation of p.R856H (c.2567G>A) in *AR* gene. This mutation was previously defined to cause the disease.[1]

Conclusion: Androgen insensitivity syndrome has a wide range of clinical spectrum. Even members of the same family may have different clinical pictures. Therefore, siblings of diagnosed cases should have genital system examination, chromosomal analysis, and mutation screenings. It is important that families should be informed about prenatal diagnosis and preimplantation genetic diagnosis.

Referance

1. Akcay T, Fernandez-Cancio M, Turan S, Güran T, Audi L, Bereket A. AR and SRD5A2 gene mutations in a series of 51 Turkish 46,XY DSD children with a clinical diagnosis of androgen insensitivity. Andrology 2014 Jul;2(4):572-8. doi: 10.1111/j.2047-2927.2014.00215.x. Epub 2014 Apr 16.