Primary gonadal dysgenesis in male 46,XY patients with NR5A1 variants predominantly affects Sertoli cell function

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Background

- Steroidogenic factor 1 (encoded by the NR5A1 gene) is a transcriptional regulator of genes involved in gonadal development and steroidogenesis.
- Mutations in NR5A1 are associated with a wide phenotypic spectrum in 46,XY individuals ranging from partial/complete gonadal dysgenesis, ambiguous genitalia, hypospadias, to infertility.
- However, little is known about the pubertal development and the longitudinal course of endocrine markers for Sertoli and Leydig cell function from infancy to adolescence in these patients.

Objective and Method

- Objective: To investigate the pubertal course and the Sertoli and Leydig cell function in 46,XY patients with an NR5A1 variant reared as males.
- Method: Longitudinal analyses of clinical data on pubertal development, the gonadotrophins LH/FSH, testosterone, and the Sertoli cell markers anti-Müllerian hormone (AMH) and inhibin B.

Patient characteristics

<table>
<thead>
<tr>
<th>Last visit</th>
<th>Mutation</th>
<th>External genitalia</th>
<th>Location of gonads</th>
<th>Mullerian structures</th>
<th>Androgen therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 9,9y</td>
<td>c.362delG</td>
<td>Proximal hypospadia</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>2 18,2y</td>
<td>c.115A&gt;C</td>
<td>Proximal hypospadia</td>
<td>ing / ing</td>
<td>Rudimentary vagina</td>
<td>15,3-17,2y</td>
</tr>
<tr>
<td>3 16,8y</td>
<td>c.312_317delins ADAAAGAAGG/C</td>
<td>Penoscrotal hypospadia, bifid scrotum</td>
<td>ing / ing</td>
<td>No</td>
<td>since 16,0y</td>
</tr>
<tr>
<td>4 16,1y</td>
<td>c.630_636del GTACGGC</td>
<td>Sertoli hypospadia, bifid scrotum</td>
<td>ing / ing</td>
<td>No</td>
<td>not yet</td>
</tr>
<tr>
<td>5 12,8y</td>
<td>c.1200_1201delCC</td>
<td>Buried penis</td>
<td>ing / scr</td>
<td>No</td>
<td>not yet</td>
</tr>
<tr>
<td>6 0,9y</td>
<td>c.1347+7C</td>
<td>Perineal hypospadia</td>
<td>scr / scr</td>
<td>No</td>
<td>not yet</td>
</tr>
</tbody>
</table>

Table 1: Patient characteristics. NA: not available, ing: inguinal, scr: scrotal.

Pubertal development

- Primary gonadal dysgenesis in 46,XY individuals with NR5A1 variants is associated during adolescence with:
  - Spontaneous pubertal signs
  - Decreased testicular volume
  - Hypergonadotrophic hypogonadism
  - Spontaneous testosterone production
  - Low Sertoli-cell markers.
- More clinical studies are needed to better predict gonadal function (spermatogenesis and testosterone production), and to derive therapeutic implications for clinical practice.

Conclusion

Figure 2A: LH levels in patients 2-6 from birth to adulthood. Black borders indicate testosterone therapy.

Figure 2B: FSH levels in patients 2-6 from birth to adulthood. Black borders indicate testosterone therapy.

Figure 2C: Testosterone levels in patients 1-6 from birth to adulthood. Black borders indicate testosterone therapy.

Figure 2D: Anti-Müllerian hormone (AMH) levels in patients 2, 3, 5 and 6 from birth to adulthood.

Figure 2E: Inhibin B levels in patients 2-6 from birth to adulthood. Black borders indicate testosterone therapy.

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