Clinical Vignette

NR5A1-related Disorders: Case Report, Review of Phenotypes and Issues in Genetic Counseling

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Abstract

Nuclear Receptor Subfamily 5 Group A Member 1 (*NR5A1)* encoded steroidogenic factor-1 (SF-1) regulates transcription of genes involved in steroidogenesis, sexual development and reproduction. SF-1 protein is expressed in the bipotential gonad and later in developing ovaries, testes and adrenal cortex. Pathogenic variants in *NR5A1* are known to be associated with a wide spectrum of disorders of sex development. Individuals with a variant in *NR5A1* can present with either 46,XX sex reversal 4 (MIM# 617480), 46,XY sex reversal 3 (MIM# 612965), adrenocortical insufficiency (MIM#612964), premature ovarian failure 7 (MIM#612964) or spermatogenic failure 8 (MIM#613957). We hereby report a 7-months-old infant with ambiguous genitalia and a known variant, c.251G>A p. (Arg84His) in *NR5A1* in heterozygous state inherited from his mother. We also review the phenotypes and genetic counseling issues pertaining to these disorders.

Keywords: Nuclear receptor subfamily 5 group A member 1; Steroidogenic factor-1; steroidogenesis; 46,XX sex reversal 4; 46,XY sex reversal 3; adrenocortical insufficiency; premature ovarian failure 7

Introduction

Pathogenic variants in *NR5A1,* which codes for Nuclear Receptor Subfamily 5 Group A Member 1 (*NR5A1)* encoded steroidogenic factor-1 (SF-1) are known to cause 46,XX sex reversal 4 (MIM# 617480), 46,XY sex reversal 3 (MIM# 612965), adrenocortical insufficiency (MIM#612964), premature ovarian failure 7 (MIM#612964) or spermatogenic failure 8 (MIM#613957). Heterozygous variants in *NR5A1* have been identified in 10-15% of individuals with 46,XY DSD (Suntharalingham et al., 2015). We discuss a 7-months-old with ambiguous genitalia and a known variant, c.251G>A p. (Arg84His) in *NR5A1* in heterozygous state inherited from his mother and review the phenotypes and genetic counseling issues pertaining to *NR5A1*-related disorders.

Patient details

A 7-months-old infant, reared as a male, born to a non-consanguineous couple, had ambiguous genitalia noted at birth. He was the first born of his 21-years-old mother. His development was normal. On examination, he had hypospadias, palpable gonads in labioscrotal folds and microphallus. No dysmorphic features were noted. Ultrasonography of abdomen and pelvis showed the absence of Mullerian structures like uterus and ovaries. Karyotype was 46,XY. His serum sodium was 138 mmol/L and serum potassium level was 5mmol/L. His hormone levels are provided in Table 1. The differential diagnoses considered were partial XY gonadal dysgenesis and testosterone synthetic defects. Exome sequencing of the proband showed a known heterozygous variant, c.251G>A p.(Arg84His) in exon 4 in *NR5A1* causative of 46,XY sex reversal 3. This variant was absent in our in-house data of 650 individuals but was present in one individual in gnomAD in heterozygous state. Multiple *in silico* analysis tools (MutationTaster, MutationAssessor, SIFT) predicted this variant to be damaging to NR5A1 protein function. The amino acid arginine at position 84 is highly conserved across species and is located between zinc fingers and A-box domains of SF1 in the carboxyterminal DNA binding region of NR5A1 protein. This variant was shown to affect

Table 1 Hormone profile of the proband.

Parameters	Levels in proband	Normal range
Testosterone	0.15 ng/mL	0.08-0.48 ng/mL
Luteinizing hormone	0.9 mIU/mL	1.7-8.6 mIU/mL
Anti-Mullerian hormone	19.55 ng/mL	2.2-4.0 ng/mL
Dehydroepiandrosterone sulphate	6 mg/dL	0.47-19.4 mg/dL

DNA binding and transcriptional activation but had little effect on cellular localisation (Köhler et al.,2008). Sanger sequencing confirmed the variant in the proband and showed maternal inheritance of this variant.

Discussion

Nuclear Receptor Subfamily 5 Group A Member 1 (NR5A1) encoded steroidogenic factor-1 (SF-1) regulates transcription of genes involved in steroidogenesis, sexual development and reproduction. SF-1 protein is expressed in the bipotential gonad and later in developing ovaries, testes and adrenal cortex (Domenice et al., 2017). Individuals with heterozygous pathogenic variants in *NR5A1* variants present with a spectrum of phenotypes like 46,XX sex reversal 4 (MIM# 617480), 46,XY sex reversal 3 (MIM# 612965), adrenocortical insufficiency (MIM# 612964), premature ovarian failure 7 (MIM#612964) or spermatogenic failure 8 (MIM#613957). Table 2 lists the different phenotypes in 46,XY and 46,XX individuals.

Individuals with 46,XY DSD may have hypospadias, ambiguous genitalia with hypoplastic phallus or complete external female genitalia, infertility due to oligospermia/azoospermia and rarely primary adrenal insufficiency. The most common phenotype is ambiguous genitalia without Mullerian structures (Suntharalingham et al., 2015).

Individuals with 46,XX DSD and *NR5A1* variants may develop premature ovarian failure, primary adrenal insufficiency, primary or secondary amenorrhea and defective steroidogenesis. A primary adrenal phenotype is a rare presentation.

One of the proposed reasons for the wide range of phenotypes is interaction of *NR5A1* with other target genes like *SRY, SOX9, STAR, WT1* and *AMH*, in gonadal and adrenal developmental pathways. The phenotypic severity of these disorders also varies, suggesting contribution of modifier genes or an oligogenic pattern of inheritance (Fabbri-Scallet et al.,2019).

Most of the variants reported in *NR5A1* are in heterozygous state and occur *de novo*. However around 30% of these variants are known to be inherited from the mother in a sex-limited dominant fashion (Ferraz-de-Souza et al., 2011). In the study by Fabri Scallet et al., 2019, of the 118 individuals whose parental segregation data was available, 47 were *de novo*, 16 had paternally inherited variants, 41 had maternal inheritance and 3 individuals had biallelic variation. The fathers who carried the variation, did not have abnormal phenotype in majority. However hypospadias was seen in five of them. Premature ovarian failure was observed in 11 of the 41 mothers who carried the variant. The predominant mode of inheritance was then ascertained to be autosomal dominant with variable expressivity and incomplete penetrance (Fabri Scallet et al., 2019).

The variant identified in our patient was originally reported by Kohler et al., 2008 as a presumed *de novo* variant (the mother of the patient did not have the variant, but the father's sample was not available for testing) in a patient with 46, XY DSD and ambiguous genitalia (Köhler et al., 2008). The same variant in heterozygous state was later reported in two additional individuals with variable phenotypic features like genital ambiguity, clitoromegaly, inguinal gonads and deranged androgen and gonadotropin levels (Robevska et al., 2018). Information on parents' genotype was not available. This variant was seen in one apparently healthy East Asian male in gnomAD database with an allele frequency of 0.000004114. This could be because of variability in severity of phenotype resulting in mild manifestations. All types of single nucleotide variants including loss-of-function variants (nonsense and frameshift variants) as well as missense variants in primary or alternate DNA binding domains of *NR5A1*, are known to cause 46,XY DSD (Fabbri-Scallet et al.,2018). Small deletions, insertions and intronic

Table 2 Phenotypic features in 46,XY and 46,XX individuals.

46,XY	46,XX
Primary adrenal insufficiency	Primary adrenal insufficiency
Hypospadias	Premature ovarian failure
Male factor infertility due to oligospermia or azoospermia	Primary or secondary amenorrhea
Anorchia, ambiguous genitalia with hypoplastic phallus or complete external female genitalia	-

variations are also reported in some individuals (Fabbri-Scallet et al., 2019).

In the family we describe, the proband inherited the variant from his mother who appeared non-penetrant for this variant. This phenomenon of sex-limited dominant inheritance poses a challenge in genetic counseling of such families. Females with heterozygous variants in *NR5A1* are at risk for premature ovarian failure. But sometimes these women may not demonstrate signs of early menopause or may have completed their family before onset of menopause. In such instances, it may appear that they are non-penetrant and they may transmit the variant to their sons who may be affected (Ferraz-de-Souza et al., 2011). This could resemble an X linked recessive pattern of inheritance. The mother of the child we saw was advised evaluation for premature ovarian failure. Though the chance of inheriting the same variant in proband's siblings is 50%, the phenotypic features and severity in an affected individual will be highly variable and determined by the chromosomal sex. Also, phenotypic variability would not be detected by antenatal ultrasonography or any other prenatal diagnostic modality. Families should be offered adequate support for making decisions regarding sex of rearing, medical and surgical management and reproductive planning. Some of the important aspects to be discussed on follow-up are risk of adrenal insufficiency and testicular tumors. Where applicable, options of fertility preservation should be considered for affected individuals as there are reports of progressive decline in testicular function as well as the possibility of ovarian dysfunction/ primary ovarian insufficiency in 46,XX carriers (Philibert et al.,2011)

This report depicts the phenotypic variability and specific counseling issues in NR5A1- related disorders. Families dealing with such complex issues may confront significant psychological stress related to gender identity development and gender dysphoria. Hence, a multi-disciplinary approach of experts in clinical genetics, newborn care, psychologists/psychiatrists and endocrinologists are warranted for comprehensive care of these individuals and families.

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