Case Report

Different Clinical Manifestations Related to Subvirilization in Three XY Patients With the Same Pathogenic Variant of Steroidogenic Factor 1

Maria Fernanda Ochoa, MD 1, Francisca Yankovic, MD 2, Helena Paggi, Biochem 1, Alejandro Martinez, MD 1,*

1 Endocrinology Unit, Division of Pediatric, Pontificia Universidad Católica, Santiago, Chile
2 Urology Division of Clinica Santa María, Santiago, Chile

Article info

Article history:
Available online 9 December 2020

Key words:
sexual differentiation disorder
steroidogenesis
type 1 steroidogenic factor

Abstract

Objective: During the prenatal period, steroidogenic factor 1 is required for the development of the adrenal glands and for gonadal determination and differentiation, and after birth, it regulates gonadal progenitor cell formation and their survival. Here, we describe the clinical phenotype of three 46,XY patients (2 brothers and an unrelated subject) with disorder of sex development due to the same genetic variant.

Methods: All patients underwent hormonal and pelvic ultrasound studies. Sequence analysis and deletion/duplication testing of a panel encompassing 8 genes (AR, DHH, MAP3K1, NROB1, SRD5A2, SRY, WT1, and nuclear receptor subfamily 5, group A, member 1 [NR5A1]) were performed in the index cases. All family members were tested for the presence of the NR5A1 variant.

Results: A variant previously described as likely pathogenic in NR5A1 (c.251G>A, p.Arg84His) that segregated in 1 family with different degrees of under-virilization was found. The family 1 index case (IV2) and his brother (IV3) had an external masculinization scale score of 5/12, but only the index case had Müllerian remnants; however, the family 2 patient had a milder score of 9/12. The older female relatives of family 1 who harbor this variant experienced premature menopause.

Conclusion: To our knowledge, this is the first report where the c.251G>A (p.Arg84His) variant is associated with the presence of Müllerian remnants in 46,XY subjects and primary ovarian insufficiency in 46,XX individuals. The segregation of this variant with clinical manifestations provides further evidence for considering it as pathogenic.

© 2020 AACE. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Introduction

Steroidogenic factor 1 (SF1) belongs to the family of nuclear transcription factors and regulates many genes involved in reproduction, steroidogenesis, and sexual differentiation. SF1 is expressed early during fetal development in the adrenal cortex, where it regulates the synthesis of several enzymes, such as STAR, CYP11A1, and CYP17A1, and the biosynthesis of steroid hormones. Pathogenic variants in the gene coding for SF1 (nuclear receptor subfamily 5, group A, member 1 [NR5A1]; OMIM* 184757) represent the second most frequent genetic factor associated with disorder of sex development (DSD) in 46,XY individuals.

SF1 protein expression is observed during fetal life, from the time that the bipotential gonad develops throughout sex determination. In the developing testis, SF1 is expressed by fetal Sertoli cells, where it upregulates the expression of 2 genes crucial for male sex determination and differentiation, SRY-box transcription factor 9, and anti-Müllerian Hormone (AMH), through synergistic interactions with SRY. SF1 is also expressed within Leydig cells, where it controls various factors involved in steroidogenesis, ultimately leading to male virilization in utero and in the prepubertal gonad. On the other hand, in postnatal life, SF1 regulates the
formation and survival of gonadal progenitor Sertoli and Leydig cells.  

Consistent with the multiple roles of SF1 in both testicular development and steroidogenesis, variants in NR5A1 have been associated with a diverse and ever-growing spectrum of 46,XY DSD phenotypes. These include gonadal and testicular dysgenesis with or without Müllerian remnants, ambiguus genitalia, mild and severe forms of hypospadias, as well as varying degrees of under-virilization, such as micropenis and cryptorchidism.

In 46,XX subjects, SF1 expression occurs during early ovarian development and sex differentiation, leading to normal ovarian morphogenesis. In granulosa cells, its expression is associated with follicular development, and in theca cells, it regulates ovarian steroidogenesis. Accordingly, alterations in SF1 expression have been demonstrated as a cause of primary ovarian insufficiency (POI) in women.

We describe the clinical and genetic findings in 2 brothers and in another unrelated subject with 46,XY DSD with the same pathogenic variant in the SF1 gene, as well as in the female relatives.

Clinical Cases

Family 1

The index case (IV2) was a 4-year-old 46,XY boy with DSD, the second child of nonconsanguineous parents. On physical examination, he presented with an external masculinization scale score of 5/12 (labioscrotal fusion = 3, micropenis = 0, urethral meatus = 0, right gonad = 1, left gonad = 1), and his pelvic ultrasound showed no Müllerian remnants. The hormonal profile at 3 days of life was as follows: cortisol level of 19.9 μg/dL (>10), testosterone level of 82.2 ng/dL (75-400), and androstenedione level of 272 ng/dL (10-279).

The genetic study of a DSD panel (AR, DHH, MAP3K1, NROB1, SRD5A2, SRY, WT1, and NR5A1) showed a heterozygous variant in NR5A1 c.251G>A (p.Arg84His, NM_004959.5), which has been previously described (rs375469069). This variant was also present in the affected brother as well as in his mother, sister, grandmother, and 3 of 4 great aunts. The mother was evaluated at the age of 32 years because she experienced secondary amenorrhea for 6 months. Her hormonal profile at that time was estradiol level of 91.7 pg/mL (12.4-233), AMH level of 5.33 ng/mL (0.7-7.5), luteinizing hormone level of 14.5 mIU/mL (2.4-12.6), and follicle-stimulating hormone level of 8.5 mIU/mL (3.5-12.5), which did not suggest premature ovarian failure, and she was considered to have ovarian dysfunction due to obesity and insulin resistance. The grandmother and 2 maternal great aunts had premature menopause at approximately 30 years, suggesting POI (Fig.).

Family 2

The index case was a 16-week-old 46,XY infant with DSD who was born with a micropenis, an external masculinization scale score of 3/12 (labioscrotal fusion = 3, micropenis = 0, urethral meatus = 3, right gonad = 1.5, left gonad = 1.5) and without Müllerian remnants. His concomitant hormonal profile was as follows: cortisol level of 17.5 μg/dL (>10), testosterone level of 150 ng/dL (75-400), luteinizing hormone level of 8.8 mIU/mL (0.02-7), follicle-stimulating hormone level of 9.2 mIU/mL (0.16-4.1), and AMH level of 31 ng/mL (32.7-262). Analysis of the DSD panel showed the same pathogenic variant in NR5A1 (p.Arg84His). This variant was found neither in the father nor in the mother, maternal grandmother, or maternal aunt.
Discussion

SF1 is a transcription factor that regulates gonadal differentiation and determination and can cause DSD when altered. This study reports three 46,XY subjects with different degrees of subvulvarization harboring the same pathogenic variant (p.Arg84His) in NR5A1. Older female relatives with this variant reported premature menopause, suggesting POI. To our knowledge, these are the first reported 46,XY Chilean patients with DSD due to alterations of SF1.

This missense variant has been previously categorized as likely pathogenic in subjects with DSD7 based on functional studies reported 46,XY Chilean patients with DSD due to alterations of SF1. In 2018,11 was associated with different degrees of under-virilization, similar to that observed in our patients, as in the cases of other variants reported. As other authors have hypothesized, this could be explained by epigenetic changes, environmental stimuli, or sequence variants in other genes.13

Because SF1 has multiple roles in gonadal determination and differentiation, it can cause a continuum of ovarian deficiency and the resulting phenotype.7 They present most frequently de novo, as in our second family; however, in approximately 30% of children, the variant is dominantly inherited from the mother with sex-dependent traits, as in the first family.

In the 46,XY subjects of family 1, the variant p.Arg84His was found to segregate with premature menopause in the grandmother and maternal great aunts; the mother presented amenorrhea at age 32 but normal hormonal results. According to the Human Gene Variant Database, 22 variants in the SF1 gene are associated with premature menopause and diminished ovarian reserve.14 Because SF1 has multiple roles in gonadal determination and differentiation, the resulting phenotypes when SF1 expression is altered can be difficult to categorize, either as ovarian dysfunction or alterations in steroidogenesis, even if the same variant is present.

The majority of 46,XY subjects with DSD due to NR5A1 variants are affected by a loss-of-function variant on 1 allele of the gene, leading to haploinsufficiency and the resulting phenotype.7 They present most frequently de novo, as in our second family; however, in approximately 30% of children, the variant is dominantly inherited from the mother with sex-dependent traits, as in the first family.

In the 46,XX subjects of family 1, the variant p.Arg84His was found to segregate with premature menopause in the grandmother and maternal great aunts; the mother presented amenorrhea at age 32 but normal hormonal results. According to the Human Gene Variant Database, 22 variants in the SF1 gene are associated with premature menopause and diminished ovarian reserve.14 Because SF1 has multiple roles in gonadal determination and differentiation, the resulting phenotypes when SF1 expression is altered can be difficult to categorize, either as ovarian dysfunction or alterations in steroidogenesis, even if the same variant is present.

Because variants in the SF1 gene result in a variable phenotype and in the risk of premature ovarian failure, a genetic study that allows an integral diagnosis and genetic counseling for the index case and their families is important.

Conclusion

The c.251G>A (p.Arg84His) variant in the gene encoding SF1 is associated with different degrees of under-virilization in males with DSD and in women with premature menopause and diminished ovarian reserve. Because it segregates with phenotypic manifestations, this variant can be reclassified as pathogenic.
Acknowledgment

Authorized by the ethics committee of the Universidad Católica of Santiago in Chile.

Disclosure

The authors have no multiplicity of interest to disclose.

References

1. Achermann JC, Ito M, Ito M, Hindmarsh PC, Jameson JL. A mutation in the gene encoding steroidogenic factor-1 causes XY sex reversal and adrenal failure in humans. Nat Genet. 1999;22:125–126.
2. Achermann JC, Ozisik G, Ito M, et al. Gonadal determination and adrenal development are regulated by the orphan nuclear receptor steroidogenic factor-1, in a dose-dependent manner. J Clin Endocrinol Metab. 2002;87:1829–1833.
3. Lin L, Achermann JC. Steroidogenic factor-1 (SF-1, Ad4BP, NR5A1) and disorders of testis development. Sex Dev. 2008;2:200–209.
4. Domenice S, Machado AZ, Ferreira FM, et al. Wide spectrum of NR5A1-related phenotypes in 46,XY and 46,XX individuals. Birth Defects Res C Embryo Today. 2016;108:309–320.
5. Eggers S, Sadedin S, van den Bergen JA, et al. Disorders of sex development: insights from targeted gene sequencing of a large international patient cohort. Genome Biol. 2016;17:241.
6. Sreenivasan R, Ludbrook L, Fisher B, et al. Mutant NR5A1/SF-1 in patients with disorders of sex development shows defective activation of the SOX9 TESCO enhancer. Hum Mutat. 2018;39:1861–1874.
7. Ferraz-de-Souza B, Lin L, Achermann JC. Steroidogenic factor-1 (SF-1, NR5A1) and human disease. Mol Cell Endocrinol. 2011;336:198–205.
8. Ahmed SF, Khwaja O, Hughes IA. The role of a clinical score in the assessment of ambiguous genitalia. BJU Int. 2000;85:120–124.
9. Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17:405–424.
10. Köhler B, Lin L, Ferraz-de-Souza B, et al. Five novel mutations in steroidogenic factor 1 (SF1, NR5A1) in 46,XY patients with severe underandrogenization but without adrenal insufficiency. Hum Mutat. 2008;29:59–64.
11. Roheva G, van den Bergen JA, Ohnesorg T, et al. Functional characterization of novel NR5A1 variants reveals multiple complex roles in disorders of sex development. Hum Mutat. 2018;39:124–139.
12. Pedace L, Laimo L, Preziosi N, et al. Longitudinal hormonal evaluation in a patient with disorder of sexual development. 46,XY karyotype and one NR5A1 mutation. Am J Med Genet A. 2014;164A:2938–2946.
13. Camats N, Descartes-Cancio M, Audi L, Schaller A, Fluck CE. Broad phenotypes in heterozygous NR5A1 46,XY patients with a disorder of sex development: an oligogenic origin? Eur J Hum Genet. 2018;26:1329–1338.
14. Stenson PD, Ball EV, Mort M, et al. Human gene mutation database (HGMD): 2003 update. Hum Mutat. 2003;21:577–581.
15. Landrum MJ, Lee JM, Benson M, et al. ClinVar: improving access to variant interpretations and supporting evidence. Nucleic Acids Res. 2018;46:D1062–D1067.
16. Jaillard S, Sreenivasan R, Beaumont M, et al. Analysis of NR5A1 in 142 patients with premature ovarian insufficiency, diminished ovarian reserve, or unexplained infertility. Maturitas. 2020;131:78–86.