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Case Report

Novel *STAR* Gene Variant of Congenital Lipoid Adrenal Hyperplasia With Testicular Adrenal Rests

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Abstract

A mutation in the steroidogenic acute regulatory protein (*STAR*) gene, which encodes a protein that plays a crucial role in steroid hormone synthesis, causes a severe form of congenital adrenal hyperplasia (CAH) known as lipoid CAH (LCAH). LCAH presents with primary adrenal insufficiency (PAI) as well as atypical genitalia. Individuals with LCAH require adrenal steroid hormone supplements for survival. Masculinization in males with *STAR* deficiency varies from incomplete to normal virilization. Radiological examinations reveal enlarged and lipid-laden adrenals.

A 10-year-old boy born of second-degree consanguinity presented with weight gain and hyperpigmentation for 1 year. He was diagnosed with PAI at age 7 months and treated with hydrocortisone and fludrocortisone. Dynamic adrenal gland testing revealed undetectable hormone reserves. Imaging detected hypoplastic adrenals and a small testis with testicular adrenal rests (TART). Genetic analysis indicated a novel homozygous pathogenic variant of *STAR* in exon 7, c.814C > G(pArg272Gly) associated with LCAH (OMIM No. 201710). Testing revealed that asymptomatic family members and relatives were heterozygotes for the variant. The patient was diagnosed with nonclassic LCAH with hypoplastic adrenals and TART. Adequate hormone supplementation resulted in TART regression. This genetic variation is reported for the first time.

Key Words: lipoid congenital adrenal hyperplasia, primary adrenal insufficiency, testicular adrenal rests, adrenal hypoplasia, disorders of sexual differentiation, *STAR* gene

Abbreviations: ACTH, adrenocorticotropin; CAH, congenital adrenal hyperplasia; CLCAH, classic lipoid congenital adrenal hyperplasia; LCAH, lipoid congenital adrenal hyperplasia; MRI, magnetic resonance imaging; NCLCAH, lipoid congenital adrenal hyperplasia; PAI, primary adrenal insufficiency; *STAR*, steroidogenic acute regulatory protein gene; TART, testicular adrenal rests.

Introduction

Lipoid congenital adrenal hyperplasia (LCAH) is a rare autosomal recessive disorder caused by a steroidogenic acute regulatory protein (*STAR*) mutation (1). Adrenal steroid hormone production is impaired both in adrenal and gonadal cells with cholesterol ester accumulation in the cell cytosol. The human *STAR* protein facilitates cholesterol movement from the outer to the inner mitochondrial membrane to be converted to pregnenolone by P450SCC (side chain cleavage, CYP11A1). Affected children exhibit primary adrenal insufficiency (PAI). A majority of 46 XY individuals with classic LCAH (CLCAH) are typically reared as females because of the absence of virilization and undescended testis, which are frequently located in the abdomen. Imaging reveals enlarged and lipid-rich adrenals (2).

LCAH cases are reported mainly in people of Japanese, Korean, and Palestinian descent (3, 4). The *STAR*-Gln258* mutation with complete loss of function is identified as a founder effect in Korea and other East Asian countries (4).

Case Presentation

A 10-year-old boy presented with excessive weight gain (4 kg in 1 year), extreme fatigue, and skin hyperpigmentation over the extensor aspect of joints on the hands, elbows, and knees. He was the youngest of 3 children and was born at term with second-degree consanguinity (Fig. 1). He cried soon after birth (birth weight of 2 kg). The delivery and postnatal period were uneventful. The small gestational age indicated no identifiable cause. At age 7 months, he was hospitalized for fever and recurrent vomiting and was diagnosed with PAI (Table 1). He was treated with hydrocortisone and fludrocortisone. His records revealed persistently increased adrenocorticotropin (ACTH) and decreased cortisol levels. His eldest sibling died at age 2 years of fever and hypotension. The second pregnancy

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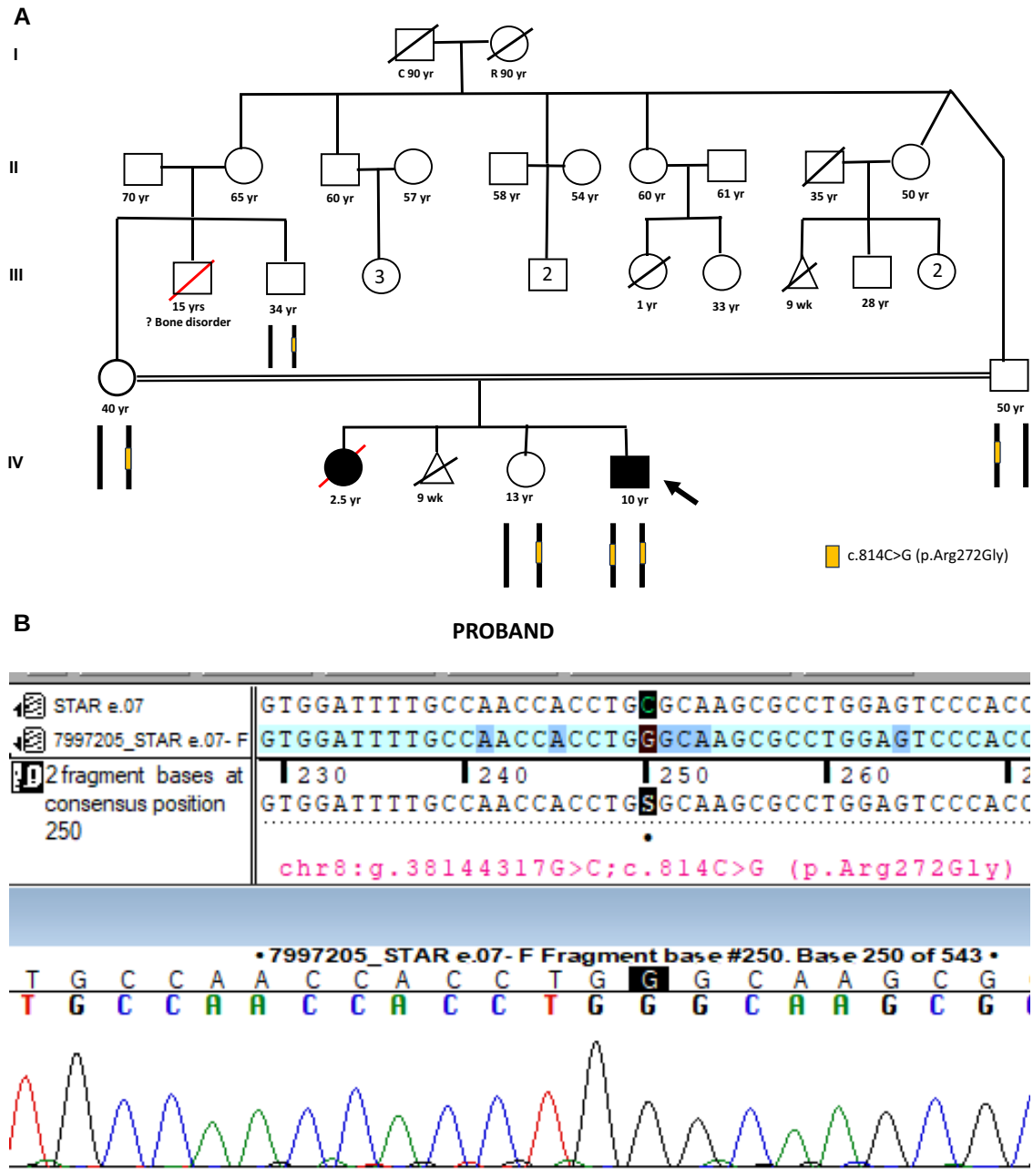

Figure 1. A, Consanguineous pedigree showing heterozygous unaffected parents and sister. Homozygous affected proband. B, Sanger sequence of a proband with the chromatogram.

resulted in an abortion at 3 months. The third sibling is aged 12 years and asymptomatic.

Physical examination revealed a height and weight of 141 cm and 61.5 kg, respectively, with a body mass index of 30.93. His height was in the 50th to 70th percentile and his weight was greater than the 97th percentile (Indian Academy of Paediatrics growth charts). His father's and mother's heights were 168 and 163 cm, respectively. His pulse rate and blood pressure were 89 beats/min and 114/66 mm Hg, respectively. Axillary and pubic hair were absent. The scrotum was well developed with rugosity and mild pigmentation, and testes were descended on both sides, with a volume of 3 mL (Prader orchidometer) and a phallic length of 3 cm (pubertal stage Tanner stage 1). The systemic examination indicated normal findings.

Diagnostic Assessment

Adrenal reserve testing was not previously recorded. Hydrocortisone was changed over to dexamethasone for adrenal reserve testing. Dynamic testing detected no basal and ACTH-stimulated adrenal glucocorticoid and mineralocorticoid steroid reserves (Table 2). The human chorionic gonadotropin test indicated subnormal testicular function (Table 3). Ultrasound of the scrotum revealed hypoechoic tissue in the parenchyma of the normal testes, demonstrating increased

Table 1. Hormonal profile from time of diagnosis (aged 7 months) until presentation to our department February 21, 2023

Test	Normal range	27-May 13	31-Aug 13	30-Nov 13	14-Jun 14	16-Dec 14	19-Nov 16	14-Mar 20	06-Mar 21	10-Mar 22	21-Feb-23	9-Mar 23	13-Sep 23
ACTH 8 AM	6-46 pg/mL (1.32-10.12 pmol/L)	>1250 pg/mL (>275.2 pmol/L)	351 pg/mL (77.29 pmol/L)	11.3 pg/mL (2.49 pmol/L)	591 pg/mL (130.14 pmol/L)	19 pg/mL (4.18 pmol/L)	623 pg/mL (137.19 pmol/L)	1546 pg/mL (340.43 pmol/L)	218.8 pg/mL (48.18 pmol/L)	570 pg/mL (125.52 pmol/L)	752.1 pg/mL (165.612 pmol/L)	63.67 pg/mL (14.02 pmol/L)	51.05 pg/mL (11.24 pmol/L)
Serum cortisol (8 AM)	6.7-22.6 mcg/dL (184.9-623.8 nmol/L)	26 mcg/dL (717.6 nmol/L)					1.9 mcg/dL (52.44 nmol/L)					0.19 mcg/dL (5.244 nmol/L)	
Serum sodium	133-143 mmol/L (133-143 mEq/L)	138 mmol/L (138 mEq/L)	135 mmol/L (135 mEq/L)	131 mmol/L (131 mEq/L)	137 mmol/L (137 mEq/L)	140 mmol/L (140 mEq/L)	136 mmol/L (136 mEq/L)	136 mmol/L (136 mEq/L)	141 mmol/L (141 mEq/L)	140 mmol/L (140 mEq/L)	137 mmol/L (137 mEq/L)	— —	137.4 mmol/L (137.4 mEq/L)
Serum potassium	3.5-5.1 mmol/L (3.5-5.1 mEq/L)	4.9 mmol/L (4.9 mEq/L)	4.3 mmol/L (4.3 mEq/L)	4.8 mmol/L (4.8 mEq/L)	4.5 mmol/L (4.5 mEq/L)	4.5 mmol/L (4.5 mEq/L)	4.81 mmol/L (4.81 mEq/L)	4.1 mmol/L (4.1 mEq/L)	4.53 mmol/L (4.53 mEq/L)	4.2 mmol/L (4.2 mEq/L)	4.6 mmol/L (4.6 mEq/L)	— —	5 mmol/L (5 mEq/L)

Abbreviation: ACTH, adrenocorticotropin.

Table 2. Adrenocorticotropin stimulation testing for adrenal reserve[a]

Tests		Normal range	Basal
17 OH progesterone	ng/mL	0.03-0.90 ng/mL	0.03 ng/mL
	(nmol/L)	(0.09-2.72 nmol/L)	(0.09 nmol/L)
11 Deoxy cortisol	ng/mL	0.2-1.58 ng/mL	0.02 ng/mL
	(nmol/L)	(0.58-4.57 nmol/L)	(0.058 nmol/L)
Cortisol	mcg/dL	6.7-22.6 mcg/dL	<0.16 mcg/dL
	(nmol/L)	(184.9-623.8 nmol/L)	(<4.42 nmol/L)
Progesterone	ng/mL	0.10-0.84 ng/mL	<0.08 ng/mL
	(nmol/L)	(0.32-2.67 nmol/L)	(<0.25 nmol/L)
11 Deoxy corticosterone	ng/dL	< 31 ng/dL	<16 ng/dL
	(nmol/L)	(<0.91 nmol/L)	(<0.48 nmol/L)
Aldosterone	ng/dL	2.52-39.2 ng/dL	<0.97 ng/dL
	(nmol/L)	(0.07-1.09 nmol/L)	(<0.027 nmol/L)
Renin	ng/mL/h	0.5-3.3 ng/mL/h	2.57 ng/mL/h
	(mcg/L/h)	(0.5-3.3 mcg/L/h)	(2.57 mcg/L/h)
DHEAS	mcg/dL	24.40-247.00 mcg/dL	0.1 mcg/dL
	µmol/L	(0.66-6.7 µmol/L)	(0.0027µmol/L)
Androstenedione	ng/mL	0.7-3.6 ng/mL	<0.3 ng/mL
	(nmol/L)	(2.44-12.57 nmol/L)	(<1.05 nmol/L)
Total testosterone	ng/mL	0.07-1.3 ng/mL	<0.49 ng/mL
	(pmol/L)	(242-4420 pmol/L)	(<169.9 pmol/L)

Abbreviation: DHEAS, dehydroepiandrosterone sulfate.
[a]Values at 30 and 60 minutes were no different from the basal values.

vascularity on Doppler images, indicating testicular adrenal rests (TART) (Fig. 2A and 2B). Magnetic resonance imaging (MRI) axial T2-weighted images revealed hypoplastic adrenals (Fig. 2G). Scrotum MRI revealed T2 hypointense lesions in both testes, indicating TART (Fig. 2H).

Treatment

ACTH levels were suppressed to normal after initiating hydrocortisone of 10 mg/m^2/day in the evening and fludrocortisone of 0.1 mg/m^2/day.

Outcome and Follow-up

Hyperpigmentation and fatigue were improved. Repeated ultrasound at 6 months (Fig. 2C and 2D) and 8 months (Fig. 2E and 2F) revealed decreased size and increased calcification of TART.

Clinical exome sequencing by next-generation sequencing by an outsourced College of American Pathologists–certified commercial laboratory (MEDGENOME-CLIA–certified laboratory) revealed a homozygous variant in the *STAR* gene at exon 7, c.814C > G(pArg272Gly)(SCV004042697.1) in the patient (5). *STAR* gene mutations are associated with LCAH (OMIM No. 201710). The *STAR* gene at exon 7, c.814C > G(pArg272Gly) homozygous variant has not been reported in the 1000 Genome, Genome Aggregation Database (v3.1), and TOPMed databases and has demonstrated a minor allele frequency of 0.002% in the company's

database. The homozygous variant is categorized as a variant of unknown significance as per the American College of Medical Genetics and Genomics–Association for Molecular Pathology criteria. The in silico predictions by PolyPhen-2 (HumDiv), Scale-Invariant Feature Transform, Likelihood Ratio Test, and Mutation Taster 2 of the variant are damaging. The reference codon is conserved across species. The asymptomatic family members demonstrated a heterozygous variant. Fig. 1B shows the chromatogram of the patient.

Discussion

A 10-year-old boy was born at term of second-degree consanguineous marriage and was on treatment for PAI since childhood. He presented with weight gain and hyperpigmentation. Dynamic testing revealed no adrenal reserve. Radiological evaluation indicated hypoplasia of the adrenals and TART. Genetic testing revealed a novel homozygous missense variant of the *STAR* gene *at* exon 7, c.814C > G(pArg272Gly-homozygous) (SCV 004042697.1) (5), with his family members carrying the

Table 3. Human chorionic gonadotropin test to evaluate testicular function on the 5th and 30th day

Tests		Normal range	Basal	6th d	30th d
Total testosterone	ng/mL	0.07-1.3 ng/mL	<0.049 ng/mL	0.27 ng/mL	0.35 ng/mL
	(pmol/L)	(242-4420 pmol/L)	(<166.6 pmol/L)	(918 pmol/L)	(1190 pmol/L)
Free testosterone	pg/mL	1.3-55.2 pg/mL	0.69 pg/mL	0.83 pg/mL	1.88 pg/mL
	(pmol/L)	(4.5-191.4 pmol/L)	(2.39 pmol/L)	(2.88 pmol/L)	(6.52 pmol/L)
DHEAS	µg/dL	24.4-247 µg/dL	<0.1 µg/dL	—	1.4 µg/dL
	(µmol/L)	(0.66-6.70 µmol/L)	(<0.003µmol/L)		(0.003 µmol/L)
Androstenedione	ng/mL	0.7-3.6 ng/mL	<0.3 ng/mL	—	<0.3
	(nmol/L)	(2.44-12.57 nmol/L)	(<1.05 nmol/L)		(<0.3 nmol/L)
AMH	ng/mL	8.9-109 ng/mL	>23 ng/mL	—	—
	(pmol/L)	(63.6-778.6 pmol/L)	(>164 pmol/L)		
Inhibin	pg/mL	169-216 pg/mL	112.47 pg/mL	—	—
	ng/L	(169-216 ng/L)	(112.47 ng/L)	—	—

Abbreviation: AMH, antimüllerian hormone; DHEAS, dehydroepiandrosterone sulfate.

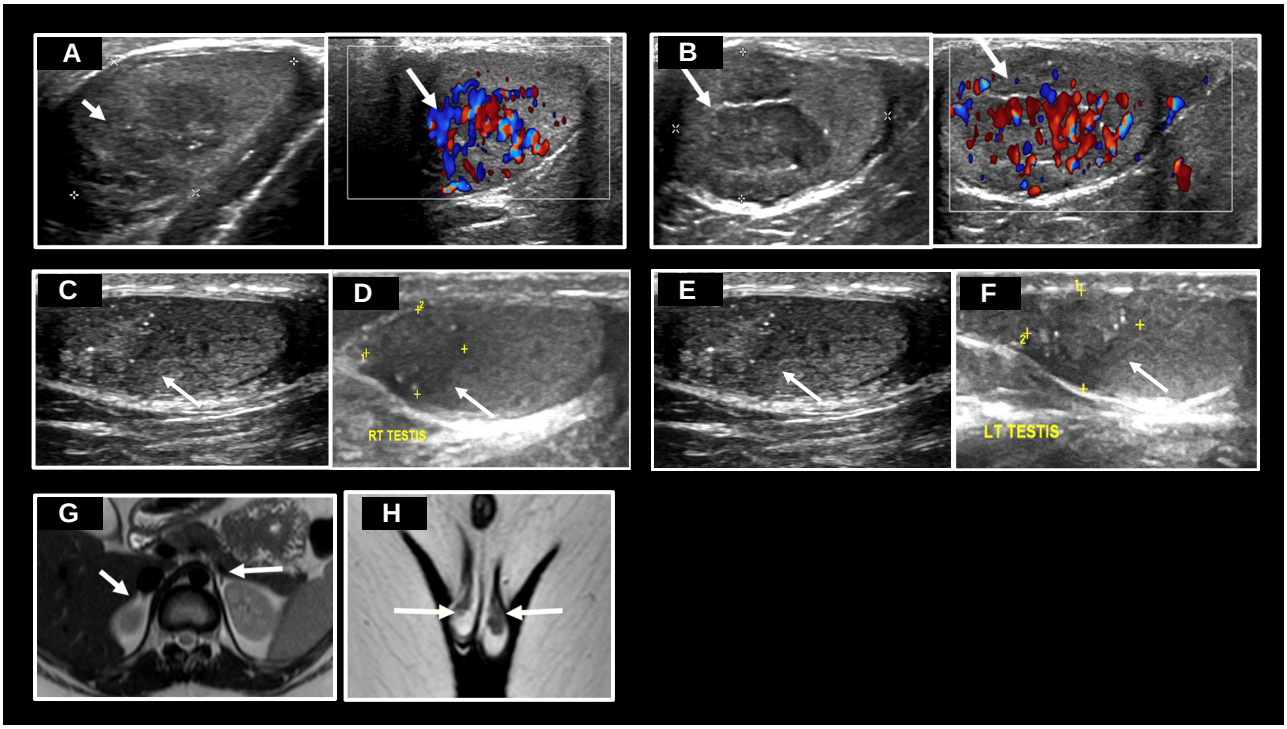

Figure 2. A, Ultrasound and Doppler images of right testis showing adrenal rest (white arrows), size 11.2 × 10 mm. B, Ultrasound and Doppler images of left testis showing adrenal rest (white arrows), size 12.5 × 8 mm. C, Ultrasound image of right testis 6 months later, adrenal rest (white arrow) size 10 × 6.5 mm. D, Ultrasound image of right testis 8 months later, adrenal rest (white arrow) size 10 × 6.2 mm. E, Ultrasound image of left testis 6 months later, adrenal rest (white arrow) size 8 × 5.6 mm. F, Ultrasound image of left testis 8 months later, adrenal rest (white arrow) size 6.9 × 4 mm. G, Magnetic resonance image (MRI) T2W axial image of adrenal glands—very small glands—white arrows. H, MRI T2W coronal image of scrotum—T2 hypointense adrenal rests in both testes (white arrows).

heterozygous form. The homozygous nature of the variant and bioinformatics studies indicate that this could be the causative variant, although there is no functional evidence to confirm this causality.

Human *STAR* is located on chromosome 8p11.2 and consists of 7 exons that translate into a protein of 285 amino acids (6). The amino acid sequence 67 to 280 of the *STAR* protein is highly conserved. The mutations may be missense or frameshift mutations. Missenses are the most prevalent, followed by frameshift, splicing, and nonsense mutations (3, 6). Missense mutations occur in the region between 169 and 275 amino acid sequences and are clustered in exons 5 to 7, while frameshift mutations are observed throughout the gene (7). Nonsense or frameshift mutations are determined only in CLCAH (7).

The literature indicates either homozygous or compound heterozygous DNA variants that result in the CLCAH phenotype in the *STAR* gene at the Gln258 region. So far, the variants described result in the following DNA variants and amino acid changes in various populations globally: *STAR* gene (a) exon 7, c.898C > T(p.Q258X) in Japan and Korea; (b) exon 5, c.671G > T(A182L) in Palestinian Arabs; (c) exon 5, c.431T > G(p.R182H) in Saudi Arabia; (d) exon 3 c.229C > T(p.Q77X) and exon 7.c. 722C > T(p.Q258X) in China; (e) exon 5, c.444C > A(p.N148 K) and exon 5, c.557C > T(p.R193X) in White individuals (2, 5, 8, 9). NCLCAH demonstrated only a partial loss-of-function mutation.

Here, we report a novel missense variant in *STAR* gene exon 7, c.814C > G(pArg272Gly) (homozygous) of CLAH (SCV.004042697.1) (5). A missense mutation at the same genomic coordinates as ours with the amino acid cysteine in *STAR* (–) c.814C > T(p.Arg272Cys) has been reported in Japan (2, 3). All the patients in this group had complete male external genitalia and had pubertal development without androgen supplementation. However, this study mentioned no radiological appearance of the adrenals. Studies in India have revealed 2 novel mutations: premature termination *STAR*(–) exon 4, c.441G > A (p.W147X), a missense mutation *STAR*(–) exon 6, c.653C > T (p.A218V), and frameshift deletion c.del 815 G (or p.R272PfsX35). All of these 3 patients had 46 XY karyotypes with female external genitalia (10). Another study from India of patients with PAI and inguinal testis revealed a homozygous mutation *STAR*(–) exon 4, c.441G > A (p.W147X) (10).

The disrupted gene of LCAH is expressed only in the gonads and adrenals but not in the placenta. The C-terminal region is the biologically important cholesterol-binding site, and the N-terminal region is the mitochondrial target sequence. STAR deletion in the N-terminal region does not cause loss of function, whereas *STAR* deletion in the C-terminal region (crucial for activity) causes severe functional defects. The 2-hit model explains the pathophysiology; the first hit demonstrated the loss of the *STAR*-mediated acute steroidogenic response, causing an 80% decrease in *STAR*-dependent steroidogenesis. Intracellular cholesterol esters and oxidation product accumulation characterize *STAR*-independent steroidogenesis. In the second hit, the cells engorge with the accumulation of these products, damaging the cytoarchitecture through biochemical and physical displacement (2, 3).

Adrenal and gonadal steroid deficiencies related to lipid accumulation cause problems in patients with LCAH (2, 3). Neonatal salt-wasting, hyperkalemia, hypovolemia, dehydration, acidosis, female external genitalia in 46 XY, and death in infancy are the clinical descriptions of CLCAH (3, 10). Hyperpigmentation due to ACTH hypersecretion is observed in two-thirds of infants. The 46 XY infants have impairments in testosterone synthesis. LCAH treatment typically involves deficient hormone replacement. Adequate supplements of steroids cause hyperpigmentation reduction and TART regression (Fig. 2C-2F).

LCAH is categorized into classic and nonclassic forms (Table 4) (2). The onset of PAI depends on the degree and timing of stress that the patient encounters. CLCAH and NCLCAH demonstrate the absence of adrenal enlargement (2, 11). Adrenal hypoplasia in NCLCAH has been reported in Chinese patients (1, 12).

LCAH should be differentiated from other glucocorticoid and mineralocorticoid deficiencies. Enzymatic defects in steroidogenesis can present as PAI in a neonate and the first year of life. Precursor hormones preceding the enzymatic block in CAH are elevated and the adrenals are visualized and may be bulky. Congenital adrenal hypoplasia (X-linked adrenal hypoplasia congenita), where the adrenals are not visualized by imaging methods, is the most difficult to differentiate (3). Cholesterol biochemistry defects, peroxisomal problems, and mitochondrial disorders are associated with skeletal abnormalities and other endocrinopathies (13). Other causes of PAI are IMAGe syndrome with immunodeficiency, where adrenal

Table 4. Lipoid congenital adrenal hyperplasia (2)

	CLCAH	NCLCAH
Age of onset of PAI	Neonatal period	Late onset of PAI 1 y or older
Skin hyperpigmentation	Present (90%)	Present (100%)
External genitalia	Female or minimally masculinized genitalia, irrespective of chromosomal sex	Completely masculinized male external genitalia with karyotype 46XY
Plasma ACTH	High	High
Serum cortisol	Low	Low
Serum Aldosterone	Low	Preserved mineralocorticoid function
Plasma renin	Higher	Lower compared to CLCAH
Hyponatremia	Present	Present
Hypoglycemia	Present	Present
Radiology	Lipoid-laden adrenals by CT (68%)	Lipoid-laden adrenals by CT (40%)
Pathogenic variant of *STAR*	Complete loss of function	Partial loss of function
Spontaneous puberty	Yes in 90% of XX females	Yes in 100 XY males and XX females
Glucocorticoid supplementation	100%	100%
Mineralocorticoid supplementation	100%	64%

Abbreviations: ACTH, adrenocorticotropin; CLCAH, classic lipoid congenital adrenal hyperplasia; CT, computed tomography; LCAH, lipoid congenital adrenal hyperplasia; NCLCAH, lipoid congenital adrenal hyperplasia; PAI, primary adrenal insufficiency; STAR, steroidogenic acute regulatory protein.

hypoplasia is present. However, these conditions exhibit hypogonadotropic hypogonadism and skeletal changes (13).

Patients with CAH experience TART, with a prevalence of 40% (14). TART is always bilateral and asymptomatic. TART originates from pluripotent cells of the urogenital ridge, or adrenogonadal primordium. Aberrant adrenal cells end up within the testis or ovaries, which usually regress within the first year of life. ACTH receptors are found in TART (14). Elevated ACTH and increased growth-promoting factors are crucial stimulating factors of growth and hyperplasia of TART. This is supported by the high and low prevalence of TART in severe and nonclassic CAH (moderate ACTH elevation), respectively (14). High ACTH levels in this patient explain the TART.

Moreover, TART exhibits testicular characteristics. The pubertal rise in luteinizing hormone causes TART cell proliferation as luteinizing hormone receptors are also found in TART (15). Bilateral presentation helps to differentiate them from testicular Leydig cell tumors. Intensified glucocorticoid treatment may reduce the TART size (14) as seen in our patient. The presence of TART in NCLCAH remains unreported in the literature.

Therefore, the present *STAR* gene exon 7, c.814C>G(pArg272Gly) variant may be related to a continuum of the spectrum between NCLCAH and CAH. The novel variant of NCLCAH with hypoplastic adrenals and TART is an unusual finding. The major limitation of this case report was the rarity of the case and the lack of financial wherewithal to complete the functional studies for this variant.

Learning Points

- PAI in the neonatal and early-infancy periods should be investigated for enzymatic defects in adrenal steroidogenesis.
- Patients with CLCAH and NCLCAH require adrenal steroid hormone replacement therapy for survival.
- Adrenals and gonadal imaging is important in patients with LCAH.
- Optimal adrenal steroid hormone replacement therapy reverses TART in patients with LCAH.
- Monitoring growth and height is important while receiving adrenal steroid replacement in patients with LCAH.

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Contributors

C.V.H. designed the clinical evaluation, investigation, genetic studies, literature search, and write-up of the manuscript. H.S.V. and M.Z. helped in adrenal dynamic testing and clinical evaluation. A.S.T. participated in radiological evaluation. S.R. participated in laboratory investigations. R.J. participated in clinical evaluation.

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None declared.

Informed Patient Consent for Publication

Signed informed consent obtained directly from the patient's relatives or guardians.

Data Availability Statement

Original data generated and analyzed for this case report are included in this published article.

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