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NR5A1 Gene Mutation: Variable Phenotypes, New Variants, Different Outcomes

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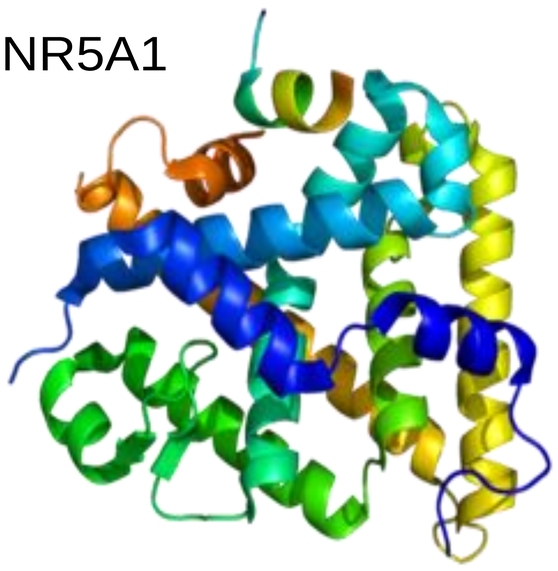
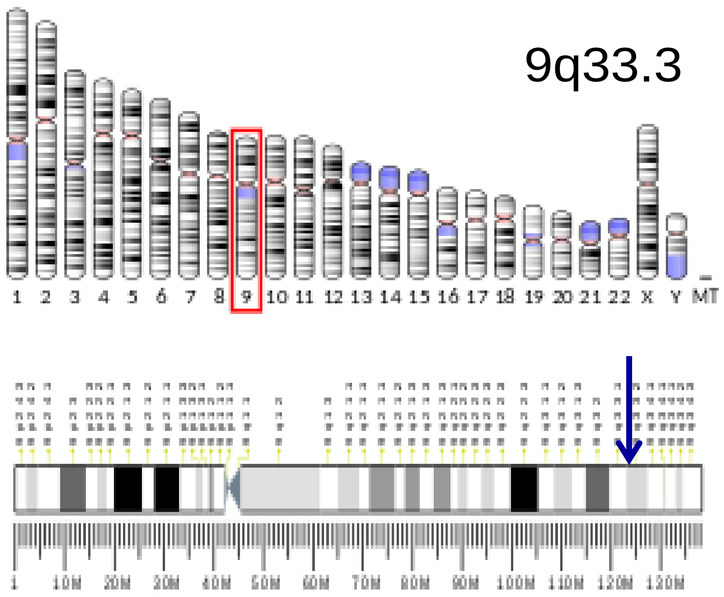
BACKGROUND

NR5A1 (nuclear receptor subfamily 5 group A member 1) is a transcriptional regulator of adrenal and gonadal development and function. In humans, heterozygous and homozygous *NR5A1* mutations have been described in people with 46,XY disorders of sex development (DSD). The clinical, endocrine and genetic features of three 46,XY children from two unrelated families (A and B) with *NR5A1* genetic variants are reported.





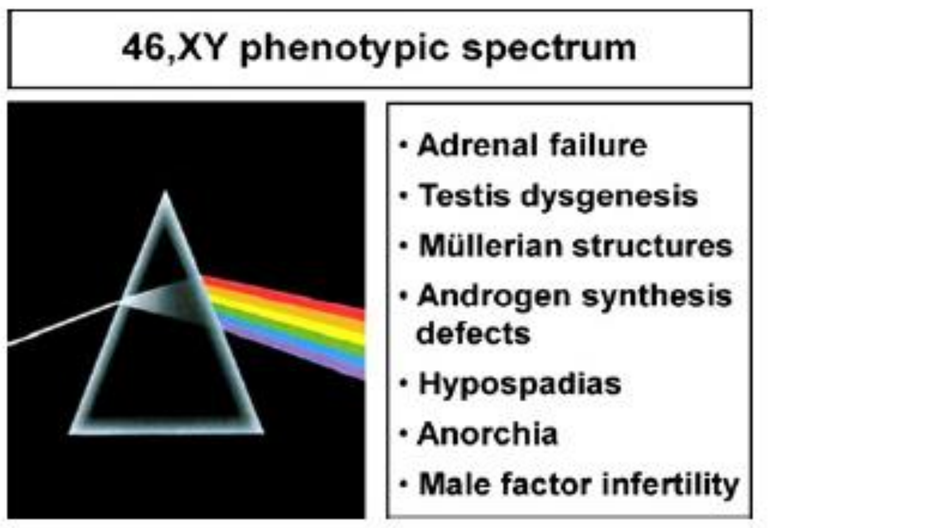


Fig. The spectrum of phenotypes that have been reported in association with SF-1/*NR5A1* changes in humans (46,XY).

Patients and methods. Two sisters from family A and a boy from family B were studied. Endocrine parameters were assessed by standard laboratory methods. NGS analysis was performed using Sure Select (Agilent) customized DSD panel and captured products were sequenced by Miseq (Illumina).

Results. Two sisters (14.5 years; 13.9 years) were referred for evaluation of absent pubertal development. On clinical examination, they showed breast development Tanner Stage 1, but pubic hair Tanner Stage V. Genital examination demonstrated clitoromegaly, well-formed labia, and presence of a single orifice compatible with persistence of the urogenital sinus. Endocrine assessment demonstrated low estradiol levels with elevated gonadotrophins in both the sisters (basal FSH 87.49 IU/L and 135.10 UI/L respectively, basal LH 20 IU/L and 30 IU/L, respectively). Increased concentrations of testosterone for females normative values were also found. Karyotype was 46, XY. Pelvic ultrasound did not shown any Müllerian structures; gonads were not individuated. According with parents, female sex was confirmed in both sisters after deep psychological investigation and gonads removed. The boy presented at the age 18 months for bilateral undescended testes and severe peno-scrotal hypospadias. At puberty, he showed slow pubertal progression with low testicular volume. His endocrine data demonstrated hypergonadotropic hypogonadism (FSH 63 IU/l; LH 14.4 IU/l; Testosterone 2.5 ng/ml) and normal adrenal function. Using a DSD 14-gene next generation sequencing (NGS) panel, we identified two heterozygous missense *NR5A1* variants in the patients: c.248T>A, p.Val83Glu in the sisters; c.937C>T, p.Arg313Cys in the boy. The former was predicted pathogenetic by *in silico* analysis, the latter was reported in HGMD database (CM118686) and previously identified in our 46,XY DSD italian patient. Parents are under investigation. Sex related hormonal substitutive therapy was started. All the children presented good psycho-social outcome according to assigned sex.

CONCLUSIONS

Present data confirmed that *NR5A1* gene mutations may present with variable genital phenotypes. Anyway, reproductive function was impaired. Any clinical or endocrine data seem to be unable to differentiate these patients from other 46,XY DSD. In persons with NR5A1 mutations, different decisions in sex assignment may permit good somatic and psychological outcome, but any option requires optimal substitutive therapy.