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Nonclassic lipoid adrenal hyperplasia with R272C *STAR* mutation: a case report

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Disclosure Statement The authors have nothing to declare.

Background

The steroidogenic acute regulatory protein (StAR) is crucial for the transportation of cholesterol to the mitochondria, where it is converted to pregnenolone. Complete loss of StAR function impairs adrenal and gonadal steroidogenesis since the fetal period, called congenital lipoid adrenal hyperplasia (CLAH). Nonclassic lipoid adrenal hyperplasia (NCLAH) is a recently recognized disorder characterized by partial StAR function[1)], and several mutations associated with NCLAH have been reported[2)].

Objective

To report clinical, biochemical, genetic, and functional data for a mutation of the *STAR* gene.

Patient

The patient was a 12-year-old Japanese male. He was born with normal male genitalia, and had hyperpigmentation.

At 2 years of age, he presented with adrenal failure accompanied by infection. His prior medical history was uneventful. Serum cortisol was undetectable, and did not respond to ACTH stimulation. Aldosterone showed a low response in the furosemide-upright test, and a CT scan showed normal-sized adrenal glands. He was diagnosed as familial glucocorticoid deficiency, and treated with hydrocortisone.

At 11 years of age, he had normal pubertal development, but his serum dehydroepiandrosterone sulfate (DHEA-S) level was inappropriately low.

At 2 yr of age

Rapid ACTH stimulation test (0.25 mg/m

		0	30	60
F	mcg/dL	1.1	1.2	1.1

Furosemide-upright test (1 mg/kg)

		0	30	60	90	120
PRA	ng/mL/h	37.6	77.3	77	67.4	77.1
Ald	pg/mL	25	48	64	63	68

DHEA-S	37	mcg/dL
MC2R gene	no mutation	

At 11 yr of age

ACTH	848	pg/mL
F	< 1.0	mcg/dL
17OHP	0.2	ng/mL
DHEA-S	14	mcg/dL
LH	4.19	mIU/mL
FSH	3.21	mIU/mL
T	1.99	ng/mL
Testis	R 8 mL	L 8 mL

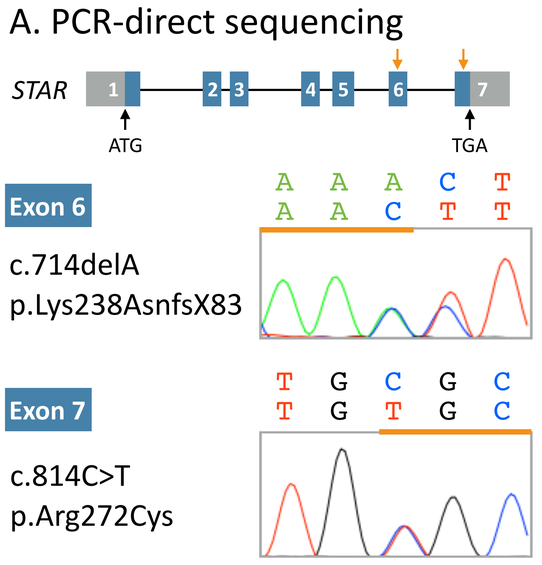
Methods

We analyzed all coding exons and flanking introns of *STAR* by PCR-direct sequencing, the ability of StAR mutants to convert cholesterol to pregnenolone, protein expression, and subcellular localization. Pregnenolone was determined by LC-MS/MS.

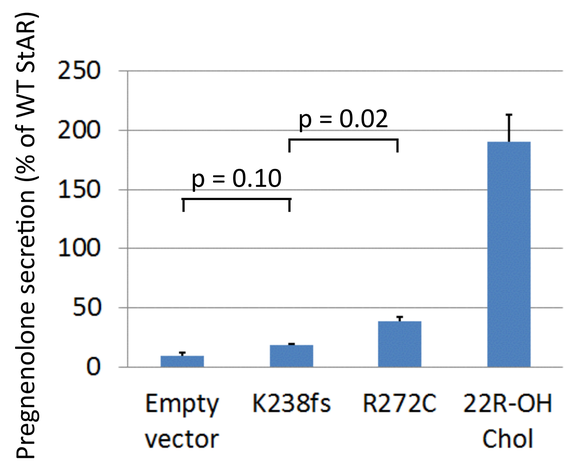
Results

Compound heterozygous mutations, K238fs and R272C, were identified (Fig. A). The K238fs and R272C mutants retained 18.3 ± 1.3% and 39.0 ± 3.9% of the wild-type StAR activity, respectively (Fig. B). Western blot analysis and subcellular localization revealed no significant differences between wild-type and these mutants (Fig. C, D).

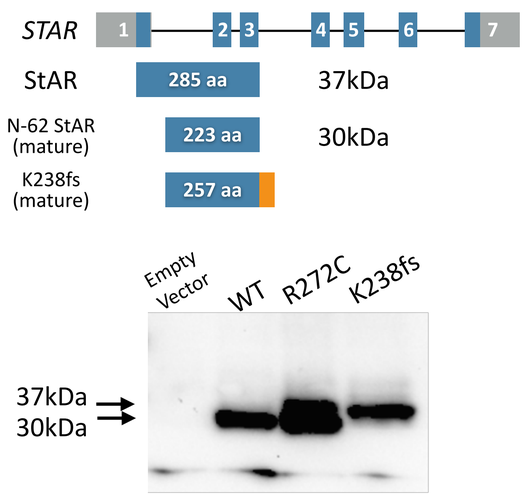
A. PCR-direct sequencing



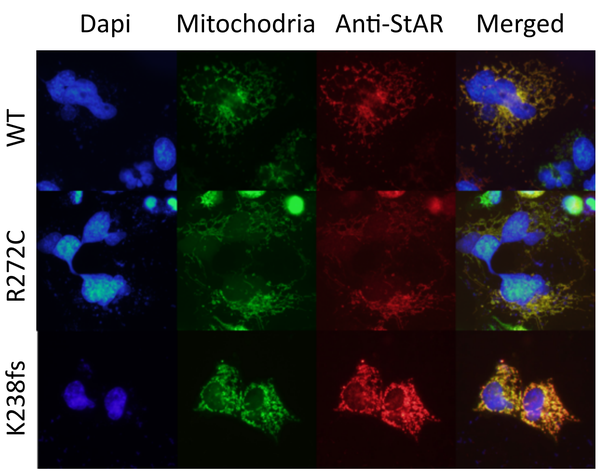
B. *In vitro* functional analysis



C. Protein expression



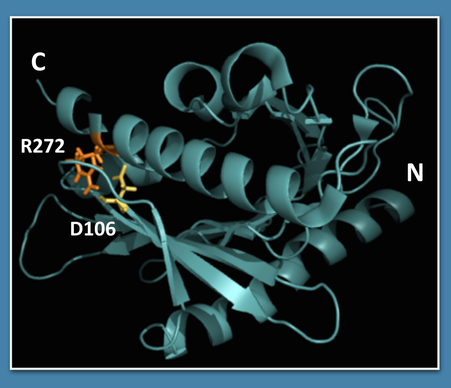
D. Subcellular localization



Discussions

Our patient presented with adrenal failure at 2 years of age and normal male external genitalia. This mild phenotype may be related to residual StAR activity.

Previous reports showed that *STAR* mutations in individuals with NCLAH retained 3–50% of *in vitro* WT activity[2)]. R272C had 39% activity, which may have contributed to the mild phenotype. The D106/R272 hydrogen bond forms a part of the cholesterol binding pocket[3)]. R272C was predicted to disrupt the hydrogen bond, and undergo a conformational change induced by the disulfide bond. On the other hand, StAR activity did not differ significantly between K238fs and an empty vector. K238fs/Q258X is associated with CLAH[4)], so K238fs was considered a null mutation, clinically.



The carrier frequency for these mutations may be high in Japan as Q258X. K238fs/Q258X was previously reported in Japanese patients with CLAH[4)], and R272C/Q258X was recently reported in a Japanese patient with primary adrenal failure without enzymatic defect[5)].

Conclusions

The patient with R272C mutation retained partial StAR activity, consistent with the mild clinical manifestations observed.

References

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