CONGENITAL ADRENAL HYPERPLASIA CAUSED BY COMPOUND HETEROZYGOSITY OF TWO NOVEL CYP11B1 GENE VARIANTS

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INTRODUCTION

Congenital adrenal hyperplasia (CAH) is an autosomal recessive disorder caused by pathogenic variants in seven genes involved in the cortisol and aldosterone biosynthetic pathway. 11β-hydroxylase deficiency (11βOHD), is attributed to pathogenic variants in the CYP11B1 gene encoding for the enzyme 11β-hydroxylase (11βOH).

CASE PRESENTATION

A female patient was referred to the pediatric endocrinologist due to syncopal episode.

She presented:
- Premature adrenarche at the age of 6 years
- Menarche at the age of 12 years
- Height of 154.5cm, weight of 50kg (age 13 years old)
- Acne, hirsutism, citoromegaly and normal blood pressure.
- Laboratory findings are shown in Table 1.

The mother of index patient:
- Diagnosed with CAH (age of 10 years)
- Under treatment with methylprednisolone.
- Molecular investigation of the CYP21A2 gene was negative.

METHODS

PCR and bidirectional sequencing of the CYP11B1 gene

Novel variants were evaluated:
- By 7 bioinformatics software tools
- Classified according to the ACMG guidelines
- Frequency of novel variants searched in the Genome Aggregation Database.

RESULTS

Molecular investigation of the CYP11B1 gene

- Patient and her mother were heterozygotes for the p.K370Q (exon 6) and the p.G379S (exon 7)
- Father was heterozygote for the p.K370Q (p.[K370Q];[=]).
- Segregation analysis of the two siblings revealed that
  - Patient and her mother were compound heterozygotes for p.K370Q and p.G379S
  - Father was heterozygote for the p.K370Q (p.[K370Q];[G379S]) (Figure 1).

Variant p.K370Q

- Predicted pathogenic by the seven tools employed
- Classified as Variant of Uncertain Significance (VUS) - ACMG criteria

Variant p.G379S

- Predicted as pathogenic by 3/7 tools
- Classified as likely pathogenic - ACMG criteria.

None of the variants were present in gnomAD database (Table 2).

CONCLUSIONS

In this study

- In this study two novel CYP11B1 gene variants, p.K370Q and p.G379S, were identified in an adolescent female and her mother previously diagnosed with CAH, without genetic etiology.

In cases with a high suspicion for CAH and absence of CYP21A2 gene pathogenic variants, molecular analysis of CYP11B1 should be taken into consideration.

Molecular investigation of the CYP11B1 gene revealed two novel pathogenic variants in the index patient and her mother confirming the clinical diagnosis and allowing for proper genetic counseling of the family.

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