Lipoid Congenital Adrenal Hyperplasia With a Novel StAR Gene Mutation

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ABSTRACT: Lipoid congenital adrenal hyperplasia (LCAH) is characterized by disturbance of adrenal and gonadal steroidogenesis (OMIM:201710). It is caused by mutation in the Steroidogenic Acute Regulatory Protein (StAR). We report a classic case of LCAH in a neonate (46, XY) with phenotypic female genitalia who presented with significant salt loss with a novel homozygous variant mutation c.745-1G>C p. in StAR gene.

KEYWORDS: Lipoid congenital adrenal hyperplasia, novel, StAR gene

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Introduction

Lipoid congenital adrenal hyperplasia (LCAH) (OMIM n.201710) is a rare autosomal recessive disorder. It is characterized by a disturbance of steroidogenesis of the adrenal cortex, and gonads resulting in impaired conversion of the cholesterol to pregnenolone.[1]

Steroid biosynthesis begins with the transport of cholesterol from the outer membrane to the inner membrane of the mitochondria. This is a crucial step promoted by Steroidogenic Acute Regulatory Protein (StAR). Cholesterol is then converted to pregnenolone by a cleavage reaction catalyzed by cytochrome P450scc enzyme (encoded by CYP11A1 gene on chromosome 15).[2,3] The StAR gene is mapped on chromosome 8p11.2, consists of 7 exons, and is expressed in the adrenals and gonads, but not in the placenta.[3]

Disease-associated variants of the StAR gene are subdivided into classic, and non-classic forms depending on the age of presentation, and the activity of the StAR gene. Classic LCAH is a severe form defined as neonatal- or early infantile-onset with complete loss of StAR activity, resulting in significant salt loss, deficiency of glucocorticoid, mineralocorticoid and sex steroids, high adrenocorticotropic hormone (ACTH) levels, and high plasma renin activity.[3]

Loss of StAR activity results in deposition and accumulation of cholesterol leading to enlarged adrenal glands, and destruction of Leydig cells leading to a lack of testosterone biosynthesis.[4]

The absence of testosterone in early fetal life, between 6 and 12 weeks of gestation, in affected 46 XY genetic males leads to a phenotype of female external genitalia with the testes, and Wolffian duct derivatives remaining hidden inside the abdomen. In contrast, 46 XX genetic females do not have any problems related to production of sex steroids until puberty because female sex steroid production is minimal during fetal life, and prepubertally.[5,6]

Nonclassical LCAH is a milder form, characterized by late-onset and a partial loss of StAR function where 10% to 25% of StAR activity is retained. It manifests with only glucocorticoid deficiency, mild mineralocorticoid deficiency, and residual testicular function. Consequently, the 46 XY karyotype could develop masculinized external genitalia.[7,8]

The epidemiological data of LCAH StAR mutation has been repeatedly identified in specific ethnic backgrounds. The p.Q258* mutation was reported in 70% of Chinese, Japanese, and Korean patients[9,10] while the p.L260P mutation was reported mostly in Swiss populations.[11] On the other hand, the p.R182L, and c.201_202delCT mutations were reported among Palestinian Arabs,[12-14], and the p.R182H mutation was reported from eastern Saudi Arabia.[13]

We herein describe the clinical, laboratory, imaging, and molecular genetic findings of a Saudi neonate with LCAH with a novel homozygous variant mutation c.745-1G>C p. in the StAR gene.

Case Report

A 21-day-old infant with phenotypical female genitalia, born full-term to consanguineous parents of Saudi Arabian descent. The baby was the first baby in the family, with no previous

abortions or neonatal deaths. The birth weight was 3.2 kg, the head circumference was 35 cm, and the length was 46 cm. The patient was admitted to the nursery for 2 days as a case of physiological jaundice and received phototherapy, and was then discharged home in good health after undergoing newborn screening.

At the age of 10 days, the patient started to experience decreased oral intake, recurrent vomiting, poor weight gain, decreased activity, and excessive crying. The parents sought medical advice, and the patient's physical examination revealed an ill-appearing, irritable, moderately dehydrated neonate with skin hyperpigmentation all over the body with phenotypical female genitalia. The hyperpigmentation was not evident at birth.

Upon admission at the age of 10 days, her vital signs were as follows: Heart rate: 136 beats/minute, blood pressure: 82/56 mmHg, temperature: 36.6°C, and respiratory rate: 58 beats/minute. Her weight had dropped from 3.2 to 2.8 kg. The external genitalia were that of typical female genitalia, with no palpable abdominal or inguinal masses. There was no family history of a similar condition, as well as a negative family history of endocrine or metabolic diseases or neonatal deaths.

Blood samples were drawn for the necessary laboratory tests to exclude sepsis, metabolic crisis, and adrenal insufficiency. The cortisol level was relatively low, serum potassium was high, serum sodium, and aldosterone levels were low. Renin level was elevated, and serum pH through venous blood gas showed metabolic acidosis. She was also hypoglycemic. Therefore, initial resuscitation was done, along with rehydration therapy, hydrocortisone administration, and correction of blood glucose, and electrolyte disturbances. The laboratory data of the patient is shown in Table 1.

Since primary adrenal insufficiency was diagnosed, investigations were carried out in order to reach a diagnosis.

In the ultrasound pelvis done, neither the uterus nor the gonads were detected, and the adrenal glands were massively enlarged. MRI pelvis done, and revealed a prominent both right, and left adrenal glands measuring 20 mm × 10 mm and 15 mm × 10 mm respectively. The uterus was not detected, while testes were identified bilaterally in the proximal inguinal regions (Figure 1).

Although the newborn screening for 17-hydroxyprogesterone was normal, serum ACTH and renin levels were elevated. On the other hand, aldosterone, pregnenolone sulfate, and (Dehydroepiandrosteron) DAHES levels were low. The hormonal findings are summarized in Table 1.

Chromosomal genetic testing was performed, and revealed a 46, XY karyotype.

Table 1. Laboratory data of the patient.

LABORATORY TEST	RESULT	NORMAL RANGE
Biochemical data		
Na	103 mmol/l	
K	8.3 mmol/l	
Glucose	50 mg/dl	
BUN	7 mmol/l	
Creatinine	52 umol/l	
Venous blood gas		
Ph	7.22	
Pco2	35 kpa	
Hco3	14 mEq/l	
Hormones level		
Cortisol	88.70 nmol/l	
Aldosterone	14.6 ng/l	30-790
Renin	960.80 ng/l	11.2-147
Aldosterone/renin activity	0.0	
ACTH	1236 pg/ml	7.2-46
17-OH progesterone	0.10 ng/	
Pregnenolone sulfate	27.8 ug/l	350-1500

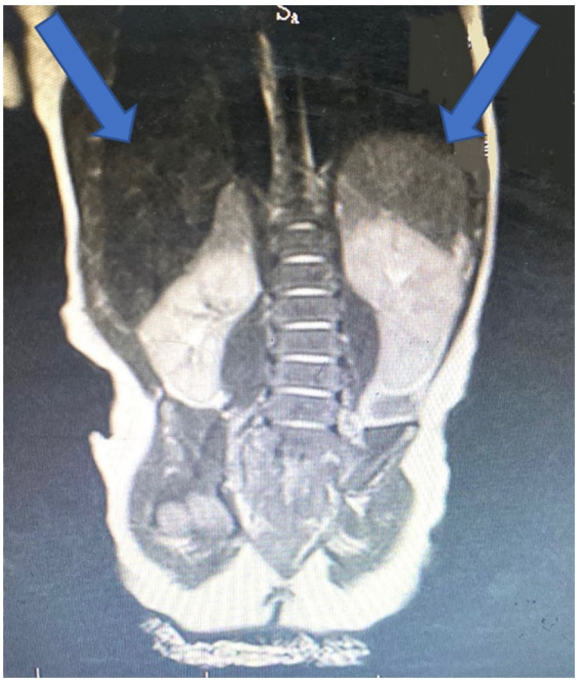

Figure 1. MRI showed bilateral prominent adrenal glands.

Molecular genetic analysis using whole exome sequencing (WES)

Methods. Genomic DNA was fragmented, and the axons of the known genes in the human genome, as well as the corresponding exon-intron boundaries were enriched using Roche KAPA capture technology (KAPA HyperExome Library), and then amplified, and sequenced simultaneously by Illumina technology (next-generation sequencing, NGS) using an Illumina system.

Table 2. Molecular genetic testing of the patient (whole exome sequencing).

GENE (ISOFORM)	PHENOTYPE MIM NUMBER (MODE OF INHERITANCE)	VARIANT	ZYGOSITY	MAF GNOMAD (%)	CLASSIFICATION
StAR (NM_000349.3)	201710 (AR)	c.745-1G>C p.? chr8:38001905	hom	0.00099	Likely pathogenic

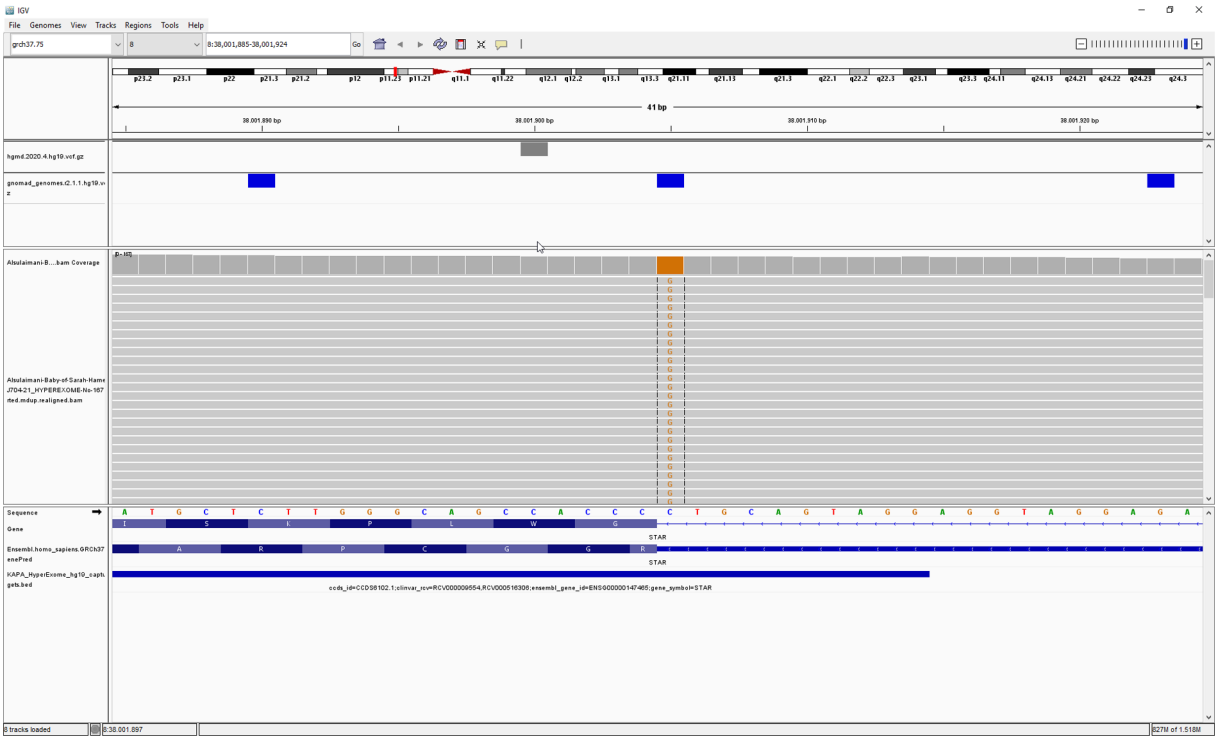

Figure 2. Patient's whole exome sequencing.

The target regions were sequenced with an average coverage of 150-fold. For about 100.0% of the regions of interest a 15-fold coverage was obtained, and for about 99.9% a 20-fold coverage was reached.

NGS data were aligned to the hg19 genome assembly. Moreover, variant calling, and annotation were performed by an in-house developed bioinformatics pipeline. Identified SNVs, and lNDELS were filtered against external, and internal databases focusing on rare variants with a minor allele frequency (MAF) in genomAD of 1% or less and removing known artifacts, and variants in regions with highly homologous regions.

Afterward, classification of variants was conducted based on ACMG guidelines[15,16] considering database entries (incl. HGMD), bioinformatics prediction tools, and literature status. A change in pathogenicity classifications over time cannot be excluded. Variants annotated as common polymorphisms in databases or literature or that were classified as (likely) benign were neglected.

Putatively pathogenic differences between the wildtype sequence (human reference genome according to UCSC Genome Browser, hg19, GRCh37), and the patient's sequence mentioned were assessed using an in-house established quality score. Variants not passing the quality threshold were verified using polymerase chain reaction amplification followed by conventional Sanger sequencing. Sample identity was ensured by internal quality management procedures.

Results. WES Identified the homozygous variant c.745-1G>C p. in StAR (OMIM:600617) which leads to a splice variant that changes the 2-base region at the 3′ end of an intron. To the best of our knowledge, the variant has not been described in the literature so far (HGMD 2020.4). The variant is found in 0.00099% of the overall population (1 heterozygous, 0 homozygous; gnomAD). Considering the available information, the variant is classified as likely pathogenic (Table 2; Figure 2).

The results in the context of clinical findings, and other laboratory data confirm the diagnosis of LCAH in our patient.

Fludrocortisone and hydrocortisone replacement therapy was instituted, and resulted in dramatic improvement.

The parents were called for a meeting with a multidisciplinary team of physicians for a discussion of the diagnosis, and further management plan of the patient. The team consisted of a pediatric endocrinologist, a pediatric surgeon, a pediatric geneticist, and a psychologist. An agreement was reached to perform bilateral gonadectomy, and to raise the child as a female.

Discussion

LCAH is a very rare, potentially lethal, congenital disease that requires timely life-saving treatment. In this report, we describe a (46, XY) phenotypical female newborn of consanguineous parents who was diagnosed soon after birth with classic LCAH after the manifestation of primary adrenal insufficiency and genetic analysis revealed the homozygous novel variant c.745-1G>C p in the StAR gene.

Table 3 summarizes previously reported patients with StAR gene mutation. About 1 Saudi report was released from the eastern region describing 8 patients of consanguineous backgrounds. About 7 of them carried the same R182H mutation and 1 carried the M144R mutation.[13] The R182H mutation was also reported among 5 out of 6 Palestinian patients from 3 families of consanguineous carrier parents. All patients were homozygous for the new founder c.201_202delCT mutation.[4,14] On the other hand, 1 Scandinavian infant born to a non-consanguineous couple carried 2 de novo heterozygous mutations StAR c.444COA (StAR p.N148K), and StAR c.557COT (StAR p.R193X) in the StAR gene.[17] A case series of 5 Caucasian patients with LCAH were all homozygous to the p.R188C mutation, with all patients belonging to an isolated Canadian population of European ancestry.[7,17] This highlights that StAR mutations can be either inherited or de novo mutations, thus LCAH should be considered in suspected patients all over the world.

Our patient's onset of the disease was early during the neonatal period with acute presentation of primary adrenal insufficiency. The Palestinian patients had the same presentation.[14] Although the 8 patients from eastern Saudi Arabia had the same R182H mutation as the Palestinian patients, their onset of symptoms varied from 1 to 14 months of age.[13]

One interesting study described the clinical data over 38 years of follow-up of 2 French-Canadian siblings. Patient A was (46, XY), and patient B was (46, XX). They presented with the classical clinical manifestations of LCAH, and they had the same homozygous StAR gene mutation (L275P). However, the severity of their presentation differed, where patient A had a later onset, and less severe corticosteroid deficiency than patient B, but both patients had a less severe mineralocorticoid deficiency. Patient A (46, XY) showed clinical and biochemical signs of early and severe deficiency of testosterone secretion, as he was born with external female genitalia with a bilateral inguinal hernia. Laparotomy was performed at the age of 13 years, there were no Müllerian or Wolffian structures present, and the gonads were removed. Patient B (46, XX), showed spontaneous pubertal development, and she had spontaneous regular non-ovulatory menstruations for many years. Moreover, successful pregnancy occurred under stimulation of clomiphene for ovulation along with progesterone supplementation.[5]

A Chinese report described an infant with CLAH due to c. 229C>T (p.Q77X) mutation in exon 3 and c. 722C>T (p.Q258X) mutation in exon 7 of the StAR gene. The patient had a typical early-onset adrenal crisis at the age of 2 months with phenotypical female genitalia, and hyperpigmentation. Karyotype was (46, XY) and ultrasonography revealed the presence of testes-like masses in the pelvic cavity. Neither ovaries nor a uterus was identified. Bilateral gonadectomy was done at the age of 15 years followed by estrogen replacement therapy, after which she was able to reach her final adult breast development and height.[18]

One other report was released from Italy on an Italian female infant who presented in late infancy with a clinical picture of acute adrenal insufficiency. Her ultrasound showed a normal uterus, and ovaries. Her karyotyping showed a normal (46, XX) female. She had 2 compound heterozygous variants c.562C>T (p.Arg188Cys) and c.577C>T (p.Arg193Ter) in the StAR gene.[19]

These substantial variations in the age of onset of symptoms, and severity of the disease can be explained by the 2-hit model proposed by Miller.[1] The first hit is the actual loss of StAR-dependent steroidogenesis activity. This allows normal placental steroidogenesis, but with very low levels of steroid hormones produced. This in turn explains why infants with untreated LCAH can survive without treatment for several months.[2,4] On the other hand, the second hit disrupts the low levels of StAR-independent steroidogenesis which occurs later in life. This result in an overload, and accumulation of lipid droplets that destroy the cell directly or indirectly (auto-oxidation effect) resulting in loss of the remaining StAR-independent cholesterol transport.[20]

Limitations

Being a case report is a limitation of the current study. Having a registry of StAR gene mutation patients will definitely improve knowledge about the disease, and its long term functional, and psychological implications.

Table 3. Summary of previously reported patients with StAR gene mutation.

AGE OF PRESENTATION	PRESENTING SYMPTOMS	KARYOTYPE	GENE MUTATION	REFERENCES
About 8 patients from 6 Saudi Arabian families who were first diagnosed at 1 to 14 mo of age (median, 4-7 mo; mean, 7 mo)	At presentation, all had hyponatremia, hyperkalemia, elevated ACTH, and low cortisol. Pregnenolone, progesterone, 17-hydroxypregnenolone, 17-hydroxyprogesterone, testosterone, androstenedione, and dehydroepiandrosterone sulfate were all low in those patients in whom it was measured.	Five patients were 46,XY, and 3 were 46,XX	DNA sequencing showed that 1 patient was homozygous for the StAR mutation M144R, and the other 7, from 5 apparently unrelated families, were homozygous for the StAR mutation R182H	Chen et al[13]
About 8 Palestinians from 4 unrelated families, all affected individuals presented neonatally	All affected individuals presented with undetectable adrenocortical hormones, and are responding to replacement therapy. Only 2 sisters had neurodevelopmental deficits.	Three patients were 46,XY, and 5 were 46,XX	Sequence analysis of StAR revealed homozygosity for c.201_202delCT mutation in all 8 cases	Abdulhadi-Atwan et al[14]
2.5 mo patient of Scandinavian origin	Adrenal salt wasting crisis. The baby presented with the normal female external genitalia, including the absence of gonads in the labial folds, and also showed no abnormality in a routine normal newborn screen. She had hyperpigmented areolas, labia majora, and skin relative to her parents.	46,XY	Two de novo heterozygous mutations StAR c.444COA (StAR p.N148K), and StAR c.557COT (StAR p. R193X) in the StAR gene	Kaur et al[17]
About 3 children from 2 families who presented with primary adrenal insufficiency at 2 to 4 y of age	Patient 1, a Pakistani phenotypic female, had an uneventful infancy, experienced fever, and vomiting at 2 y of age, and was hypoglycemic during a viral illness at 4 y. Progressive hyperpigmentation prompted referral at 4.5 y. Patients 2 and 3, Pakistani brothers from a consanguineous family, were born after uneventful pregnancies, and had normal male genitalia with descended testes. The older boy developed hyperpigmentation at 1.5 y; The younger brother also became progressively pigmented. At 2.8 y of age.	About 1 patient was 46,XX, and the other 2 were 46,XY	Homozygous StAR mutations Val187Met and Arg188Cys	Baker et al[7]
Patient A, 11 mo; Patient B, 1.5 mo	Patient A suffered from gastroenteritis, hyperthermia, and dehydration. Blood pressure was 100/50, heart rate 120/min, and respiratory rate 24 to 28/min. Blood glucose was 3.8 mmol/L, sodium 121 mmol/L, chloride 93 mmol/L, potassium 5.4 mmol/L, and serum bicarbonate was 7 mmol/L. Intravenous fluid, and glucose were administered to correct this situation. About 4 d after the cessation of the intravenous therapy, electrolytes disturbance, and metabolic acidosis relapsed. Patient B She had skin hyperpigmentation since the age of 1.5 mo. At 4.5 mo, she was hospitalized for fever, anorexia, fatigue, and weight loss, and was treated with antibiotics (pharyngitis) for 10 d.	Patient A, 46,XY; Patient B, 46,XX	Homozygous StAR gene mutation (L275P)	Khoury et al[5]
2 mo of age	The patient had typical early-onset adrenal crisis at 2 mo of age. She had normal-appearing female genitalia.	46, XY	C. 229C>T (p.Q77X) mutation in exon 3 and c.722C>T (p.Q258X) mutation in exon 7 of the StAR gene	Zhao et al[18]
Late infancy	Clinical picture of acute adrenal insufficiency	46, XX	2 compound heterozygous variants c.562C>T (p.Arg188Cys) and c.577C>T (p.Arg193Ter) in the StAR gene	Bizzarri et al[19]

Author Contributions

Ayman A Bakkar: Conceptualization; Data curation; Investigation; Methodology; Writing—original draft; Writing—review and editing. **Abdulaziz Alsaedi:** Investigation; Writing—original draft; Writing—review and editing. **Naglaa M Kamal:** Investigation; Writing—original draft; Writing—review and editing. **Enad Althobaiti:** Investigation; Writing—original draft; Writing—review and editing. **Lujain A Aboulkhair:** Methodology; Project administration; Writing—original draft. **Abdullah M Almalki:** Investigation; Methodology; Writing—original draft; Writing—review and editing. **Shaima A Alsalmi:** Methodology; Project administration; Writing—original draft. **Qaydah Alharthi:** Methodology; Project administration; Writing—original draft. **Sara A Abosabie:** Data curation; Methodology; Writing—original draft. **Salma AS Abosabie:** Data curation; Methodology; Writing—original draft.

Ethical Approval and Consent to Participate

The study was approved by the research and ethical committee of Alhada Armed Forces Hospital, Taif, Saudi Arabia. Approval Number is 2022-697. Parents of the reported child signed a written informed consent for their child's participation in the current study.

Consent for Publication

Parents of the reported child signed a written informed consent for the publication of the current study.

Availability of Data and Materials

All data and materials related to the study are included in the current manuscript.

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