CLINICAL AND MOLECULAR CHARACTERIZATION OF ONE NR5A1 GENE MUTATION FOUND IN A PATIENT WITH 46, XY DSD

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INTRODUCTION:

Steroidogenic factor-1 (SF-1), encoded by the NR5A1 gene, regulates several genes involved in male sexual determination, such as SOX9 and AMH, cholesterol mobilitation and syntesis of a number steroidogenic enzymes, like 3βHSD, and androgen biosyntesis, like INSL3. Mutations in NR5A1 have been associates to a broad phenotypic spectrum in 46, XY subjects, including pure gonadal dysgenesis, infertility, anorchia or hypospadias, often in in conjunction with normal adrenal function.

PATIENTS AND METHODS:

Male patient.

At birth: Scrotal Hypospadias, micropenis, undescended teste and bifid scrotum.

Study:

1. karyotype 46 XY

2.Biochemical analysis (one month old): LH: 2.5 mU/ml, FSH: 3.7 mU/ml, Testosterone: 67.5 ng/ml, DHT: 1.7 ng/ml, DHEA-S: 400 ng/ml, Cortisol: 10.4 mcg/dl.

3.Abdominal ultrasound: normal

4. Good response of the penis to treatment with testosterone.

Familial background: maternal uncle presented with scrotal hypospadias at birth.

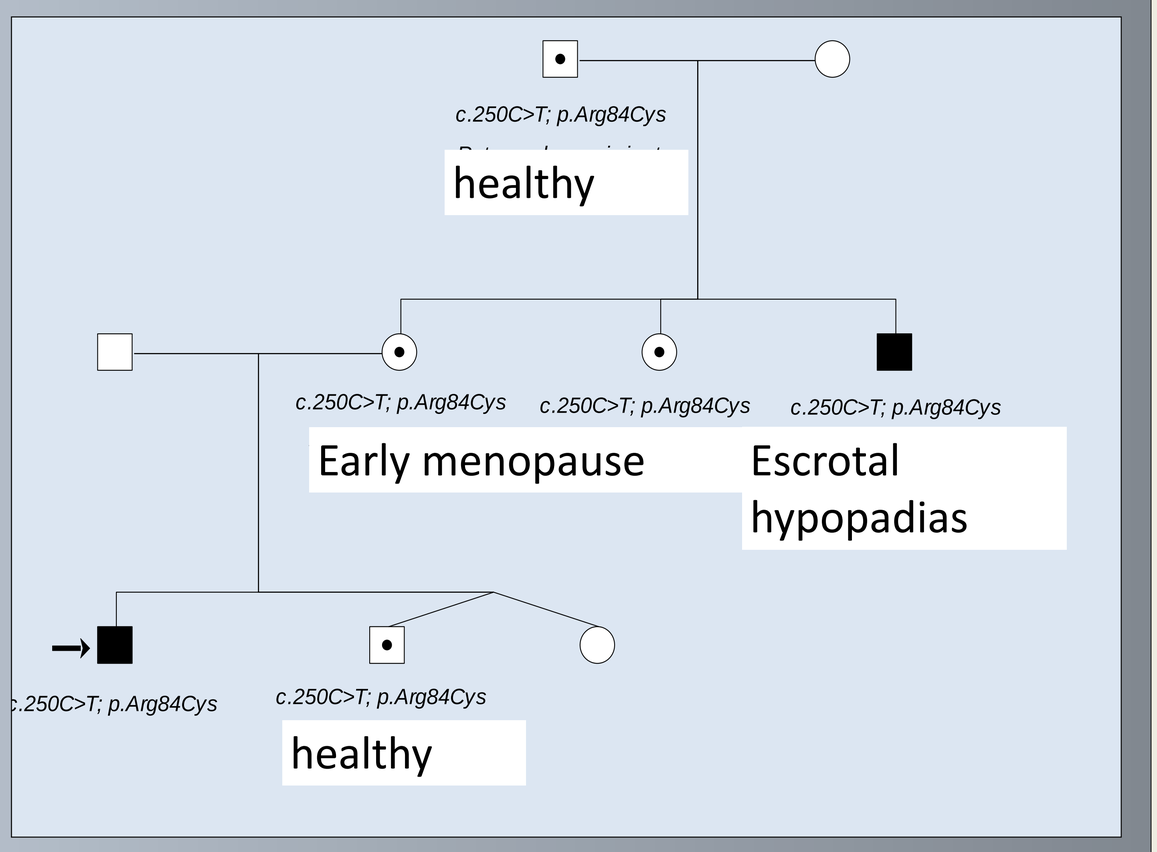
Genomic DNA was isolated from peripheral blood leukocites and genetic characterization was performed using a targeted gene panel by NGS. PCR and Sanger sequencing was used for variant confirmation and the test parentes and affected family members to establish the mode of inheritance

RESULTS:

HETEROZYGOUS NR5A1 C.250C>T; p. Arg84Cys mutation.

Functional studies demostrated that this mutation:

- diminishes DNA binding site affinity
- diminished transcriptional activity.



CONCLUSSIONS:

Our results agree with previous studies in which the complex penetrance, expressivity and inheritances of the alterations found in the NR5A1 gene, give rise depending on the mutation to phenotypes in 46 XY patients that encompass from pure gonadal dysgenesis to completely asyntomatic carriers, whereas in 46 XX patients lead to mild fotmos suchs as primary ovarian failure.

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