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

E. FYLAKTOU, P. SMYRNAKI , A. SERTEDAKI, and CH. KANAKA-GANTENBEIN

First Department of Paediatrics, Medical School, National and Kapodistrian University of Athens, Athens, Greece,"Agia Sophia" Children's Hospital, Athens, Greece

ESPE 2021 The 59th Annual Meeting Online 22-26 September 2021

HELLENIC REPUBLIC National and Kapodistrian University of Athens EST. 1837

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, clitoromegaly 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.

Table 1. Hormonal profile and ACTH stimulation test of the index patient

Hormonal findings	Value	Normal Range
17-OH progesterone (ng/ml)	**5.36**	0.07 - 1.7
Testosterone (ng/ml)	**0.57**	0.046 - 0.383
DHEA-S (μg/ml)	**4.02**	0.32-3.73
Androstenedione (ng/ml)	**19.44**	0.2-1.9
11- deoxycortisol (nmol/L)	**98.1**	1.4-5
11-deoxycorticosterone (pg/ml)	**1808**	40-200
Aldosterone (ng/dl)	**2.1**	4-31
Plasma Renin Activity (PRA) (ng/ml/h)	0.2	0.15- 6.56
Cortisol (ng/ml)	177.38	43-240
Adrenocorticotropic Hormone (ACTH) (pg/ml)	**216**	6-60

ACTH stimulation test		
Time (min)	17-OH progesterone (ng/ml)	Cortisol (μg/dl)
0	2.85	10.3
30	4.00	11.2
60	4.83	12.5

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** (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).

Fig. 1 Family pedigree with the novel *CYP11B1* gene variants identified

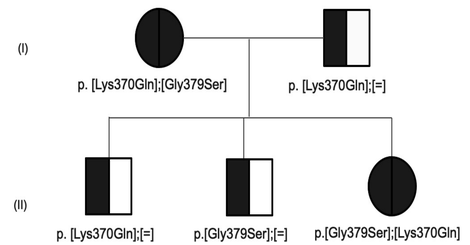

Table 2. In silico analysis of *CYP11B1* gene novel variants identified

CYP11B1 Variant	Polyphen -2	SIFT	Mutation Taster	UMD predictor	Panther	Pmut	ΔΔG calculation	gnomAD Frequency		ACMG classification
							Dynamut (kcal/mol)	Exome	Genome	
p.K370Q (c.1108A>C)	Probably Damaging	Affect protein function	Disease causing	Probably pathogenic	Probably Damaging	Disease	-0.165 destabilization	Not reported (mean coverage 84.5)	Not reported (mean coverage 29.8)	VUS (Class 3)
p.G379S (c.1135G>A)	Probably Damaging	Tolerated	Disease causing	Polymorphism	Probably Damaging	Neutral	0.513 no destabilization	Not reported (mean coverage 69.3)	Not reported (mean coverage 30.8)	Likely pathogenic (Class 4)

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.

ACKNOWLEDGEMENTS

The authors would like to thank the family for participating in this study.

The authors would also like to thank Mrs Eleni Golfinopoulou for her expert technical assistance.

CONTACT INFORMATION

Eirini Fylaktou

First Department of Paediatrics, Medical School

National and Kapodistrian University of Athens, "Agia Sophia" Children's Hospital

E-mail: efylaktou@med.uoa.gr