

## ARTICLE

# Novel *StAR* Gene Mutation Identified in a Moroccan Patient with Lipoid Congenital Adrenal Hyperplasia

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### ABSTRACT

Congenital Adrenal Hyperplasia (CAH) is an autosomal recessive condition that results from the deficiency of one of the steroidogenesis enzymes responsible for cortisol biosynthesis. In the majority of cases, CAH is caused by 21-hydroxylase deficiency. More rarely, the deficiency concerns 11 $\beta$ -hydroxylase, 3 $\beta$ -hydroxysteroid dehydrogenase, 17 $\alpha$ -hydroxylase, or exceptionally *StAR* and P450 oxidoreductase. Here, we report the case of a 3 year and 4 months old male child, born from a consanguineous marriage who presented at 15 months old with the salt-loss syndrome. Physical examination found generalized melanoderma, micropenis and bilateral cryptorchidism. Biological assessment at the time of diagnosis revealed hyponatremia, hyperkalemia, functional renal failure, hypoglycemia, low blood cortisol level, and high blood level of ACTH, suggesting primary adrenal insufficiency. The patient presented also with the abnormality of sexual differentiation with a 46 XY karyotype, testosterone level was low at the baseline and after HCG stimulation, pelvic ultrasound and Magnetic Resonance Imaging (MRI) showed bilateral testicular atrophy in the inguinal position. The genetic study revealed a likely pathogenic homozygous variant in the *StAR* (steroidogenic acute regulatory) gene. Therapeutically, our patient was hydrated by saline solution and treated with hydrocortisone and fludrocortisone, then benefited from a surgical testicular correction marked by a favorable evolution. Although mutations in *StAR* gene are rare, they can be responsible for the defect in the early stage of steroidogenesis and therefore cause a deficiency in adrenal and sexual hormones biosynthesis.

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## 1. Introduction

Congenital Adrenal Hyperplasia (CAH) is the result of an adrenal enzymatic block. Depending on the deficient enzyme, the biosynthesis of one or more hormones and sometimes an excess of synthesis of other hormones can occur. CAH is a genetic condition of autosomal recessive inheritance, commonly caused by 21-hydroxylase enzymatic deficiency [1]. Steroidogenic acute regulatory deficiency (*StAR*) is responsible for a rare and severe form of CAH where its incidence in the general population remains unknown. To date, only Eighty-five cases from Japanese, Korean and Palestinian cohorts have been published in the literature [1]. Here, we report a patient with a defect in the adrenal and sexual hormones secondary to a mutation of the *StAR* gene highlighting the epidemiological, genetic, and phenotypic aspects of *StAR* gene mutations.

## 2. Case Report

3 years and 4 months old boy, born to a family with first degree consanguineous marriage. His siblings do not present any related health problem. The past medical history of his mother is marked with two incidents of spontaneous abortions.

Our patient was initially hospitalized at the age of 15 months old for several episodes of acute dehydration aggravated by convulsive tonic-clonic seizures and complicated by a coma. Physical examination in admission revealed an acute dehydration associated with generalized melanoderma, micropenis, and bilateral cryptorchidism (Figure 1) Laboratory analysis revealed a salt-loss syndrome with sodium levels of 113.1 mEq/l (139 mEq/l normal), high natriuresis to 112 mEq/l, potassium levels of 6.28 meq/l (3.5 – 5.2 mEq/l), a functional acute renal failure and hypoglycaemia at 0, 50 g/L, evoking primary adrenal insufficiency which was confirmed by a low level of 8 a.m. cortisol at 72 ng / ml (40-200 ng/l) and a high level of adrenocorticotrophic hormone (ACTH) at 1250 µg / ml (10.3- 48, 3 µg/ml).

Other laboratory workup showed a low basal testosterone at 0.03 ng/ml then at 1.01 ng / ml (0.03-0.32) after stimulation with Human Chorionic Gonadotropin Hormone (HCG). Noteworthy that this patient's karyotype was normal with 46 XY.

Pelvic ultrasound and pelvic MRI showed bilateral testicular atrophy in the inguinal position. This clinical presentation with double deficiency in adrenal and sex hormones, triggered after obtaining an informed consent from parents a genetic study that revealed the absence of mutations in *SF1* gene (steroidogenic factor 1) and *DAX1*

gene (DSS-AHC critical area on the X chromosome, gene 1) and the presence of a likely pathogenic homozygous variant in the *StAR* gene.

The mutation was detected at position number 41 of the coding region of the gene with transposition of Adenine to Cytosine c.41A> C resulting in a missense variant in the proteic sequence replacing Tyrosine with Serine. This variant p.Tyr14Ser affects a very conserved amino acid and In Silico predictive tools (SIFT, TASTER mutation and Polyphen-2) confirmed its deleterious aspect (Figure 2).

Our patient was treated with intravenous hydrocortisone, relayed by oral hydrocortisone at 30 mg/m<sup>2</sup>, after correction of acute dehydration, with progressive graduation at 15 mg /m<sup>2</sup> per day, associated with fludrocortisone at 50 µg per day. Surgical treatment on the ascending testicle has been performed. The evolution was marked three years later by the appearance of right cervical lymphadenopathy with a positive tuberculin skin test > 20 mm, and lymph node biopsy revealed tuberculous lymphadenitis with no histological sign of malignancy; for which the patient was put on antituberculosis treatment with a favorable evolution.

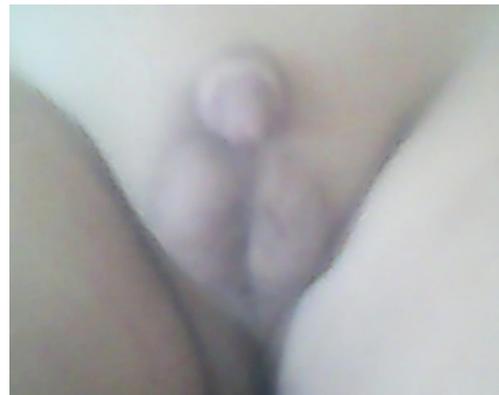


Figure 1. micropenis and absence of testicles in scrotal palpation

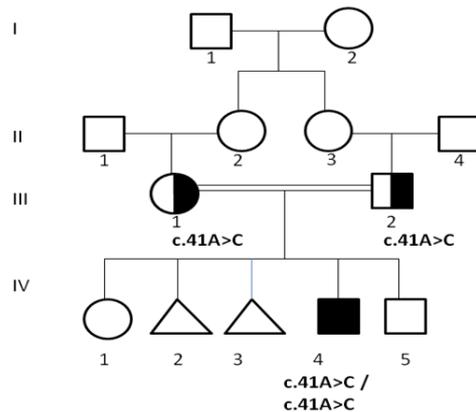


Figure 2. Pedigree presenting the genetic finding in the patient family

**Haplotypes:**

a: **Mutation c.41A>C or p.Tyr14Ser corresponding to exon 1 of StAR gene**

b: Normal\*

c: Normal\*

d: **Mutation c.41A>C or p.Tyr14Ser corresponding to exon 1 of STAR gene**

**Note:** \* Normal: this chromosome does not carry mutations detected in the sick child.

Father: a-b

Mother: c-d

Sick child: a-d

Sister: b-c

Brother: not studied

**3. Discussion**

Cholesterol is an important part of cellular membranes and is the substrate for biosynthesis of steroids, oxysterols and bile acids. Moreover, the mechanisms directing cholesterol trafficking inside cell gained more attention through the discovery of the steroidogenic acute regulatory protein *StAR*<sup>[1]</sup>.

*StAR* is expressed in the adrenals and gonads, but not in the placenta. Congenital lipid adrenal hyperplasia, a rare and severe disorder of human steroidogenesis, results from mutations in *StAR*, providing a *StAR* knockout of nature that has provided key insights into its activity. Cell biology experiments show that *StAR* moves large amounts of cholesterol from the outer to the inner mitochondrial membrane, but acts exclusively on the outer membrane<sup>[2]</sup>.

Cholesterol will then be supported by the CYP11A1 protein (P450<sub>scc</sub>) involved in the first stage of adrenal and testicular steroidogenesis.

**3.1 The Role of STAR**

*StAR* acts exclusively on the outer mitochondrial membrane to bind cholesterol and is inactivated when imported into the mitochondria<sup>[3]</sup>. This process is important in the regulation of steroidogenesis.

*StAR* gene mutations have now been described less than 200 patients with lipid CAH, mostly from Japanese cohorts. In most studies the reported patients were siblings, or they were born from consanguineous marriages<sup>[4]</sup>. The present study is the first one to identify the *StAR* Mutation c.41A>C in a patient of Moroccan ancestry. Noteworthy, that in Moroccan patients the most frequent etiology of congenital adrenal hyperplasia is a 21-hydroxylase deficiency.

*StAR* missense mutations causing lipid CAH are mostly concentrated from exons 5–7. Whereas in our case it was located in the exon 1. Deletion of only ten carboxyl-terminal amino acids reduces *StAR* activity by half, and

deletion of only 28 carboxyl-terminal amino acids deletes all activity<sup>[5]</sup>. The small number of missense mutations that cause lipid CAH all lie between amino acids 169 and 275<sup>[6]</sup>. In the absence of *StAR* expression, steroidogenic cells still produce 10–14% pregnenolone<sup>[1]</sup>.

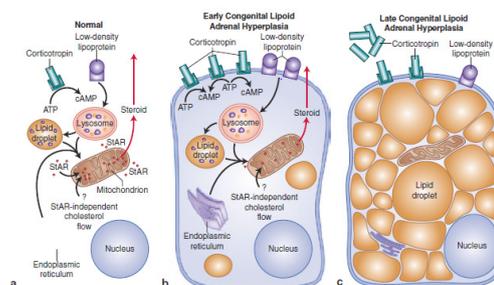
In general, mutations in the *StAR* gene usually lead to a classic form of the disease characterized by early onset adrenal insufficiency and gonadal failure, the latter showing gender dimorphism both in severity and in time of onset.<sup>[7,8,9]</sup>

An attenuated form of the disease, “non-classic lipid CAH,” is caused by mutations in which 10–25% of normal *StAR* activity is retained<sup>[6,10]</sup>. These patients typically experience adrenal insufficiency several years after infancy and the 46,XY individuals may masculinize normally, and mineralocorticoid secretion may be minimally affected<sup>[11]</sup>. In our patient, a mutation of the *StAR* gene was detected in the homozygous state and confirmed by sequencing using the Sanger method and the family study. This c.41A>C or p.Tyr14Ser mutation affects a conserved amino acid up to *C. elegans* (12 species studied) and gives a serine amino acid with a very large chemical difference [Grantham distribution: 144 (0 - 215)]

As shown in the pedigree (Figure 2), both the father and the mother are healthy carriers of the mutation. The eldest daughter is mutation free, while our patient is homozygous for the mutation. The little brother and the rest of the family members were not explored. The association with tuberculous lymphadenitis would only be fortuitous since Morocco is a country of endemic tuberculosis, with an annual incidence of 92/100 000<sup>[12]</sup>.

**3.2 Physiopathological of CAH due to StAR Mutation**

*StAR* promotes steroidogenesis by increasing the movement of cholesterol into mitochondria, but in the absence of *StAR*, steroidogenic cells still make small amounts of steroids by *StAR*-independent steroidogenesis<sup>[3,6,13]</sup>. This observation led to the two-hit model of lipid CAH<sup>[13]</sup> (Figure 3).



**Figure 3.** Two-hit model of congenital lipid adrenal hyperplasia (lipid CAH) " image slightly modified from Himangshu SN Engl J Med 1996; 335:1870-1879"

**Note:**

*a. In normal adrenal cells, cholesterol is primarily derived from low-density lipoproteins, and the rate-limiting step in steroidogenesis is movement of cholesterol from the outer mitochondrial membrane (OMM) to the inner mitochondrial membrane (IMM).*

*b. Early in lipoid CAH, StAR independent steroidogenesis moves small amounts of cholesterol into mitochondria, yielding sub-normal steroidogenesis; adrenocorticotrophic hormone (ACTH) secretion increases, stimulating further accumulation of cholesteryl esters in lipid droplets.*

*c. As lipids accumulate, they damage the cell through physical engorgement and by the action of cholesterol auto-oxidation products; steroidogenic capacity is destroyed, but tropic stimulation continues. Ovarian follicular cells remain unstimulated and undamaged until puberty, when small amounts of estradiol are produced, as in b, causing phenotypic feminization, with infertility and hypergonadotropic hypogonadism<sup>[14]</sup>.*

This explains the phenotypic aspect of our patient and the delayed onset of symptoms until the age of 3 years and 4 months.

**3.3 Diagnostic of CAH due to StAR Mutation**

Lipoid CAH patients have normal external female genitalia either with XX or KY karyotype which makes it easy to differentiate them from XX patients with 21-hydroxylase deficiency who are virilized. In the other hand Lipoid CAH patients harbor low level of all steroid hormones, while 21-hydroxylase deficient patients show high level of 21-deoxysteroids and 17-hydroxyprogesterone. Our patient with lipoid CAH also demonstrated low level 17-hydroxyprogesterone of less than 0.3 ng/ml which ruled out the possibility of a 21 hydroxylase enzymatic block.

3 $\beta$ -hydroxysteroid dehydrogenase (3 $\beta$ HSD) deficiency caused by high level of 17-hydroxypregnenolone is a differential for lipoid CAH. In our case; and although the 17-hydroxypregnenolone assay was not performed, the normal dehydroepiandrosterone sulfate (DHEA) findings excluded the diagnosis of 3 $\beta$ HSD deficiency.

The differentiation between lipoid CAH and congenital adrenal hypoplasia with a normal looking XY female genitalia is considered another clinical challenge that might be addressed by imaging; showing absent adrenal glands in congenital adrenal hypoplasia.

**4. Conclusion**

In the Moroccan population, the high frequency of consanguineous marriage uncovers several genetic conditions masked in the context of less consanguinity. Therefore, genetic screening should be recommended in high-risk families in order to decrease the occurrence of the genetic conditions and meanwhile prevents its complications that may be life-threatening. The present case report with acute adrenal insufficiency secondary to *StAR* gene mutation is an example of the critical importance of presymptomatic genetic diagnosis.

**Declaration of interest**

The authors declare that there is no conflict of interest.

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