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Clinical follow-up of the first SF-1 deficient female patient

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Introduction

Steroidogenic factor 1 (SF-1/ NR5A1) plays a crucial role in regulating adrenal development, gonad determination and differentiation, and in the hypothalamic-pituitary control of reproduction and metabolism. In men (46, XY) mutations in SF-1/ NR5A1 gene cause a wide phenotypic spectrum that ranges from complete testicular dysgenesis with Müllerian structures and amenorrhea, through individuals with mild clitoromegaly or genital ambiguity, to severe penoscrotal hypospadias or even anorchia and oligospermia.
In women (46, XX), the role of SF-1 seems to be less clear. In recent years mutations in SF-1/ NR5A1 were shown to be associated with impairment of ovarian development and function leading to primary ovarian insufficiency due to low ovarian reserve. However, SF-1 mutations account for a small proportion of premature ovarian insufficiency (1.4% to 5%) and abnormal reproductive functions.

Conclusion

After allowing us to establish that ovarian development does not depend on SF-1 integrity, our patient gave us the unique chance to prospectively study the influence of SF-1 loss-of-function on pubertal development and ovarian function. Our case report shows one to date uniquely described phenotypic variant of SF-1 mutation in a 46, XX affected person with adrenocortical insufficiency but no ovarian dysfunction nor disturbance of pubertal development, hence indicating that SF-1 is not needed for normal sexual maturation nor pubertal ovarian function. By prospectively following the patient during adulthood we will have an unique opportunity to explore the natural history of SF-1 mutation in a 46, XX patient and shed further light on the role of SF-1 in the ovary.

Case report

We described the first case of a SF-1 deficient 46, XX girl in whom adrenal insufficiency was the only clinical sign of the loss-of-function mutation (AJHG 2000, 67:1563). Direct sequencing of PCR fragments amplified from genomic DNA of the patient revealed the presence of a heterozygote G to T transversion in exon 4 of the NR5A1 gene, leading to the missense p.R255L in the hinge region of SF-1/ NR5A1 protein. Functional studies demonstrated that the mutated SF-1/ NR5A1 did not bind properly to the known responsive element of the human CYP11A (cholesterol side-chain cleavage) promoter. At that time, ovarian development and function seemed normal on the base of normal ovarian morphology at US and repeatedly normal gonadotropins and ovarian markers (inhibins). Nevertheless, it remained unknown then whether this mutation would interfere with ovarian function at onset of puberty and beyond.
Our follow-up was based on 6-monthly visits at our outpatient clinic, with measurements of auxological parameters (height and weight) and evaluation of pubertal development.

Table 1. Clinical and biochemical findings

Age	Bone Age	Tanner Stage	ACTH 10-55 pg/ml	LH/ FSH U/l	AMH >7.1 pmol/l
3Y8M	3Y	B1, P1			
6Y11M	5Y9M	B1, P1			
10Y6M		B2, P2			
11Y	10Y6M	B3, P3		0.7/ 3.2	
11Y7M		Menarche			
11Y10M	12Y6M	B4, P4			
12Y10M			>1250	6.9/ 5.5	
13Y4M	14Y8M				
13Y11M			28	14.3/ 6.4	17
16Y9M			11	19.7/ 6.3	36

Clinical course

To date, this young woman shows a normal psychomotor development, has a normal puberty with normal breast development (Tanner stage 4) and regular menstruation.
Blood samples were twice taken during mid-cycle peak. Appropriately gonadotropins, especially LH, were increased. Anti-Müller-Hormone reflects normal ovarian reserve. Her final height is slightly under the target height, probably due to glucocorticoid therapy.
The current treatment of her adrenal insufficiency consists of hydrocortisone (17.4mg/m2/day) and fludrocortison (0.05mg/day).

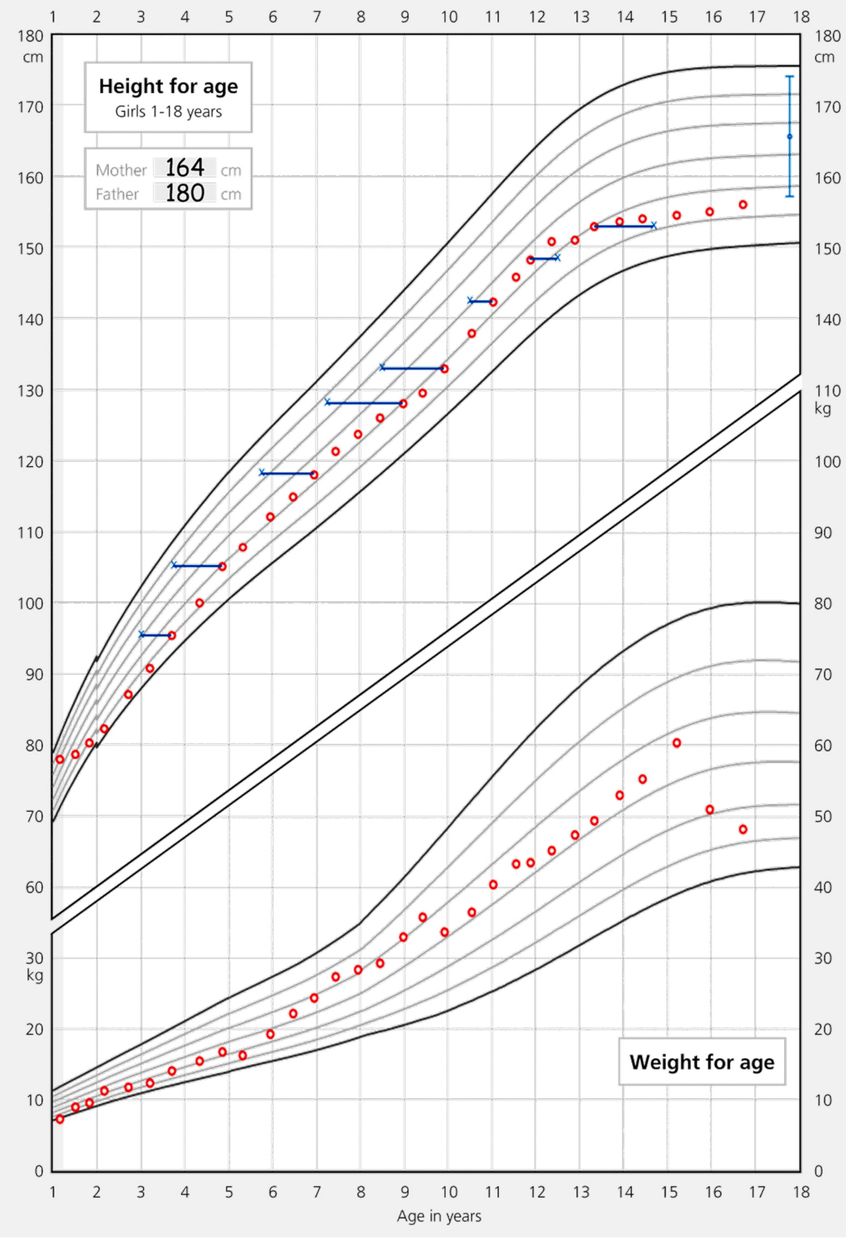

Figure 1. Growth curve ►

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