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

	Last visit	Mutation	External genitalia	Location of gonads	Müllerian structures	Androgen therapy
1	9,9y	c.382delG p.V128CfsX168	Proximal hypospadias	NA	NA	NA
2	18,2y	c.118A>C p.T40P	Proximal hypospadia, bifid scrotum	ing / ing	Rudimentary vagina	15,3-17,2y
3	16,8y	c.312_317delins AGAAGAAGGC p.L105EfsX45	Penoscrotal hypospadias, micropenis, bifid scrotum	ing / ing	No	since 16,0y
4	16,1y	c.630_636del GTACGGC p.Y211TfsX83	Scrotal hypospadia, bifid scrotum	ing / ing	No	not yet
5	12,8y	c.1200_1201delCC p.L401AfsX2	Buried penis	ing / scr	No	not yet
6	0,9y	c.1364T>C p.M455T	Perineal hypospadias, bifid scrotum	scr / scr	No	not yet

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

Pubertal development

Figure 1A:
Tanner P-stage and G-stage during adolescence in patients 2-5.

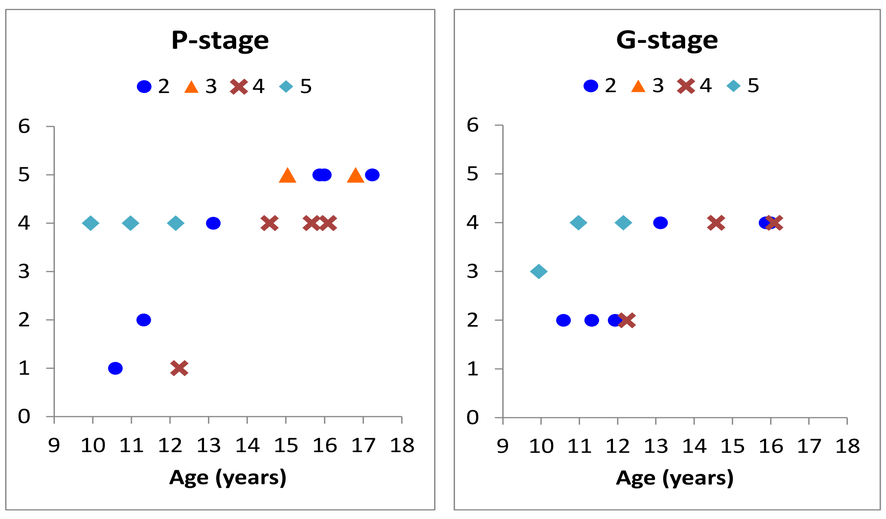
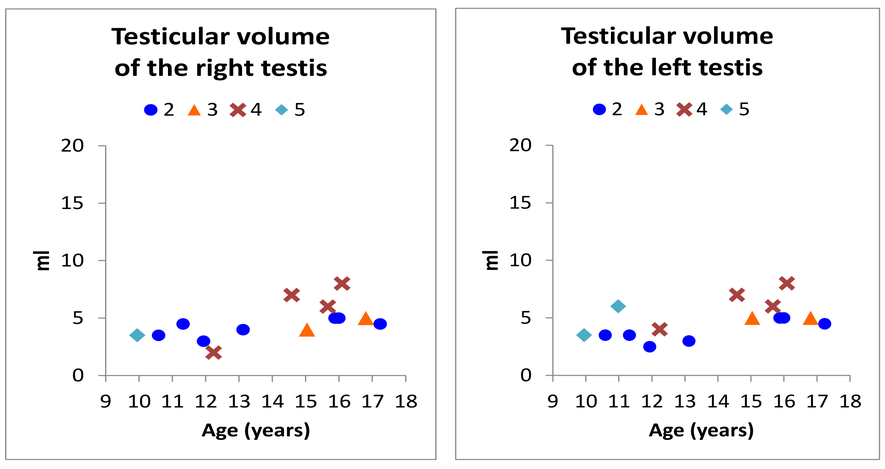


Figure 1B:
Testicular volumes of the right and left testes during adolescence in patients 2-5.



Laboratory results

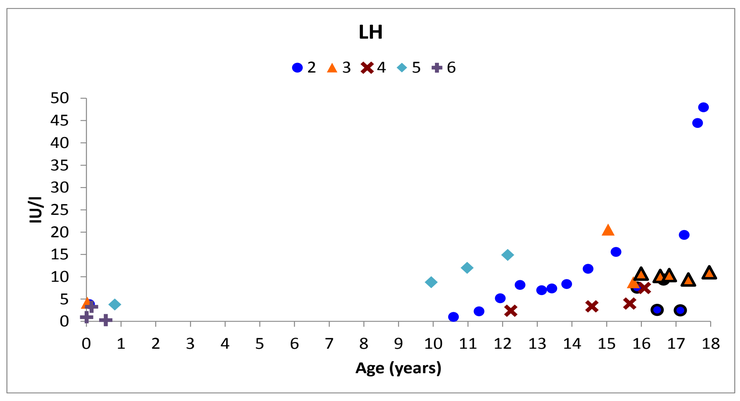


Figure 2A:
LH levels in patients 2-6 from birth to adulthood. Black borders indicate testosterone therapy.

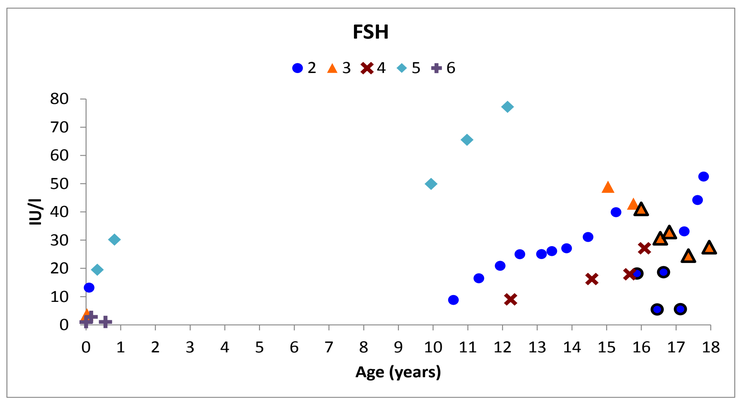


Figure 2B:
FSH levels in patients 2-6 from birth to adulthood. Black borders indicate testosterone therapy.

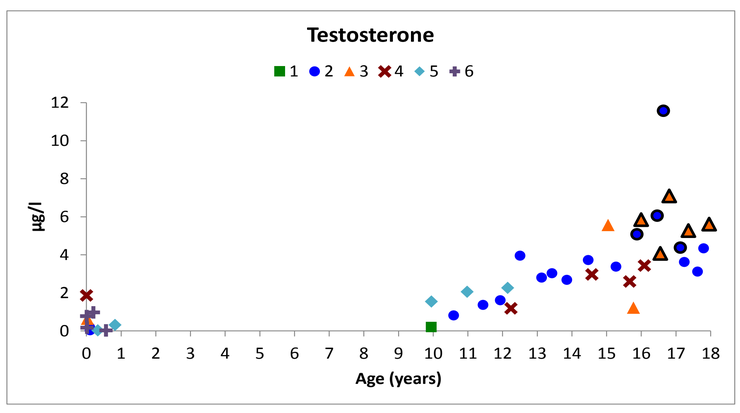


Figure 2C:
Testosterone levels in patients 1-6 from birth to adulthood. Black borders indicate testosterone therapy.

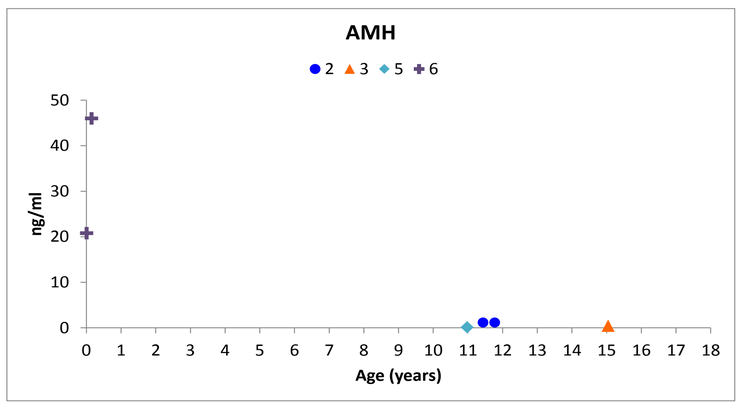


Figure 2D:
Anti-Müllerian hormone (AMH) levels in patients 2, 3, 5 and 6 from birth to adulthood.

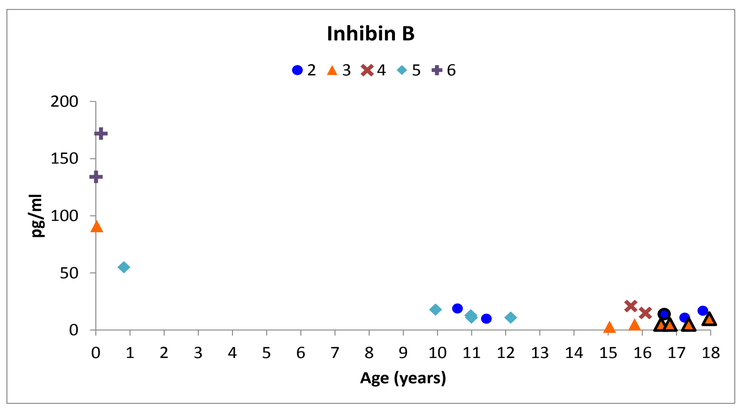


Figure 2E:
Inhibin B levels in patients 2-6 from birth to adulthood. Black borders indicate testosterone therapy.

Conclusion

- Primary gonadal dysgenesis in 46,XY individuals with *NR5A1* variants is associated during adolescence with
  - Spontaneous pubertal signs
  - Decreased testicular volume
  - Hypergonadotropic 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.

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Sex differentiation, gonads and gynaecology or sex endocrinology

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