

Case Report**Congenital lipoid adrenal hyperplasia caused by a frame-shift mutation in the steroidogenic acute regulatory protein gene**

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ABSTRACT

We present a female patient who, at the age of 35 days, presented with adrenal insufficiency with salt loss. Clinical and endocrinological investigation (low to normal levels of all adrenal steroids and raised ACTH) and imaging studies suggested congenital lipoid adrenal hyperplasia. The diagnosis was confirmed by molecular analysis that showed a frame-shift mutation 947/InsA/948 in exon 7 of the steroidogenic acute regulatory protein (StAR) gene. The patient is thriving under glucocorticoid and mineralocorticoid replacement therapy. She is now 10.5 years old and has not presented any signs of puberty.

Key words: Congenital lipoid adrenal hyperplasia, StAR gene

INTRODUCTION

Congenital lipoid adrenal hyperplasia (lipoid CAH) is the most severe form of congenital adrenal hyperplasia¹. It is an autosomal recessive disorder characterized by impaired steroidogenesis in the adrenals and gonads resulting in adrenal insufficiency with salt loss and male pseudohermaphroditism². Based on the observation that mitochondria from the adrenal glands and gonads of patients with lipoid CAH fail to convert cholesterol to pregnenolone, it was initially thought that the disease is caused by a defect in CYP11A1 (P450scc). However, in 1995 it was shown that lipoid CAH is caused by mutations of the gene

that encodes Steroidogenic Acute Regulatory (StAR) protein^{2,3}. StAR protein is indispensable for the acute regulatory phase of steroidogenesis, its role being to transfer cholesterol from the outer to the inner mitochondrial membrane in steroidogenic tissues⁴. The mechanism by which StAR mediates cholesterol transfer in the mitochondria, though not as yet fully characterized, is known to require interaction with the outer mitochondrial membrane⁵.

In lipoid CAH the adrenals become engorged with cholesterol and cholesterol esters that accumulate within the steroidogenic cells of the adrenal cortex. Some affected infants present adrenal insufficiency soon after birth, whereas others remain asymptomatic for a considerable period of time, even months⁶.

We present an XX female patient with lipoid CAH. To our knowledge, the patient is the first case of lipoid CAH of Hellenic origin.

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CASE REPORT

The infant was presented to our department in December 1992, at the age of 35 days, because of vomiting, anorexia and failure to thrive, all of which had developed gradually from the age of 10 days. The infant was the first child of phenotypically healthy non-related parents of Greek origin. Pregnancy and delivery were uneventful. Birth weight was 2700 gr. At presentation the patient was dystrophic (body weight 2200 gr), dehydrated, mildly hyperpigmented and had a cleft palate. External genitalia were that of a normal female. Arterial blood pressure was 75/42 mm Hg. Laboratory investigation disclosed acidosis pH: 7.2, hyperpotassemia (serum K^+ : 7.2 mEq/L), hyponatremia (serum Na^+ : 132 mEq/L). The blood uree nitrogen was 49 mg/dl. Blood sugar levels were normal. The clinical picture and the laboratory tests suggested adrenal insufficiency with salt loss. Endocrinological investigation (Table 1) showed deficiency of both glucocorticoids and mineralocorticoids. Ultrasonographic imaging of the adrenals showed massive enlargement of both glands (Figure 1). Karyotype was 46XX. The patient was placed on hydrocortisone, 9α fluorohydrocortisone and NaCl, and her condition improved dramatically. At the age of 5 months, after discontinuing hydrocortisone for 16 hours, a short ACTH (Synacthen 0.25 mg IV) test was performed. The levels of all steroids measured were very low to undetectable (Table 1). Clinical and laboratory data suggested that our patient had lipoid CAH. The patient's DNA analysis performed in Prof. W.L. Miller's laboratory at the Dept of Pediatrics and the Metabolic Research Unit of the University of San Francisco showed the CYP11A1 (P450scc) gene to be normal.



Figure 1. Ultrasonographic imaging showing massive enlargement of the adrenals.

After the discovery that mutations of the StAR protein are related to lipoid CAH, analysis of the StAR gene in our patient showed that she was homozygous for a frameshift mutation 947/InsA/948 in exon 7 (Figure 2). The methodology of the DNA sequencing has been described previously⁶.

DISCUSSION

Our patient is the first case of lipoid CAH from Greece whose diagnosis was confirmed by molecular genetic analysis. A similar clinical presentation could be due to congenital adrenal hypoplasia. However, in our patient, the massive adrenal hyperplasia that was shown ultrasonographically excluded that possibility.

Table 1. Endocrinological investigation at the age of 35 days and at 5 months

	35 days	5 months*	5 months*	Normal basal values
		0'	60'	
DHEA, nmol/L (ng/ml)	2.08 (0.6)	1.386 (0.4)	0.693 (0.2)	0.901-17.3 (0.26-5.0)
$\Delta 4$ -A, nmol/L (ng/ml)	2.09 (0.6)	0.698 (0.2)	0.698 (0.2)	0.209-2.7 (0.06-0.78)
17OH PG, nmol/L (ng/ml)	2.7 (0.9)	0.303 (0.1)	0.303 (0.1)	0.454-4.08 (0.15-1.35)
Testosterone, nmol/L (ng/dl)	0.104 (3.0)			0.035-0.173 (1-5)
Cortisol, nmol/L (μ g/dl)	311 (11.3)	0.0	0.0	83-633 (3-23)
Aldosterone, nmol/L (ng/dl)	0.230 (8.3)			0.055-3.66 (2-130)
ACTH, pmol/L (pg/ml)	>308 (>1400)			1.99-11.5 (9-52)
Plasma Renin Activity, μ g/L/h (ng/ml/h)	>50 (>50)			2.35-37 (2.35-37)

* ACTH test (Synacthen 250 μ g IV)

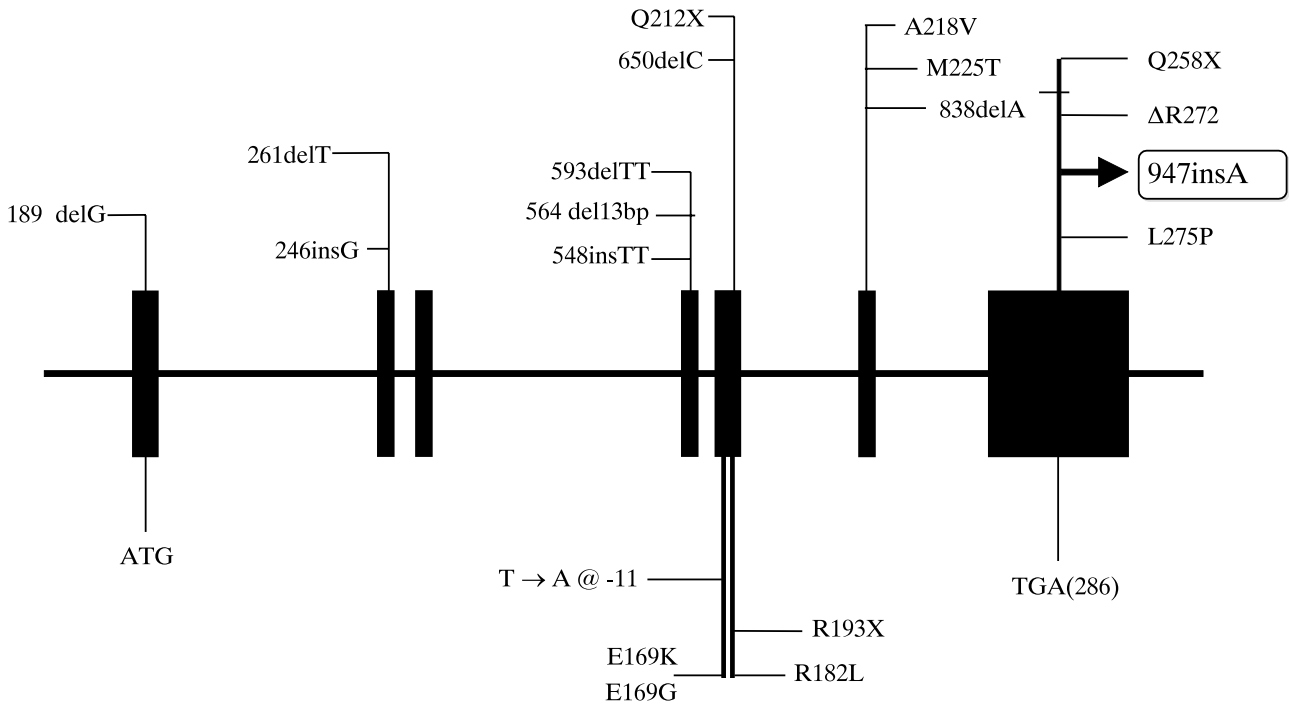


Figure 2. Diagram of the human StAR gene and the various StAR mutations. The arrow shows the site of the molecular defect in our patient (adapted from ref. 10).

Lipoid CAH is the most severe form of CAH and it is associated with deficiency of adrenal and gonadal steroids. In the first papers on the disorder⁷⁻⁹, it was reported that patients with lipoid CAH had very low or undetectable steroid levels and most of them died during infancy due to adrenal crisis. However, as experience about the disorder increased, it became clear that there were infants who could survive for months^{5,8} without receiving any form of treatment. This indicated that in some affected infants, the adrenals are capable of some steroid synthesis, though eventually this ability is abolished. This was the case in our patient who had normal serum cortisol and other steroid levels at diagnosis. However, at the age of 5 months the levels of all steroids measured were very low to undetectable. This is explained by the two-hit model of the pathophysiology of lipoid CAH proposed by Bose et al⁶.

According to the two-hit model, the pathophysiology of lipoid CAH results from two different events taking place in the adrenal cell. First, the mutation of the StAR protein gene does not permit the transfer of cholesterol from the outer to the inner mitochondrial membrane. However, about 14% of cholesterol

enters the mitochondria independently of the presence of StAR protein resulting in a low level of steroidogenesis¹⁰. This results in increased ACTH secretion that leads to increased production of cholesterol. Cholesterol accumulates in ester form in lipid droplets in the adrenal cells. The accumulation of lipid droplets results in enlargement of the cell and subsequent damage of its architecture by mechanical displacement and the action of chemical products of cholesterol auto-oxidation (second hit). In the early phase of the disorder, our patient's adrenals were able to secrete almost normal amounts of steroids stimulated by the extremely high levels of corticotropin and renin. However, the very low to undetectable steroid levels at 5 months of age are probably attributable to the severe damage of the adrenal cells by that time.

Another reason for the phenotypic variability in lipoid CAH is the severity of the StAR mutation. The StAR gene resides in chromosome 8p11.2 and consists of 7 exons. Mutations have been found in any exon and even in introns of the StAR gene. Most of the mutations result in complete elimination of StAR activity. However, mutations L275P and M225T were associated with 10% and 30% of StAR activity, re-

spectively^{6,11}. Furthermore, a Japanese male infant, who was found to be a compound heterozygote for the M225T mutant and the common Japanese mutant Q258X, is the only 46,XY patient with proven lipoid CAH that presented with mild virilization of the external genitalia¹¹. Therefore, there appears to exist a good correlation between phenotype and genotype in lipoid CAH.

Unlike the testes that are severely damaged in utero, the ovaries are reported to be unaffected until the time of puberty. Genetic female patients with lipoid CAH enter puberty at a normal age and develop cyclical menstrual bleeding¹²⁻¹⁴. It appears that estradiol produced by the StAR independent ovarian steroidogenesis is adequate to induce the development of secondary sex characteristics and endometrial growth. However, in these patients serum progesterone is not detectable indicating that either the cycles are anovulatory or ovulatory with severely deficient luteal phases. Moreover, pubertal females with lipoid CAH have increased gonadotropin levels, especially LH, that may lead to the formation of polycystic ovaries or to large ovarian cysts which may undergo torsion. Our patient at the age of 10.5 years has not yet developed any secondary sex characteristics and her basal gonadotropin levels are normal for prepubertal stage.

It seems that there are two genetic pools for StAR mutations. Most reported patients with lipoid CAH have their origin in the Arabian peninsula or Japan⁶. Lipoid CAH is an autosomal recessive disorder, and therefore an equal number of patients of both sexes is expected. However, Bose et al⁶, in their multiethnic sample of patients, found a male to female ratio of 18:3. This probably reflected easier diagnosis of lipoid CAH in 46,XY genetic males; subsequent studies have found the expected 1:1 ratio of males to females^{11,15}.

In conclusion, we present the first case of lipoid CAH from Greece whose diagnosis was confirmed by molecular analysis of the StAR gene.

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