The rare form of congenital adrenal hyperplasia caused by an autosomal dominant form of \textit{STAR} deficiency

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The steroidogenic acute regulatory protein (\textit{STAR}) is crucial for transport of cholesterol to mitochondria where biosynthesis of steroids is initiated. Loss of \textit{STAR} function due to autosomal-recessive mutations in the \textit{STAR} gene leads to lipidoid congenital adrenal hyperplasia (LCAH) which is characterized by impaired synthesis of adrenal and gonadal steroids, which causes adrenal insufficiency, primary ovarian failure in 46XX patients, or 46XY disorder of sex development (DSD). However, there were a few reports of 46 XY DSD patients with LCAH caused by a heterozygous mutation in the \textit{STAR} gene. Here, we describe another rare case of LCAH in a 46XY patient with DSD and primary adrenal insufficiency due to an autosomal-dominant mutation in the \textit{STAR} gene.

Keywords: steroidogenic acute regulatory protein, lipidoid congenital adrenal hyperplasia, adrenal insufficiency, sex development disorders.

Background

Congenital adrenal dysfunction (adrenogenital syndrome, congenital adrenal hyperplasia) is a group of autosomal recessive disorders resulting from the deficiency of one of the enzymes or transport proteins required for cortisol synthesis in the adrenal cortex [1]. Seven forms of congenital adrenal hyperplasia (CAH) have been described to date: lipidoid congenital adrenal hyperplasia (LCAH) is caused by mutations in the \textit{STAR} transport protein (steroidogenic acute response protein involved in a rapid steroidogenic stress response), whereas other forms of CAH involve a deficiency of an enzyme involved in the synthesis of cortisol.

The \textit{STAR} protein plays a key role in the initiation of steroidogenesis and regulates transport of cholesterol from the outer mitochondrial membrane into the inner mitochondrial membrane, where the enzymes involved in the conversion of cholesterol to steroid hormones are located [2]. Mutations in the \textit{STAR} gene lead to lipidoid adrenal hyperplasia characterized by impaired synthesis of all adrenal and gonadal steroid hormones, which causes primary adrenal insufficiency in conjunction with primary hypogonadism in patients with karyotype 46 XX and disorder of sex development (DSD) in patients with karyotype 46 XY [3]. All forms of CAH, including LCAH with mutant \textit{STAR} protein, are inherited in an autosomal recessive manner. However, there were a few reports of genetic defects in the \textit{STAR} protein caused by a heterozygous polymorphism in the \textit{STAR} gene [4].

Here we also present a unique case of chronic adrenal insufficiency and DSD 46 XY caused by dominant-negative mutation in the \textit{STAR} gene.

Case description

Medical record: the child was born to non-blood-related parents. It was the first delivery; the child was born large (weight 4110 g, height 54 cm) at 41 week. The Apgar score was 7/8 points. Ambiguous genitalia were obvious at birth: the penis-like clitoris, the scrotum was not formed; the urethra opened under the clitoral head, bilateral absence of testicles, urogenital sinus. The condition...

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of the child rapidly deteriorated on the second postnatal day: hypoglycemia 0.6—1 mmol/l, hyponatremia 118—121 mmol/l (the normal range is 135—150), hyperkalemia 8—8.5 mmol/l (3.8—5.5), and increasing dehydration. The condition stabilized secondary to intramuscular injection of Solu-Cortef. On examination: ACTH <5 pg/ml and Cortineff 50 μg/day: ACTH <5 pg/ml and absence of severe worsening of adrenal insufficiency symptoms (adrenal crisis) over the entire follow-up. The patient was indicated.

Due to the presence of a rare combination of primary adrenal insufficiency with DSD 46XY, molecular-genetic assay using high-throughput parallel sequencing (Ion Torrent) was performed using an author’s panel “Adrenal Insufficiency, Electrolytic Disorders” which was created in Endocrinology Research Centre, Moscow. A heterozygous mutation c.65-2A>G was revealed in the STAR gene that disrupts splicing site. This mutation was not detected in the mother and the father suggesting its de novo emergence. A similar heterozygous mutation in the STAR gene was previously described by Baquedano et al. [4], wherein the mutant protein exhibited reduced StAR activity in a dominant-negative manner.

**CONCLUSION**

this case report is unique as it involves a rare type of a mechanism in development of congenital adrenal hyperplasia associated with a heterozygous mutation in the **STAR** gene. Enzymes are known to rely upon the quantity of enzymes in the development of a disease whereas transport proteins for normal function are more dependent on dimensional configuration which is formed by both alleles. In our patient, mutation in one allele was responsible for the development of the disease. Abnormal protein structure instead of total lack of the protein accounts for a low glucocorticoid requirement in the patient, which indicates incompletely impaired transport of cholesterol into the inner mitochondrial membrane.

This case report focuses on the importance of molecular-genetic diagnostics of rare combinations of sex development disorder with impaired adrenal function. Molecular-genetic diagnostics can predict the course of disease and be used in medical-genetic counseling.

**Additional information**

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Consent of the patient. A legally authorized representative of the patient signed an informed consent on the publication of medical data in this paper in the journal Problems of Endocrinology.

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REFERENCES


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