CONGENITAL ADRENAL HYPERPLASIA CAUSED BY HOMOZYGOUS PATHOGENIC VARIANT IN THE *HSD3B2* GENE

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INTRODUCTION

Congenital Adrenal Hyperplasia (CAH) is an autosomal recessive disorder caused by impairment of one of the enzymes involved in the steroidogenesis pathway.

3β hydroxysteroid dehydrogenase type 2 deficiency (3βHSD2 deficiency) is a rare form of CAH (<0.5%) due to pathogenic variants in the *HSD3B2* gene encoding for the enzyme Type 2 3β-hydroxysteroid dehydrogenase Δ4–Δ5 isomerase (3βHSD2).

CASE PRESENTATION

A 15-day old female neonate was referred from a local hospital to the Pediatric Department of "G. Gennimatas" Hospital of Thessaloniki

- ✓ due to dehydration with hyponatremia and hyperkalemia
- ✓ hypertrophy of clitoris and labia majora

The patient was the first child of consanguineous parents

The biochemical and hormonal profile was consistent with CAH (Table 1).

She was immediately commenced on hydrocortisone (15mg/m^2/day) and fludrocortisone (200mg/day) with a good response.

Table 1. Biochemical and hormonal profile of patient

Biochemical and Hormonal findings	Value
17-OH progesterone (ng/ml)	69.5
Cortisol (μg/dl)	3.9
ACTH (pg/ml)	621
Potassium (mmol/L)	7.1
Sodium (mmol/L)	123
Testosterone (ng/dl)	309
DHEAS (μg/dl)	>1500
Androstenedione (ng/ml)	18.9
Plasma Renin Activity (PRA) (ng/ml/h)	40.4
Aldosterone (pg/ml)	289

METHOD

- PCR and bidirectional sequencing for the *CYP21A2*, *CYP11B1* and *HSD3B2* genes was carried out sequentially
- MLPA analysis was also performed for the identification of Copy Number Variations (CNVs) in the *CYP21A2* gene (P050-C1 CAH).

RESULTS

Molecular investigation of the *CYP21A2* gene

The index patient *carried the p.Q318X* pathogenic variant on a duplicated *CYP21A2* gene in heterozygosity.

Both patients were found to have the *p.Q318X* pathogenic variant on a duplicated *CYP21A2* gene in heterozygosity.

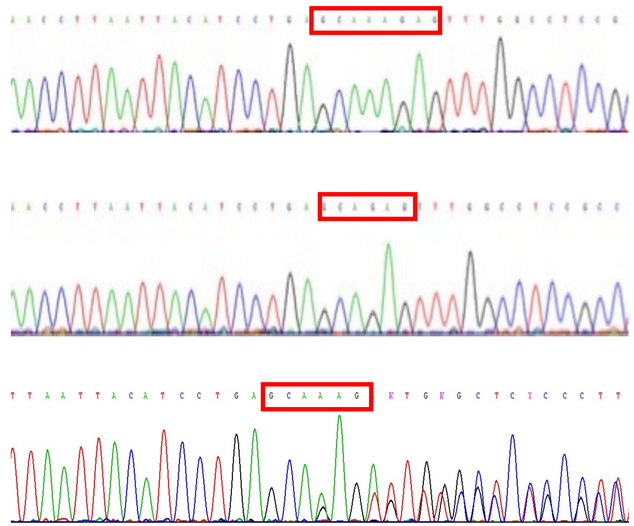
Molecular investigation of the *CYP11B1* gene

No pathogenic variants were detected in the *CYP11B1* gene on the index patient.

Molecular investigation of the *HSD3B2* gene

The index patient carried the homozygous 2bp deletion at codon 273 (p.[Lys273Argfs*7];[Lys273Argfs*7]). Parents were found to harbor the p.Lys273Argfs*7 in heterozygosity (Figure 1).

Figure 1. The chromatogram of the p.Lys273Argfs*7 identified in the *HSD3B2* gene. In the first row is the wild type sequence and in the second and the third row is the p.Lys273fs shown in homozygosity and heterozygosity respectively



CONCLUSIONS

In this study

We present a patient with a homozygous deletion in the *HSD3B2* gene **(p.Lys273Argfs*7)**

The **p. Lys273Argfs*7** has been previously reported

- ❑ In homozygosity in 3 male patients with severe salt wasting CAH
- ❑ In compound heterozygosity with p.Thr318fs variant in a female patient presenting with salt wasting CAH, pigmentation and mildly enlarged clitoris at birth.

This case is of the first female patient with a homozygous **p.Lys273Argfs*7** in the *HSD3B2* gene.

Molecular investigation is important

- ✓ to confirm clinical diagnosis
- ✓ provide proper treatment and genetic counseling to the family.

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