ESC European Society of Cardiology

European Heart Journal - Case Reports (2024) **8**, ytae307
https://doi.org/10.1093/ehjcr/ytae307

CASE REPORT
Inherited cardiac conditions/cardiomyopathies

Rare secondary hypertension caused by compound heterozygous *CYP17A1* mutations: a case report

Jianying Sun †, Tao Ma †, Tao Jiang, Yazhe Ma *, and Jie Fan *

Department of Cardiology, The First People's Hospital of Yunnan Province, The Affiliated Hospital of Kunming University of Science and Technology, 157 Jinbi Road, Kunming 650032, Yunnan, China

Received 27 December 2023; revised 14 April 2024; accepted 24 June 2024; online publish-ahead-of-print 29 June 2024

Background 17α-Hydroxylase deficiency, a rare form of congenital adrenal hyperplasia, presents diagnostic and treatment challenges because of the limited number of cases reported.

Case summary This report discusses the case of a 17-year-old Chinese girl who suffered from unexplained dizziness, headaches, and high blood pressure. She had amenorrhoea during puberty and had been diagnosed with ovarian delay. Initially, she was diagnosed with hypertension and received three antihypertensive medications. However, her blood pressure remained poorly controlled. Gene sequencing revealed 17α-hydroxylase deficiency caused by compound heterozygous mutations in *CYP17A1*. One of the mutation sites, potentially novel, has not been reported previously. Subsequently, dexamethasone therapy was initiated, her blood pressure was controlled, and the symptoms disappeared. During the 1-year follow-up, her blood pressure remained normal, and the symptoms did not recur.

Discussion 17α-Hydroxylase deficiency is a rare cause of secondary hypertension. Despite the low prevalence, it should not be overlooked in younger patients.

Keywords 17α-Hydroxylase deficiency • Case report • Congenital adrenal hyperplasia • Heterozygous mutation • Hormone replacement therapy • Secondary hypertension

ESC curriculum 8.2 Arterial hypertension • 9.3 Peripheral artery disease

Learning points

- *CYP17A1* mutation is a rare cause of secondary hypertension, with ∼100 known mutations; however, few compound heterozygous mutations have been reported.
- Its presence should prompt clinical suspicion for secondary hypertension caused by 17α-OHD when patients have delayed puberty and/or primary amenorrhoea or sexual infantilism, with or without hypokalaemia.
- Steroid replacement is the primary treatment for 17α-OHD and requires take for life.

* Corresponding authors. Tel: 86+13608811433, Email: fanj913@sina.com; Tel: 86+13522975699, Email: yazhe_ma@163.com
† J.S. and T.M. contributed equally as the first authors.
Handling Editor: Valentina Rossi
Peer-reviewers: Jianzhong Xu; Vasilios Giampatzis; Subhi Akleh; Malak Benabdellah
Compliance Editor: Deepti Ranganathan

Introduction

Congenital adrenal hyperplasia (CAH) is an autosomal recessive genetic disease. Epidemiologically, its prevalence in live-born infants ranges from 1/14 000 to 1/18 000 worldwide.[1] 17α-Hydroxylase deficiency (17α-OHD) is the rarest type of CAH, accounting for only 1% of all CAH cases.[2] 17α-OHD is caused by mutations in *CYP17A1*, which encodes the P450c17 protein, an enzyme crucial in the synthesis of glucocorticoids and sex hormones.[3] 17α-OHD blocks glucocorticoid and sex hormone synthesis pathways and stimulates the overproduction of 11-deoxycorticosterone (DOC) through a non-17α-hydroxylation pathway.[4] As an aldosterone precursor, DOC mimics the effects of mineralocorticoids, increasing blood pressure.[5] 17α-OHD often leads to the mismanagement of hypertension, and >94% of patients were misdiagnosed with hypertension, simple gonadal hypoplasia, and androgen resistance syndrome.[6]

Herein, we describe the case of a young patient with hypertension who was ultimately diagnosed with 17α-OHD, with compound heterozygous *CYP17A1* mutations. One of the mutation sites, potentially novel, has not been reported previously.

Summary figure

Time	Events	Treatment
2017	No menarche	The patient was diagnosed with ovarian retardation.
2019	The patient experienced paroxysmal dizziness, headache, and chest tightness.	No treatment was given.
Early August 2021	Abnormal blood pressure was detected during a test before COVID-19 vaccination.	Nifedipine controlled-release tablet 30 mg orally once daily.
Mid-August 2021	Blood pressure was poorly controlled.	Daily nifedipine controlled-release tablet 30 mg orally, metoprolol sustained release tablet 23.75 mg, and irbesartan 150 mg to control blood pressure.
15 February 2022	Dizziness, headache, chest tightness symptoms, and high blood pressure remained.	Admitted to our cardiac centre and stopped taking metoprolol and irbesartan but continued nifedipine controlled-release tablets 30 mg daily.
18 February 2022	Blood potassium level decreased significantly. CT detected thickening of the left adrenal junction, and other examination results were normal.	Endocrinology consultation and sex hormone and bone age X-ray examinations
2 March 2022	The patient had high levels of 11-deoxycorticosterone, low levels of sex hormones, and prolonged bone age development.	Considering that the patient may have congenital adrenal hyperplasia, chromosome karyotyping and genome sequencing were performed.
2 April 2022	The patient had compound heterozygous *CYP17A1* mutations with a karyotype of 46, XY.	Dexamethasone was administered. The blood pressure returned to normal, and dizziness, headache, and chest tightness disappeared.
22 July 2022	The patient was admitted to the Department of Urology of our hospital.	The patient underwent laparoscopic surgery, and testicular tissue was removed.
February 2023	The patient had a follow-up visit to the heart centre of our hospital.	The patient had normal blood pressure and continued taking dexamethasone.

Case presentation

The patient was a 17-year-old Chinese girl who presented with chronic symptoms of dizziness, headache, and chest tightness but had never been treated. Her blood pressure was abnormally high during a pre-vaccination check-up for COVID-19, with an average blood pressure of 164/114 mmHg. Initially, she was admitted to a local hospital and received antihypertensive treatments, including an oral regimen of nifedipine (extended-release, 30 mg daily), metoprolol (extended-release, 23.75 mg daily), and irbesartan (150 mg daily). However, her blood pressure remained poorly controlled, so she was transferred to our cardiac centre for further treatment.

She had amenorrhoea during puberty and was previously diagnosed with ovarian hypoplasia. At birth, she exhibited external genitalia consistent with a female, and her growth trajectories in height and weight were consistent with those of her female peers. On physical examination, her height and weight were 157 and 42 kg, respectively, with Tanner stages B1 and PH1, and her clitoris measured ~0.5 × 0.4 cm. Ambulatory blood pressure monitoring indicated a significant elevation in the mean blood pressure and 24 h blood pressure load, with an altered circadian rhythm. Electrolyte analysis demonstrated a marked reduction in potassium levels, and abdominal CT detected thickening at the left adrenal junction, with indistinct visualization of the uterus and ovaries. Besides low renin, hypokalaemia, and high adrenocorticotropin (ACTH) levels, results of the other tests such as liver and renal function tests, thyroid function test, measurements of albumin and troponin levels, electrocardiography, transthoracic echocardiography, renal artery and large vessel ultrasonography, and pituitary MRI were normal. Nifedipine was administered to control her blood pressure; however, it was ineffective. Considering the possibility of a rare form of secondary hypertension, further diagnostic tests were conducted.

Skeletal radiography showed delayed bone age, and comprehensive hormone profiling revealed disruptions in the metabolic pathways of mineralocorticoids, sex hormones, and glucocorticoids (*Table 1*). Whole-exome

Table 1 Biochemical and hormonal parameters of the patient

Parameter	Patient	
Age at diagnosis	17	
Height (cm)/weight (kg)	157/42	
Blood pressure (mmHg)	164/114	
Bone age (year)		
Radius, ulna, and small bones, RUS	6	↓
Carpal bones, CARP	11	↓
Karyotype	46,XY	
Na^+/K^+ (mmol/L)	138/2.9	↓
Cortisol (8 a.m. 4.6–19.5 μg/dL)	0.751	↓
ACTH (8 a.m. 7.2–63.3 pg/mL)	316	↑
Cortisone (10–53 ng/mL)	0.000	↓
11-Deoxycorticosterone (<300 pg/mL)	3061.700	↑
Corticosterone (0.18–19.70 ng/mL)	260.400	↑
LH (1.24–8.62 IU/mL)	47.040	↑
FSH (1.27–12.96 mIU/mL)	83.320	↑
TSH (0.27–4.2 mIU/mL)	2.510	
Progesterone (0.10–0.84 ng/mL)	12.100	
PRL (2.64–13.13 ng/mL)	448.570	↑
Oestradiol (<262 pg/mL)	<1.0	
Androstenedione (434–1976 pg/mL)	0.900	↓
Testosterone (0.16–1.33 ng/mL)	<0.087	↓
Renin (4.0–24.0 pg/mL)	0.600	↓
Aldosterone (40–310 pg/mL)	62	
ARR (0–30)	103.330	↑

ACTH, adrenocorticotropic hormone; LH, luteinizing hormone; TSH, thyroid stimulating hormone; FSH, follicle-stimulating hormone; PRL, prolactin; ARP, aldosterone/renin.

sequencing revealed compound heterozygous mutations in *CYP17A1*, with a 46, XY karyotype. c.985_987delinsAA (p.Tyr329Lysfs90) and c.1117del (p.His373Thrfs46) heterozygous mutations were identified, which were inherited from her mother and father, respectively (*Figures 1* and *2*). She was diagnosed with 17α-OHD and started taking dexamethasone (0.75 mg orally daily); consequently, her blood pressure returned to normal, and the symptoms disappeared. Six months later, the patient underwent laparoscopic surgery, and the testicular tissue in the groin area was removed (*Figure 3*). At the 1-year follow-up, her blood pressure remained normal with dexamethasone alone.

Discussion

This report described a patient with a feminine appearance misdiagnosed with hypertension and received inappropriate treatment. The patient had a history of primary adolescent amenorrhoea. After admission, a comprehensive series of diagnostic examinations were performed, which excluded aortitis, aortic stenosis, renal artery stenosis, and primary hyperaldosteronism. Genetic testing ultimately revealed that the patient had 17α-OHD. After diagnosis, all antihypertensive medications were discontinued, and daily oral dexamethasone therapy was started. Subsequently, her blood pressure returned to normal, and the symptoms disappeared.

CYP17A1, located on chromosome 10q24–q25, is linked to ~100 known mutations.[7,8] However, cases involving compound heterozygous mutations are not common. In the present case, the patient's parents had no clinical signs of 17α-OHD, and both only had a single heterozygous mutation in one chromosome, whereas another is normal. However, the patient exhibited heterozygous mutations at two loci on each chromosome.

c.985_987delinsAA mutation is prevalent among Chinese, which disrupts the active site of 17α-hydroxylase.[9] The c.1117del is unreported and unannotated in the ClinVar database; however, it likely was a novel pathogenic mutation site. The deletion of a base pair at this mutation site alters the reading frame, resulting in a cascade of downstream codon changes, and a stop codon appears prematurely in the 46th amino

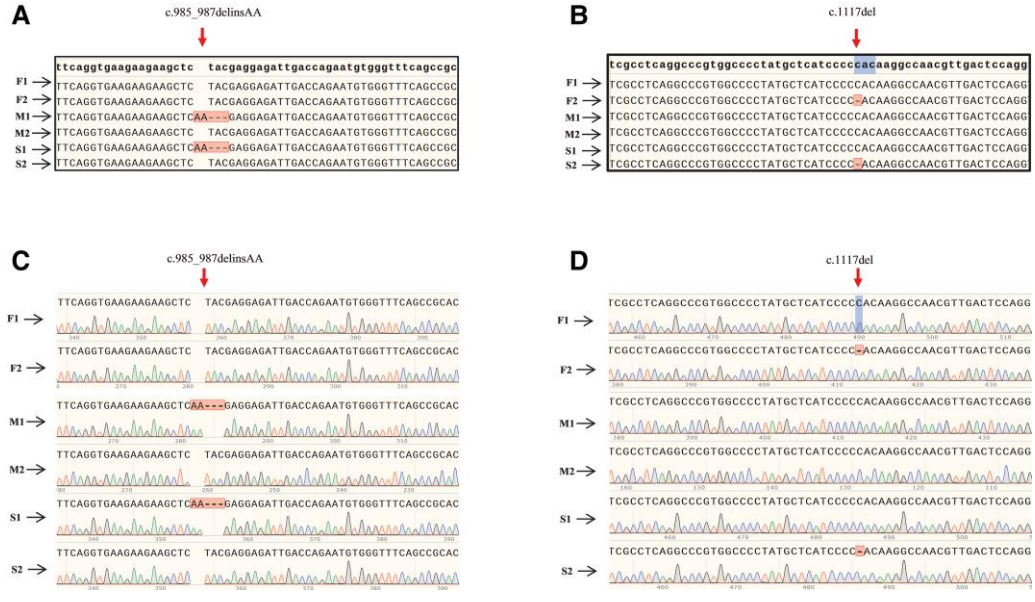

Figure 1 Identification validation of hemizygous variants in *CYP17A1* in patients with 17α-OHD. (*A*) Whole-exome sequencing identified two heterozygous *CYP17A1* variants in the patient. The NCBI reference sequence number of *CYP17A1* is GenBank: NM_000102.4. (*B*) Locations of the identified *CYP17A1* variants in relation to the critical functional domains of *CYP17A1*.

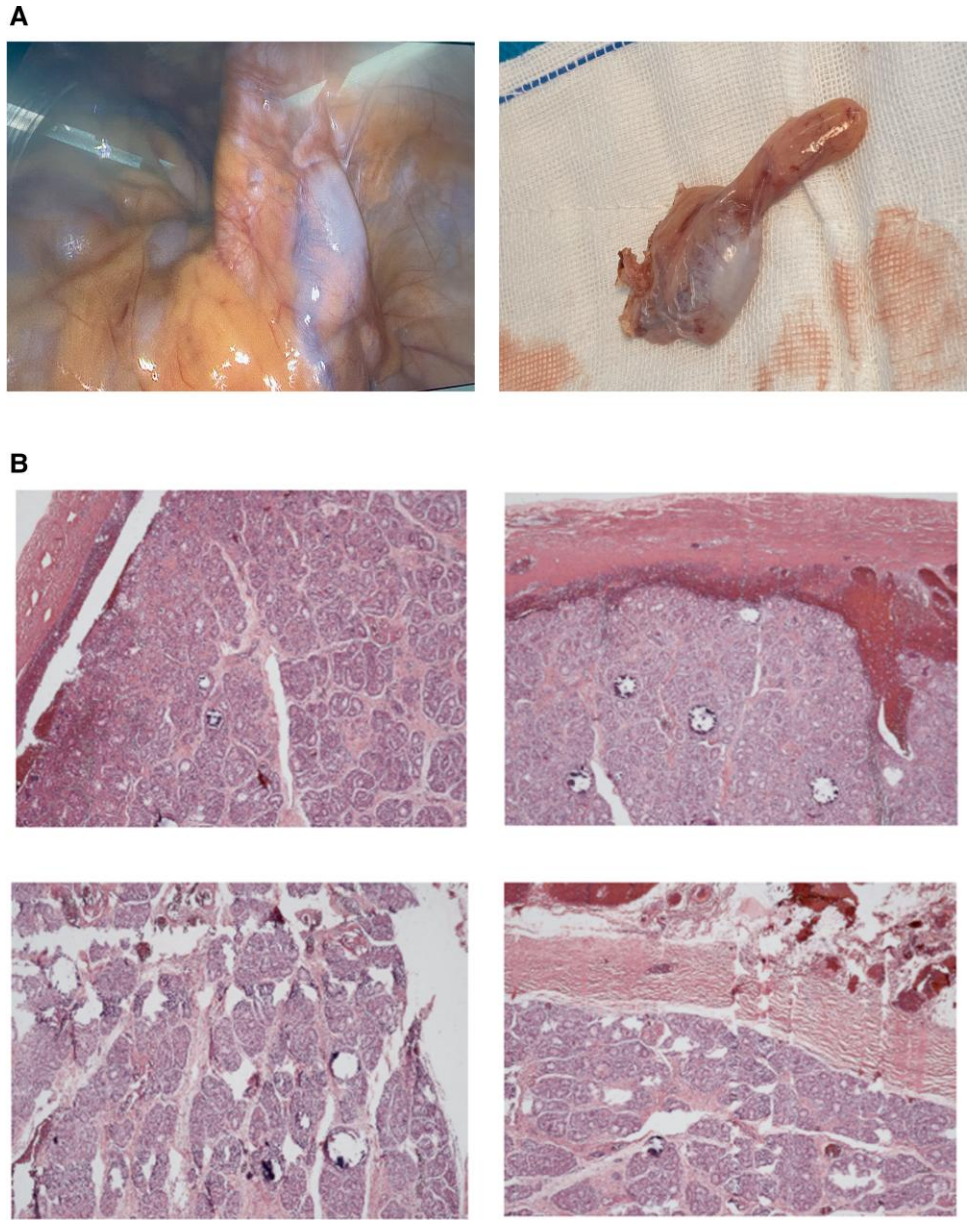

Figure 2 CYP17A1 gene Sanger sequencing results of the patient and parents. (*A*) DNA of the patient and parents at c.985_987delinsAA where F1 and F2 indicate the fasta sequence at that position on the two chromosomes of the father, M1 and M2 indicate the fasta sequence at that position on the two chromosomes of the mother, and S1 and S2 indicate the fasta sequence at that position on the two chromosomes of the patient. (*B*) DNA of the patient and parents at c.1117del with the same marker as *A*. (*C* and *D*) Peak plot results of the Sanger sequencing of *A* and *B*, respectively.

acid. The premature termination of translation result in the loss of 90 amino acids, generating a new protein with a different composition and structure from 17-hydroxylase. To support this hypothesis, we modelled the 3D structure of the human 17α-hydroxylase protein before and after the mutation (*Figure 4*). Therefore, we believe that the c.1117del is a novel pathogenic mutation. Notably, a stop codon is located in 418 base pairs downstream from both mutation sites, which warrants further investigation.

Neonatal kidneys are not sensitive to mineralocorticoids, and excess mineralocorticoids do not usually cause symptoms in infancy. Thus, 17α-OHD often goes undiagnosed until adolescence when significant clinical symptoms emerge.[10] 17α-OHD can present anytime from infancy to age 30 years, causing hypertension and hypokalaemia in nearly 95% of cases,[11] and 88% of patients are not diagnosed until adolescence or even later.[12] The onset of hypertension varies in both age and severity, even among individuals with the same mutations.[13] The clinical manifestations of 17α-OHD are influenced by genetic and environmental factors.[14] The atypical clinical signs of 17α-OHD must be differentiated from conditions such as primary aldosteronism, Turner syndrome, and P450-oxidoreductase deficiency. Initially, the patient was suspected of primary hyperaldosteronism because of symptoms such as high blood pressure and

A

Deleterious heterozygous variants of *CYP17A1* were found in patients with 17α-OHD

CYP17A1 variant	V1	V2
cDNA alteration	c.985_987delinsAA	c.1117del
Variant allele	hemizygous	hemizygous
Protein alteration	p.Tyr329Lysfs*90	p.His373Thrfs*46
Variant type	frameshift	frameshift

B

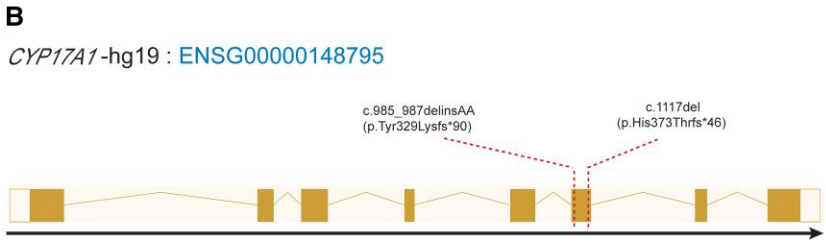

Figure 3 Both gonads of the patient were removed during surgery. (*A*) Laparoscopic view of what appears to be testicular tissue medial to the inner ring opening. (*B*) Pathological section of the gonads showing primitive spermatogenic tubules with calcification, absence of spermatogenic cells at all levels, and proliferation of supporting cells.

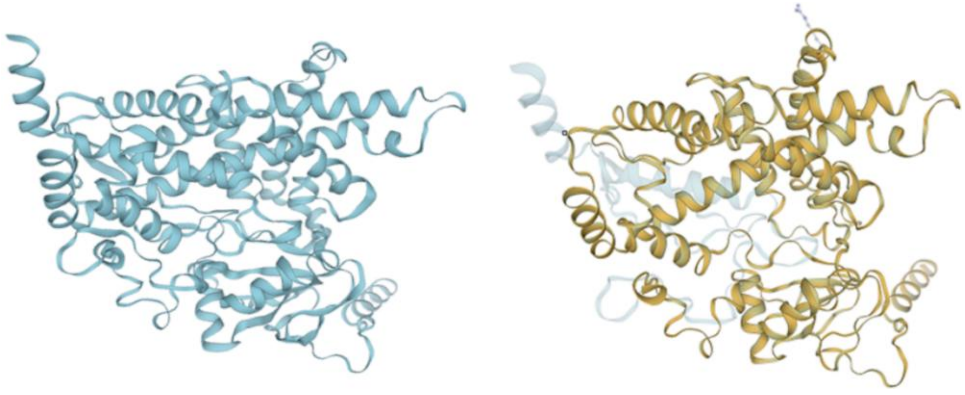

Figure 4 3D representation of the CYP17A1 protein. Left: a normal protein 3D prediction model of the gene. Right: a protein model of the gene with a c.1117del mutation. The mutant protein has fewer spirals and folds in its structure compared with the normal protein.

hypokalaemia. However, after a series of tests, she did not meet the diagnostic criteria for the disease. Considering the patient's history of primary amenorrhoea, genetic testing was performed, and the patient was eventually diagnosed with 17-OHD.

Mullerian ducts ordinarily develop into the fallopian tubes, uterus, and upper third of the vagina. During foetal development, testicular Sertoli cells produce anti-Mullerian hormone (AMH), causing the degeneration of the Mullerian ducts. Patients with 17α-OHD often have reduced AMH release, which results in the incomplete degeneration of these structures. Therefore, patients with 17α-OHD have a juvenile female vulva at birth, regardless of karyotype 46, XX or 46, XY. In this case, although the patient had a 46, XY karyotype, she was raised as a woman because she had a vulva at birth.

Although 17α-OHD is a rare cause of secondary hypertension, there are some signs providing clues to its diagnosis. Patients with clinical manifestations of endocrine abnormalities (such as male pseudohermaphroditism, delayed puberty, and primary amenorrhoea) and concomitant hypokalaemia, low plasma renin concentration or plasma renin activity, and low plasma aldosterone concentration should be suspected of 17α-OHD. Genetic testing is the key to diagnosis.[15] This case underscores the significance of recognizing genetic factors contributing to hypertension, particularly in younger individuals.

Lead author biography

Mrs Jianying Sun was a resident in the Department of Cardiology of Fuwai Yunnan Cardiovascular Hospital, China, until 2020. She is currently learning as a post-graduate in the Department of Cardiology at The First People's Hospital of Yunnan Province.

Consent: The authors confirm that written consent for submission and publication of this case report, including image(s) and associated text, has been obtained from the patient in line with COPE guidance.

Conflict of interest: None declared.

Funding: This work was supported by the National Natural Science Foundation of China (82060071 and 82260068 to J.F.).

Data availability

All data supporting the findings of this study are available within the paper. The genomics data of the patient are not yet available for public sharing; however, I am willing to provide de-tagged data for examination and verification if required during the peer-review process or if reasonably requested by other readers.

References

1. Speiser PW, Arlt W, Auchus RJ, Baskin LS, Conway GS, Merke DP, et al. Congenital adrenal hyperplasia due to steroid 21-hydroxylase deficiency: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab* 2018;**103**:4043–4088.
2. Bulsari K, Maple-Brown L, Falhammar H. Two rare forms of congenital adrenal hyperplasia, 11β hydroxylase deficiency and 17-hydroxylase/17,20-lyase deficiency, presenting with novel mutations. *Hormones (Athens, Greece)* 2018;**17**:127–132.
3. Chung BC, Picado-Leonard J, Haniu M, Bienkowski M, Hall PF, Shively JE, et al. Cytochrome P450c17 (steroid 17 alpha-hydroxylase/17,20 lyase): cloning of human adrenal and testis cDNAs indicates the same gene is expressed in both tissues. *Proc Natl Acad Sci U S A* 1987;**84**:407–411.
4. Aydin Z, Ozturk S, Gursu M, Uzun S, Karadag S, Kazancioglu R. Male pseudohermaphroditism as a cause of secondary hypertension: a case report. *Endocrine* 2010;**38**:100–103.
5. Miller WL, Auchus RJ. The molecular biology, biochemistry, and physiology of human steroidogenesis and its disorders. *Endocr Rev* 2011;**32**:81–151.
6. Miura K, Yasuda K, Yanase T, Yamakita N, Sasano H, Nawata H, et al. Mutation of cytochrome P-45017 alpha gene (CYP17) in a Japanese patient previously reported as having glucocorticoid-responsive hyperaldosteronism: with a review of Japanese patients with mutations of CYP17. *J Clin Endocrinol Metab* 1996;**81**:3797–3801.
7. Habib A, Shojazadeh A, Molayemat M, Khamirani J, Zoghi H, Dastgheib S, et al. A single-amino-acid in-frame deletion in CYP17A1 results in combined 17-hydroxylase and 17,20-lyase deficiency in an Iranian family despite the protein mutation site. *Hum Genome Var* 2021;**8**:31.
8. Kim SM, Rhee JH. A case of 17 alpha-hydroxylase deficiency. *Clin Exp Reprod Med* 2015; **42**:72–76.
9. Qiao J, Han B, Liu BL, Liu W, Wu JJ, Pan CM, et al. A unique exonic splicing mutation in the CYP17A1 gene as the cause for steroid 17{alpha}-hydroxylase deficiency. *Eur J Endocrinol* 2011;**164**:627–633.
10. Fontenele R, Costa-Santos M, Kater CE. 17α-Hydroxylase deficiency is an underdiagnosed disease: high frequency of misdiagnoses in a large cohort of Brazilian patients. *Endocr Pract* 2018;**24**:170–178.
11. Bosson D, Wolter R, Toppet M, Franckson JR, de Peretti E, Forest MG. Partial 17, 20-desmolase and 17 alpha-hydroxylase deficiencies in a 16-year-old boy. *J Endocrinol Invest* 1988;**11**:527–533.
12. Hinz L, Pacaud D, Kline G. Congenital adrenal hyperplasia causing hypertension: an illustrative review. *J Hum Hypertens* 2018;**32**:150–157.
13. Müssig K, Kaltenbach S, Machicao F, Maser-Gluth C, Hartmann MF, Wudy SA, et al. 17alpha-hydroxylase/17,20-lyase deficiency caused by a novel homozygous mutation (Y27Stop) in the cytochrome CYP17 gene. *J Clin Endocrinol Metab* 2005;**90**:4362–4365.
14. Yanase T, Simpson ER, Waterman MR. 17alpha-hydroxylase/17,20-lyase deficiency: from clinical investigation to molecular definition. *Endocr Rev* 1991;**12**:91–108.
15. Mancia G, Kreutz R, Brunström M, Burnier M, Grassi G, Januszewicz A, et al. 2023 ESH guidelines for the management of arterial hypertension the task force for the management of arterial hypertension of the European Society of Hypertension: endorsed by the International Society of Hypertension (ISH) and the European Renal Association (ERA). *J Hypertens* 2023; **41**:1874–2071.