New findings in disorders of sex development: role of *DMRT3* and *OAS3*

We have read with great interest the study by Tsai et al. (1) in this issue of *Fertility and Sterility*, where the authors indicate that *DMRT3* and *OAS3* are involved in human disorders of sex development (DSD) by controlling *ESR1* expression. These findings were supported by the identification of *DMRT3*:c.A815C and *OAS3*:c.G2606A variants in a Taiwanese family with recurrent DSD and gonadal dysgenesis. All patients with DSD were found to carry heterozygous missense variants resulting in the substitution of lysine for threonine at position 272 of *DMRT3* and arginine for histidine at position 869 of *OAS3*. DRMT3^{A815C} induced *ESR1* expression, whereas the DMRT3^{A815C}-OAS3^{G2606A} complex interacted less with RNase L, preventing *ESR1* mRNA degradation (1).

In mammals it has been established that a series of genes that encode transcription factors, signaling factors, cellular receptors, chemical messengers (hormones), and proteins that intervene in different signaling pathways are involved in the process of sexual differentiation (2). To date, two models related to sexual differentiation drivers have been proposed. In the first model, as described by Phoenix et al. 1959 and by Jost in 1965, the determining factors for the processes of sexual determination and differentiation in humans are related to either the presence or absence of the Y chromosome. Testicular formation depends on *SRY*, a gene that encodes a sufficient and necessary transcription factor to induce testicular development. After translation, the SRY protein translocates to the nucleus and binds to the enhancer region of *SOX9* to intervene in the differentiation and proliferation of Sertoli cells and the tubular organization of the testis (2). By contrast, female differentiation occurs once the germ cells enter meiosis in the absence of *SRY*, which results in the inability of *SOX9* expression along with the expression of signaling factors such as *RSPO1*, *WNT4*, and *FOXL2* that lead to ovary formation (2).

The second model, proposed by Arnold in 2009, submits that the sexual chromosomes act differently at the cellular level, depending on the XX or XY factors (2). That is, the presence or absence of *SRY* is directly related to the prevalence of different hormones produced at the gonadal level (ovaries and testicles). Thereby, any alteration or mutation that affects the biosynthesis of sexual steroid hormones associated with steroidogenic enzymes or antimüllerian hormone (2) will have a major impact on the process of sexual differentiation.

Among the sex steroid hormones, estrogens and androgens play important roles in sexual differentiation, specifically in the development and expression of male and female sexual characteristics. These effects are mediated by the estrogen and androgen receptors (ESRs and ARs) (2).

The authors presented the genetic analysis of a Taiwanese family with 22 members (three generations) with eight cases of 46,XY DSD, among whom four had 46,XY male to female sex reversal, and the other four were 46,XY males with hypospadias. Surprisingly, all patients with DSD were found to carry the same variants in the genes *DMRT3* and *OAS3* (1). Additionally, this work demonstrated the functional effect of these variants. Specifically, for *DMRT3* the authors found evidence that DMRT3^{A815C} is involved in the activation of the *ESR1* promoter in the nucleus and that the DMRT3^{A815C}-OAS3^{G2606A} complex decreases interaction with ESR1 and Rnase L mRNA, which ultimately leads to an increased *ESR1* expression in the cytosol (1).

These results could explain the feminization of the four 46,XY patients with gonadal dysgenesis, which demonstrates the critical role that estrogens play in sex determination. In fact, the administration of exogenous estrogens shortly after fertilization causes male to female sex reversal in some species (2). Although some evidence in humans has suggested increased activity in *ESR2* variants in the absence of an ER-β-specific ligand in 46,XY sex reversal (3), *ESR1* is likely to be the principal ESR associated with sex reversal in other species (4).

For hypospadias, the explanation is uncertain; there is insufficient evidence or knowledge regarding the etiology of the condition. It has been suggested that the sons of women exposed to synthetic estrogens in utero may have an increased risk of hypospadias, in addition to the complex interaction between candidate genes, environmental exposures, and gene polymorphisms in the presentation of this entity (5). We can hypothesize about the causal role of the variants described, taken together with a genetic alpha effect, which might represent a possible explanation for the hypospadias phenotype.

Although the authors' results show an interesting contribution of the *DMRT3* and *OAS3* genes in DDS through direct or indirect regulation of *ESR1*, several factors suggest the cosegregation of the variants: that the frequency of the variants found is approximately 1%, that they have not been found separately in the healthy male family members studied, and that the mothers of those affected are carriers. Furthermore, this suggests that these are hypomorphic variants, and thus are digenetic inheritance as proposed by the authors.

We consider the results presented by the authors to be conducive to new research that could elucidate the participation of these variants as well as establish their association with conditions related to DSD. Hence, it is important to highlight the need to confirm these findings in other cases with similar and different phenotypes. In addition, performing functional assays in a murine model could support these results and clarify the pathogenicity of the described variants.

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