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TEACHING CASE PRESENTATIONS

Congenital adrenal hyperplasia caused by compound heterozygosity of two novel *CYP11B1* gene variants

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Abstract

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

Case presentation A 13-year-old girl was referred to the pediatric endocrinologist due to a syncopal episode. She is the third child of non-consanguineous parents. She presented with premature adrenarche at the age of 6 years and menarche at the age of 12 years. On physical examination, her height was 154.5 cm and weight 50 kg, while she presented with acne, hirsutism, clitoromegaly, and normal blood pressure. Laboratory investigation revealed increased androgen levels and poor cortisol response to the ACTH stimulation test. From the family history, the mother was diagnosed with CAH at the age of 10 years and was under treatment with methylprednisolone. Previous molecular investigation of the *CYP21A2* gene was negative. Due to the increased androstenedione levels in the index patient, the suspicion of 11βOH was raised, and she was investigated for 11-deoxycortisol, 11-deoxycorticosterone, and *CYP11B1* gene pathogenic variants. The patient and her mother were found to be compound heterozygous for two novel variants of the *CYP11B1* gene.

Conclusion We present a case of CAH due to compound heterozygosity of two novel pathogenic variants of the *CYP11B1* gene, emphasizing the importance of molecular investigation in order to confirm clinical diagnosis and allow proper genetic counseling of the family.

Keywords Congenital adrenal hyperplasia · 11β-hydroxylase deficiency · *CYP11B1* gene mutations

Introduction

Congenital adrenal hyperplasia (CAH) is an autosomal recessive disorder caused by pathogenic variants in genes involved in the cortisol and aldosterone biosynthetic pathway. Most cases (>90%) are attributed to gene variants of the *CYP21A2* gene. The second most common form (0.2–8%) is attributed to pathogenic variants of the *CYP11B1* gene encoding for the enzyme 11βOH [1–3].

The 11βOH enzyme converts 11-deoxycortisol and 11-deoxycorticosterone (DOC) to cortisol and corticosterone, respectively. Defective 11βOH activity leads to the accumulation of steroid precursors and reduced cortisol levels, resulting in increased ACTH secretion. CAH, due to either 21 hydroxylase deficiency (21OHD) or 11β-hydroxylase deficiency (11βOHD), is clinically classified into classic and non-classic forms. Patients with the classic form of 11βOHD present with features of hyperandrogenism that may be diagnosed at any age from infancy to adulthood. Female patients present with varying degrees of external genitalia virilization [4], while males present with enlarged penis [4]. Both sexes present with precocious adrenarche that may subsequently drive the development of precocious puberty, accelerated skeletal maturation leading to short adult height, and, in two-thirds of the cases, elevated blood pressure [4, 5].

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Table 1 Patient's hormonal profile and ACTH stimulation test

Hormonal profile		
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

Values outside the normal range are depicted in bold

In the non-classic form, symptoms appear later in life and include non-GnRH-dependent precocious puberty or signs of mild hyperandrogenism. Symptoms resemble those of polycystic ovarian syndrome (PCOS), and in many cases, the patient is misdiagnosed [3]. The biochemical diagnosis is based on raised serum 11-deoxycortisol and 11-deoxycorticosterone levels together with increased adrenal androgens [3].

We herein describe the molecular investigation of a patient with CAH due to 11βOHD.

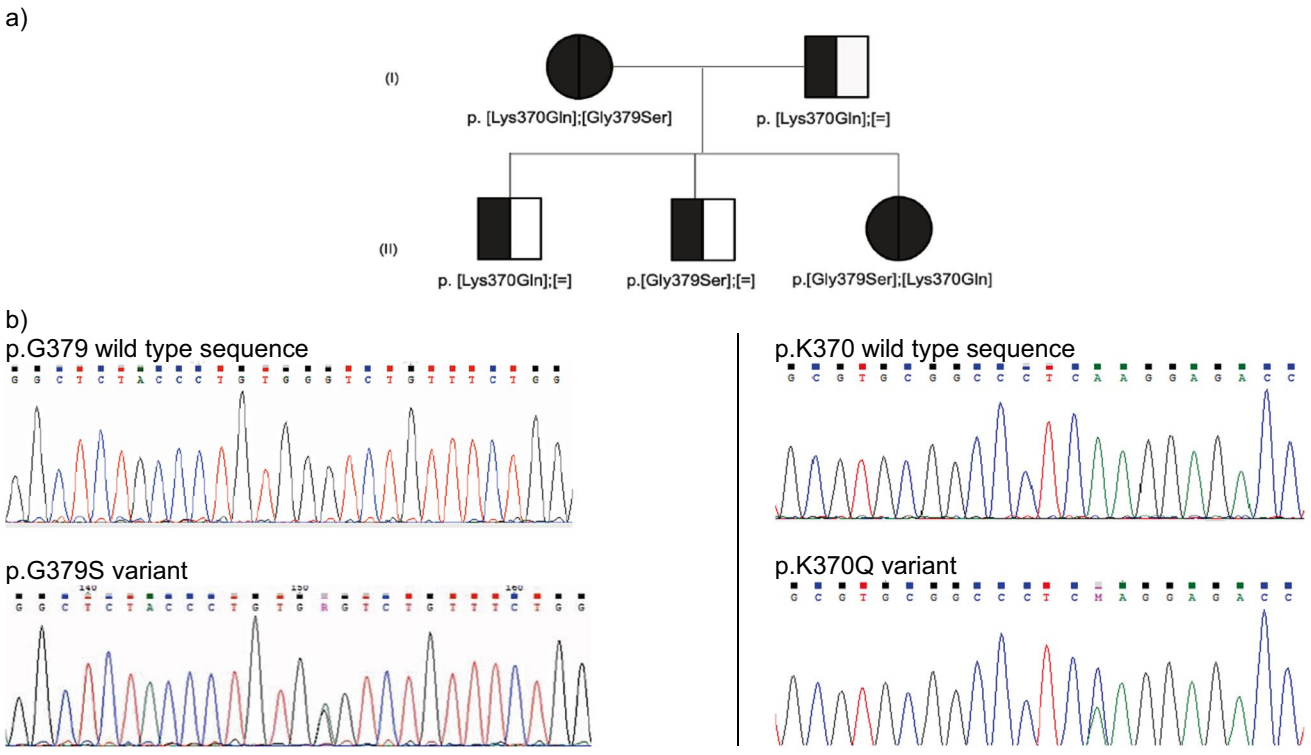

Fig. 1 **a** Family pedigree with the novel *CYP11B1* gene variants identified. **b** The chromatogram of the novel variants identified. In the first row, wild-type sequences, and in the second row, the p. G379S and the p.K370Q variant are shown

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)

Case report

A female patient (46, XX) was referred to the pediatric endocrinologist due to a syncopal episode. She is the third child of a non-consanguineous marriage, born full term with a birth weight of 3080 gr. She had no perinatal problems. At the age of 6 years, premature adrenarche was observed, and menarche occurred at the age of 12 years with no menstrual irregularities. On physical examination at the age of 13 years, her height was 154.5 cm and weight 50 kg, while she presented with acne, hirsutism, clitoromegaly, and normal blood pressure (90/70 mm Hg). Laboratory investigation revealed increased androgen levels and a poor cortisol response to the ACTH stimulation test, as depicted in Table 1. From the family history, the mother was diagnosed with CAH at the age of 10 years and had reportedly undergone plastic surgery of the external genitalia. She was under treatment with methylprednisolone. Molecular investigation of the *CYP21A2* gene previously performed in the Laboratory of Molecular Endocrinology, First Department of Paediatrics, Medical School, National and Kapodistrian University of Athens, "Agia Sophia" Children's Hospital, Athens, Greece, in the mother and her two older sons revealed no pathogenic variants. Because of the raised androstenedione levels and the absence of *CYP21A2* gene pathogenic variants in the mother and the two older siblings tested, the suspicion of CAH due to 11βOHD was raised, and the proband was investigated for 11-deoxycortisol and 11-deoxycorticosterone levels and *CYP11B1* gene pathogenic variants (Table 1).

Molecular analysis

Genomic DNA was isolated from peripheral blood samples of the patient and all family members. PCR and bidirectional sequencing of the 9 exons and flanking intronic sequences of the *CYP11B1* gene was carried out.

Analysis of the *CYP11B1* gene was based on the NCBI Reference Sequence NM_000497, and variant nomenclature was according to the HGVS Sequence Variant Nomenclature guidelines [6].

Novel variants were evaluated employing 7 bioinformatics software tools and classified according to the ACMG guidelines for the interpretation of sequence variants [7]. The frequency of novel variants was searched in the Genome Aggregation Database (gnomAD; exome and genome) [8].

The sequencing analysis of the patient and her parents revealed the presence of two novel variants, p.K370Q (c.1108A > C) in exon 6 and p.G379S (c.1135G > A) in exon 7 of the *CYP11B1* gene. The patient and her mother

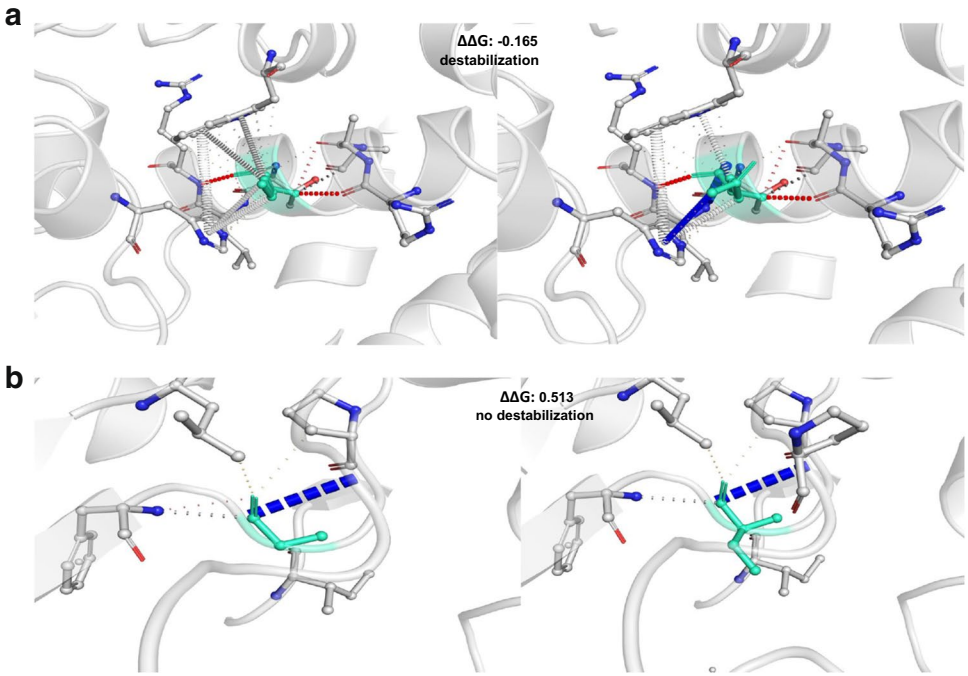

Fig. 2 3D models for *CYP11B1* gene variants p.K370Q and p.G379S. **a** CYP11B1 Variant p.K370Q 3D model. Interactions are presented for the wild type residue (left) and the mutated residue (right). Wild-type and mutated residues are presented as light green sticks. Surrounding residues involved in any type of interaction with the subject residues are also represented as sticks. There are differences observed in the formation of hydrophobic contacts (green) and halogen bonds (blue) among the wild-type and mutated residues. Figure was generated by Dynamut [9]. **b** CYP11B1 Variant p.G379S 3D model. Interactions are presented for the wild-type residue (left) and the mutated residue (right). Wild-type and mutated residues are presented as light green sticks. Surrounding residues involved in any type of interaction with the subject residues are also represented as sticks. The only difference observed is the formation of water-mediated hydrogen bonds (light red). Figure was generated by Dynamut [9]

were found to be heterozygous for the two novel variants identified, while the father was found to be heterozygous for p.K370Q (c.1108A > C). In order to further investigate the segregation of the novel variants, sequencing analysis was performed in the two older siblings, which revealed one brother to be heterozygous for p.K370Q (c.1108A > C) and the other for p.G379S (c.1135G > A). Taking these results into consideration, it was concluded that the mother and the patient were compound heterozygotes for p.K370Q (c.1108A > C) and p.G379S (c.1135G > A). The family pedigree and electropherograms of novel variants identified are shown in Fig. 1. It is of interest that both parents carry the same rare variant p.K370Q, although they are not related; however, they both originate from the same geographic area.

Variant p.K370Q was predicted as pathogenic by all 7/7 bioinformatics tools and classified as a variant of uncertain significance (VUS) according to the ACMG criteria (Table 2, Fig. 2). Variant p.G379S was predicted as pathogenic by 3/7 tools and classified as likely pathogenic according to the ACMG criteria (Table 2, Fig. 2). None of the variants were present in the gnomAD database.

Discussion

CAH is a group of autosomal recessive disorders characterized by impaired cortisol synthesis with an incidence ranging from 1:10,000 to 1:20,000 live births. To date, pathogenic variants in seven genes have been identified as being responsible for CAH caused by pathogenic variants in the *CYP21A2* gene, the gene encoding the adrenal steroid 21OH that accounts for approximately 95% of all CAH cases.

Pathogenic variants in the *CYP11B1* gene encoding the enzyme 11βOH are the second most common cause of CAH [2, 10–12]. To date, more than 100 pathogenic variants have been identified in the *CYP11B1* gene with no more than 13 pathogenic variants being responsible for the development of non-classic 11βOHD [3].

Clinical presentation ranging from mild to severe can be manifested at any age during infancy, childhood, adolescence, or later life. The clinical severity and biochemical findings may differ significantly, even within members of the same family bearing the same genotype, indicating a phenotypic variability in patients with 11βOHD (Table 3) [10, 13–15]. Thus, no genotype phenotype correlations can

Table 3 List of homozygous pathogenic variants and their clinical presentation in classic and non-classic form of 11βOHD based on literature review

Pathogenic variant	Clinical presentation	Reference
Classic		
p.G379V	Female (46,XX): Ambiguous genitalia Male (46, XY): Hyperpigmentation Both sexes: Mild hypertension, peripheral precocious puberty, hyperpigmentation, advanced bone age	[16–19]
p.T318M	Female (46,XX): Ambiguous genitalia Male(46, XY): Peripheral precocious puberty, accelerated growth Both sexes: Hypertension	[10, 18, 20, 21]
p.R448H	Female (46,XX): Ambiguous genitalia Male (46, XY): Enlarged penis, small testes, advanced bone age, premature pubarche Both sexes: Hypertension	[10, 13, 22]
p.R454C	Female (46,XX): Ambiguous genitalia, accelerated growth, amenorrhea, clitoral hypertrophy	[23]
p.R141X	Female (46,XX): Ambiguous genitalia, sexual precocity, amenorrhea, hypertension Male (46, XY): Premature and excessive development of external genitalia	[24–27]
p.Q356X	Female (46,XX): Ambiguous genitalia Male (46, XY): Peripheral precocious puberty Both Sexes: Accelerated growth	[14, 17, 28, 29]
c.53_54insT	Female (46,XX): Ambiguous genitalia Male (46,XY): Precocious puberty Both sexes: Accelerated growth, hypertension	[28, 30]
Non-classic		
p.L489S	Female (46,XX): Peripheral precocious puberty, hyperandrogenic infertility	[31]
p.R143W	Both sexes: Hirsutism and advanced bone age	[32]
p.P159L	Female (46,XX): Premature adrenarche	[33]

be established in 11βOHD as in the case of 21 hydroxylase deficiency.

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.

Variant p.G379S, classified as likely pathogenic, is located on a loop between K-helix and β1-3 sheet, adjacent to the substrate-binding site. A substitution of glycine by valine at amino acid 379 has been reported [16–19, 24] and speculated to affect the active site of the enzyme [17]. The p.G379V variant has been found in homozygosity in 10 female patients (46, XX) presenting with ambiguous genitalia, and it was associated with advanced bone age and relatively mild hypertension [18]. Grade 3 hypertension was also observed in patients harboring the p.G379V pathogenic variant in homozygosity [19].

Variant p.K370Q is classified as VUS according to the ACMG criteria and was found to be pathogenic by all in silico tools.

It has recently been shown that K370 residue of P450 11B1 (11βOH, CYP11B1), which is located within a basic patch on the K helix, is one of the key residues creating hydrogen bonds with residue D76 of adrenodoxin (Adx) [34]. Adx, a redox partner of P450 11B1, P450 11B2, and P450 17A1, is involved in steroid hormone biosynthesis by acting as an electron shuttle between ferodoxin reductase and mitochondrial P450s [35]. Therefore, we may assume that lysine substitution by glutamine at residue 370 may interfere with P450 11B1-Adx interaction.

We may thus hypothesize that variants p.K370Q and p.G379S, when present in compound heterozygosity, are responsible for the 11βOHD of our patient.

Overall, further in vitro studies are required to delineate the pathogenicity of these variants and clarify their impact on the enzymatic activity.

The patient described herein presented with mild virilization, elevated androgen levels, and normal blood pressure; therefore, her phenotype was indicative of the non-classic form of 11βOHD. Moreover, genetic diagnosis of the index patient also facilitated the identification of her mother's genetic etiology after a long delay. This is the second 11βOHD case presented in the Greek population. The first case also harbored two novel pathogenic variants in a girl with 11βOHD presenting with highly elevated levels of steroid hormones and prenatal mild virilization of the external genitalia [36].

Clinical manifestation of 11βOHD exhibits a wide range of signs and symptoms, and, in many cases, diagnosis can be missed due to the mildly elevated 17-hydroxyprogesterone levels [1, 3, 32]. Elevated basal and ACTH stimulated 11-deoxycortisol and 11-deoxycorticosterone levels (three times above the 95th percentile for the general population) have been suggested as diagnostic clues; however, they are not always specific for 11βOHD [37–39]. In our case, 11-deoxycortisol and 11-deoxycorticosterone levels were indicative of the underlying genetic cause of CAH. Therefore, it is of great importance to carefully assess all clinical and laboratory findings to identify the specific genetic defect.

In conclusion, in cases with a high suspicion for CAH and absence of *CYP21A2* gene pathogenic variants, molecular analysis of *CYP11B1* should be taken into consideration. In this study, molecular investigation of the *CYP11B1* gene revealed two novel pathogenic variants in the index patient and her mother, thus confirming the clinical diagnosis and allowing for proper genetic counseling of the family.

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Author contribution I.F.: genetic analysis and writing of the manuscript. P.S: referred the patient and provided the clinical information. A.S.: genetic analysis, reviewing and editing of the manuscript. M.D.: design of the genetic study and genetic analysis. Ch.K.G: reviewing and editing of the manuscript.

Declarations

Consent to participate Written informed consent was obtained from the parents for participation in this study.

Consent for publication Written informed consent was obtained from the parents for publication of this case report.

Conflict of interest The authors declare no competing interests.

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