Article

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Revealing a New Homozygous Variant in *CYP17A1* c.908G>A (p. Gly303Asp) by Genotyping a Chinese Patient with 46, XY 17a-Hydroxylase/17,20-Lyase Deficiency and Adrenal Space-Occupying Lesion

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Background: 17α-hydroxylase/17,20-lyase deficiency (17OHD) is an autosomal recessive genetic disorder caused by a mutation of the cytochrome P450, family 17, subfamily A, polypeptide 1 (*CYP17A1*). This study reports the case of a 22-year-old Chinese patient (46, XY) with 17OHD and a unilateral adrenal space-occupying lesion.

Methods: The patient underwent serological, radiographic, genetic, and molecular analyses including whole-genome exome sequencing through high-throughput sequencing (HTS) technology to analyze the genetic conditions of both the patient and her parents. Additionally, chromosomal karyotype analysis was performed. The impact of the novel mutation on protein conformation was investigated by examining the three-dimensional structure of human *CYP17A1* using the SWISS-MODEL website tool (PDB code 3RUK).

Results: The patient had a chromosomal karyotype 46, XY, and presented with hypertension, hypokalemia, and male pseudohermaphroditism. Furthermore, decreased levels of testosterone, dehydroepiandrosterone sulfate, and estradiol, along with increased levels of progesterone, luteinizing hormone, and follicle-stimulating hormone (FSH), were observed. DNA sequencing revealed a homozygous mutation (c.908G>A, p.G303A) in the fifth exon of the *CYP17A1*. Both parents carried a heterozygous c.908G>A mutation in the same exon, confirming the inheritance of the patient's exonic mutation.

Conclusion: For the first time, this study reports a novel homozygous mutation (c.908G>A in the fifth exon) in *CYP17A1*. Modeling analysis of *CYP17A1* suggested that the substitution of glycine with aspartic acid at position 303 induces alterations in the number, structure, and electrostatic potential of the protein's local binding sites. The p.G303A mutation may possess pathogenic properties. Our study expands the mutation spectrum of *CYP17A1*.

Keywords: congenital adrenal hyperplasia; 17α-hydroxylase/17,20-lyase deficiency; *CYP17A1*; c.908G>A

Introduction

Congenital adrenal hyperplasia (CAH) comprises a group of autosomal recessive genetic diseases characterized by the deficiency of one or more enzymes in the steroid hormone production pathway, resulting in impaired cortisol biosynthesis in the adrenal cortex [1]. CAH includes conditions such as 21-hydroxylase deficiency, 11β-hydroxylase deficiency, and 17α-hydroxylase/17,20-lyase deficiency (17OHD) [2]. Among these CAH forms, 17OHD is exceptionally rare, accounting for approximately 1% of all CAH cases with an incidence rate of approximately 1:50,000–100,000 [3]. Previous studies have demonstrated that mutations in cytochrome P450, family 17, subfamily A, polypeptide 1 (*CYP17A1*), located on chromosome 10, contribute to the manifestation of 17OHD [4] and *CYP17A1* consists of 508 amino acids, including eight exons and seven introns [5]. The gene encoding for cytochrome P450c17 expresses the activities of both 17α-hydroxylase and 17,20-lyase [6]. Mutations in this gene lead to an excess of mineralocorticoids and deficiencies in cortisol and sex hormones. CAH manifestations include low-renin hypertension, hypokalemia, and abnormalities in sexual development [7]. The diagnosis of CAH currently relies on comprehensive clinical, biochemical, and molecular characterization. However, given the variable nature of CAH-related clinical manifestations and biochemical features, genetic diagnosis is imperative. In this study, we present the clinical, biochemical, and radiographic features of a patient with 17OHD. Furthermore, genetic analyses were conducted on the patient and her parents, and a three-dimensional structural simulation of *CYP17A1* was performed. This study reports a novel variant in *CYP17A1*, contributing to the understanding of genetic variations and inheritance in 17OHD patients. These results provide a foundation for enhancing the diagnosis and treatment planning of this disease.

Patient and Methods

Patient

The subject of this study is a 22-year-old unmarried Chinese patient with hypertension, hypokalemia, and male pseudohermaphroditism. The patient is phenotypically female and was unmarried upon referral to our hospital. This study was approved by the hospital ethics committee (ethics approval number: 2023A-712).

The patient's primary symptoms were intermittent fatigue persisting for five years, with recent exacerbation in the past month. The patient was born full-term without adverse symptoms at birth and was raised as a female since childhood. Her height, weight, and intelligence levels were comparable to those of her peers. However, no secondary sexual characteristics or menstruation had emerged post-puberty. Despite visiting multiple gynecology and endocrinology departments, diagnosis results remained unclear. At 17 years old, a medical examination revealed elevated blood pressure at 148/96 mmHg, but no treatment was administered due to a lack of symptoms. Subsequent blood pressure readings ranged from 140–150/90–100 mmHg. The patient later experienced episodes of intermittent dizziness, headache, and fatigue, prompting her to seek care at another hospital. After comprehensive examinations, the patient was diagnosed with primary adrenal cortical hyperplasia and treated with dexamethasone acetate tablets (0.75 mg/night). However, the patient discontinued medication as her symptoms improved. One month before admission to our hospital, the patient experienced recurring dizziness and headache, with blood pressure fluctuating between 210–220/150–160 mmHg. Additional symptoms included fatigue, primary amenorrhea, skeletal deformities, lethargy, anorexia, and nausea, among other symptoms.

Upon admission, the patient's height was 167 cm, weight 57 kg, body mass index (BMI) 20.4 kg/m^2, and blood pressure 156/97 mmHg. She presented with clear consciousness, appropriate responses to questions, and a well-proportioned body shape with no distinctive features. Her breasts were at Tanner stage I (undeveloped) and she exhibited no axillary hair. Similarly, the external genitalia exhibited a primitive female vulva corresponding to Tanner stage I with a lack of pubic hair. Other physical examinations did not reveal any abnormalities. The patient's parents were healthy and were not consanguineously married, with no other family members exhibiting similar symptoms. The patient has a younger brother with normal sexual and intellectual development. Details regarding the patient's laboratory abnormalities process will be provided in the subsequent section. After all the examinations, the patient was diagnosed with 17OHD. And we prescribed oral prednisone acetate (5 mg in the morning and 2.5 mg in the evening).

Methods

Serological Testing

Fasting peripheral blood was collected from the patient and analyzed using the cobas-8000 automatic biochemical analyzer (Roche Diagnostics, Mannheim, Germany) to assess hepatic function, renal function, and electrolyte levels. Plasma renin activity and aldosterone levels were determined using radioimmunoassay. Additionally, chemical immunofluorescence was used to assess thyroid function, growth hormone (GH), follicle-stimulating hormone (FSH), luteinizing hormone (LH), estradiol, testosterone, progesterone, adrenocorticotropic hormone (ACTH), and cortisol levels.

Bone Mineral Density Measurement and 24-Hour Dynamic Blood Pressure Monitoring

A dual-energy X-ray bone densimeter was employed to assess the density of the radius and ulnar bones. The density was determined based on automatically provided T and Z values. Dynamic blood pressure monitoring was performed using a TM-2430 device (A&D Company, Tokyo, Japan).

Imaging Examination

Abdominal and pelvic ultrasound was examined using the LOGIQ-E9 Color Doppler ultrasound system (GE HealthCare, Chicago, IL, USA). Adrenal CT scans were conducted using the GE Discovery HD CT scanner (GE HealthCare, Chicago, IL, USA), and pelvic MR plain scans were acquired using a Ingenia 3.0T machine (Philips, Amsterdam, Netherlands).

Chromosomal Karyotype Analysis

2 mL of peripheral blood was taken, anticoagulated with heparin, and incubated in a lymphocyte medium for 72 hours. Following laboratory standard operating procedures, G banding and karyotype analysis of the patient were performed based on previous literature [8].

Genetic Testing

After obtaining informed consent from the patient, genetic testing was performed on her and her parents. However, the patient's younger brother, who did not exhibit signs of abnormal sexual or intellectual development, was not tested due to parental refusal. Peripheral blood (8 mL) was collected from the patient and her parents and anticoagulated with Ethylene Diamine Tetraacetic Acid (EDTA). DNA extraction was conducted using the TIAN amp Micro DNA Extraction Kit (DP316, TIANGEN, Beijing, China). Subsequently, a DNA library was constructed, and the target region was captured using Dynabead™ Myone™ Streptayidin T1 (Thermo Fisher Scientific, Waltham, MA, USA). Quality control was conducted by the q-PCR library. The captured DNA library was sequenced using an Illumina sequencing instrument-Hiseq 4000 (Illumina,

Table 1. Biochemical and hormonal results of pre- and post-treatment with prednisone acetate for one week.

Characteristics	Pre-treatment	Post-treatment	Reference ranges
Potassium (mmoL/L)	3.31↓	3.62	3.50–5.30
PRL (ng/mL)	8.62	19.55	2.80–29.20
FSH (mIU/mL)	97.790↑	86.750↑	2.50–10.20
LH (mIU/mL)	62.790↑	59.240↑	1.90–12.50
Estradiol (pg/mL)	13.73↓	<11.8↓	19.50–144.20
Testosterone (ng/dL)	<7.000↓	<7.000↓	8.380–35.010
Progesterone(ng/mL)	5.140↑	3.510↑	0.15–1.40
DHEA-S (μmol/L)	0.06↓	Nc	4.02–11.00
ACTH (pg/mL)	144.00↑	Nc	0.00–46.00
Cortisol (μg/dL)	<1.00↓	Nc	5.00–25.00
PRA (ng/mL/hr)	0.03↓	Nc	0.15–2.33
Aldosterone (pg/mL)	17.40↓	Nc	30.00–160.00

Abbreviation: PRL, prolactin; FSH, follicle-stimulating hormone; LH, luteinizing hormone; DHEA-S, dehydroepiandrosterone-sulfate; ACTH, adrenocorticotropic hormone; PRA, plasma renin activity; Nc, not checked.

San Diego, CA, USA). The coverage of the target region reached 99.76%, the average depth of the target region was 129.16, and the proportion of sites with a depth >20× in the target region was 98.53%. Genetic testing was conducted by Shanghai Han Yao Biomedical Technology Co., Ltd (Shanghai, China).

Molecular Modeling

The amino acid sequence of the human *CYP17A1* gene was obtained from the National Center for Biotechnology Information in the United States (http://www.ncbi.nlm.nih.gov). The protein sequence was confirmed by querying the Fasta sequence. Subsequently, the protein structure was searched in the Protein Data Bank (https://www.rcsb.org), and the structure with the code 3RUK was selected [9]. Using the SWISS-MODEL [10] (https://swissmodel.expasy.org/interactive) homology modeling method, an automated website tool was employed to predict the three-dimensional structure of the protein. Both normal and mutated amino acid sequences were used to establish three-dimensional models of the wild-type and mutant proteins, allowing for a comparison between the two and subsequent predictions of the mutant protein's function.

Results

The patient exhibited decreases in serum potassium, cortisol, aldosterone, and sex steroids, which included estradiol, testosterone and dehydroepiandrosterone-sulfate levels (Table 1). However, increases in the basal levels of ACTH, LH, FSH, and progesterone were observed (Table 1). Moreover, abnormalities were not observed in hepatic function, renal function, GH levels, or thyroid gland indicators.

The pelvic ultrasound indicated the absence of uterus or adnexa (Fig. 1a). A pelvic magnetic resonance scan further confirmed the absence of a uterus or ovary in the pelvic cavity, suggesting a congenital absence. The vaginal structure was not well illuminated, and there was an abnormal structure in the left iliac fossa, potentially identifying as a testis (Fig. 1b,c). Abdominal ultrasound revealed a hypoechoic lesion in the left adrenal region, suggesting an adrenal cortical adenoma. Adrenal CT confirmed an enlarged left adrenal gland with a mass lesion measuring approximately 41 mm × 14 mm (Fig. 1d,e).

Bone mineral density assessment yielded a T-score of –0.75, indicating no evidence of osteoporosis in the patient. Analysis of the 24-hour ambulatory blood pressure demonstrated a mean systolic pressure of 152 mmHg, a mean diastolic pressure of 103 mmHg, a maximum systolic pressure during the day of 190 mmHg, a maximum diastolic pressure of 133 mmHg, a maximum systolic pressure at night of 161 mmHg, and a maximum diastolic pressure at night of 108 mmHg.

Molecular genetic testing was performed on the patient, revealing a chromosomal karyotype of 46, XY. A homozygous mutation c.908G>A (p. Gly303Asp) was identified in the fifth exon of *CYP17A1* on chromosome 10 (Fig. 2a). This mutation is caused by substituting adenine for guanine at position 908, resulting in the conversion of the 303rd amino acid from glycine to aspartic acid. Heterozygous mutations for c.908G>A were observed in both parents (Fig. 2b,c, indicating the inheritance of *CYP17A1* mutations from both parents according to family mutation analysis.

Finally, molecular modeling of *CYP17A1* was conducted to simulate the wild-type structure and mutant structures (Fig. 3a,b). The substitution of glycine with aspartic acid at amino acid position 303, located in the α-helical structure, was expected to result in alterations in the num-

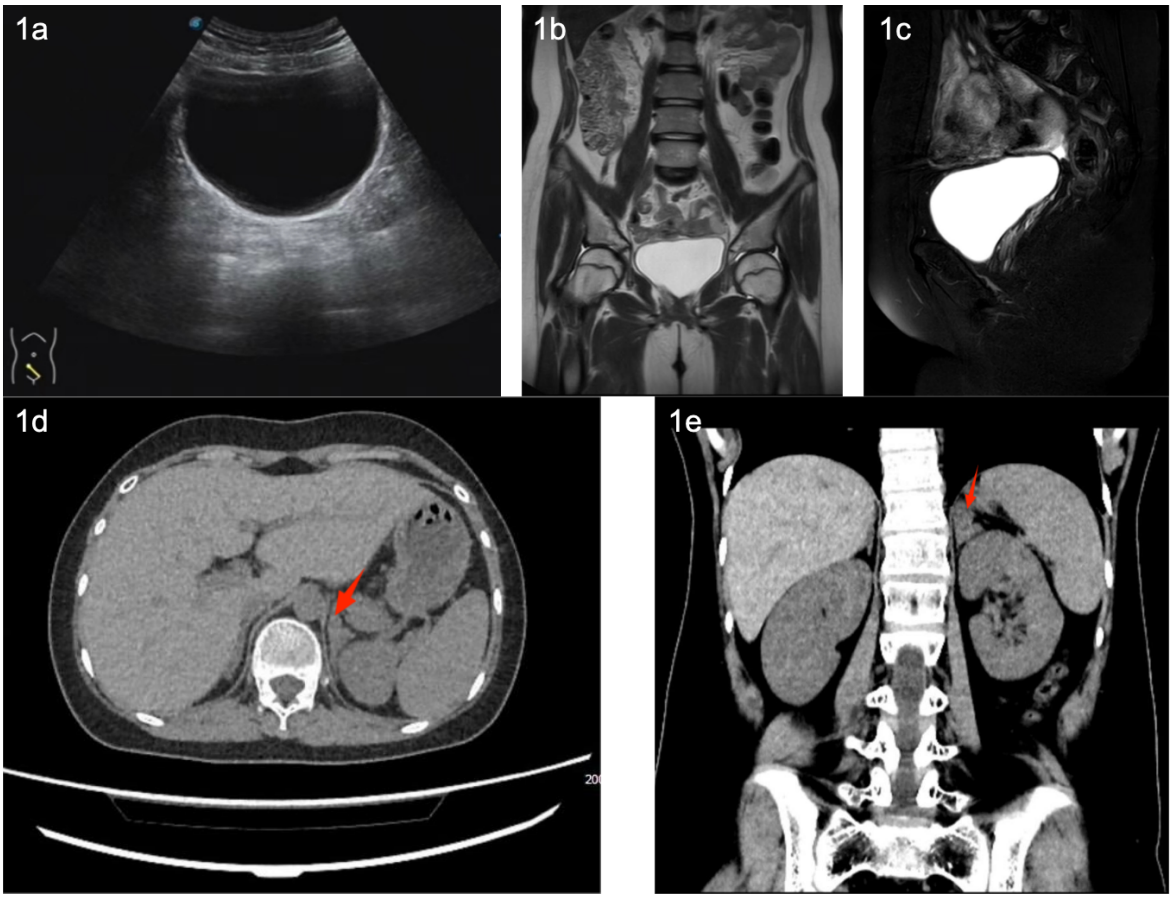

Fig. 1. Patient's imaging examination. (a) Pelvic ultrasound. (b) T2W coronal image. (c) T2W sagittal image. (d) Adrenal CT sagittal image. (e) Adrenal CT coronal image demonstrating enlarged left adrenal glands with a space-occupying lesion in the left adrenal, about 41 mm × 14 mm, indicated via red arrow.

ber, structure, and electrostatic potential of the protein's local binding sites. This change may increase hydrophilicity, suggesting the pathogenic nature of the p.Gly303Asp mutation.

Discussion

CAH is a group of autosomal recessive disorders that affect the synthesis of adrenal cortical steroids. Among all CHAs, 17OHD accounts for only 1% of cases, with most literature reporting isolated cases within close-knit families [11]. Unlike the more common CAH types, 17OHD also affects the production of sex hormones. The condition is attributed to mutations in the cytochrome P450c17 gene, specifically *CYP17A1*, an atypical cytochrome P450 enzyme governing adrenal and sex steroid hormone biosynthesis and breakdown [12]. The absence of *CYP17A1* activity leads to significantly elevated deoxycorticosterone (DOC) and aldosterone, suppressing the renin-angiotensin–aldosterone system and causing low-renin hypertension and hypokalemia [13]. The produced DOC exhibits some cortisol-like activity, compensating for the associated cortisol deficiency [14]. As a result, patients with 17OHD rarely experience an adrenal crisis [15]. Furthermore, the 17,20-lyase activity converts 17-hydroxy steroids into dehydroepiandrosterone and androstenedione. Without sufficient 17,20-lyase activity, sex hormone synthesis is inhibited [16]. Serological characteristics of 17OHD include increased progesterone levels, LH levels, and sexual development disorders. As seen in this case, patients with a chromosomal karyotype of 46, XY, experience delayed onset of secondary sexual characteristics during puberty, leading to pseudohermaphroditism, difficulty in penis and testes formation, and a phenotypically female, immature vulva [17]. Due to the degeneration of Müllerian ducts, patients also fail to develop a uterus and fallopian tubes, causing the vagina to have a blind end [18]. Consequently, children born with this condition due to external genitalia development defects may be misgendered by their parents.

Mutations in *CYP17A1* lead to distinct categories, including syndromic deficiency, partial syndromic deficiency, and isolated 17,20-lyase deficiency [19]. Among these categories, complete syndromic deficiency is the most common. Patients with the 46, XY karyotype and complete syndromic deficiency often show symptoms such as pseudohypertrophy and external genitalia feminization [20].

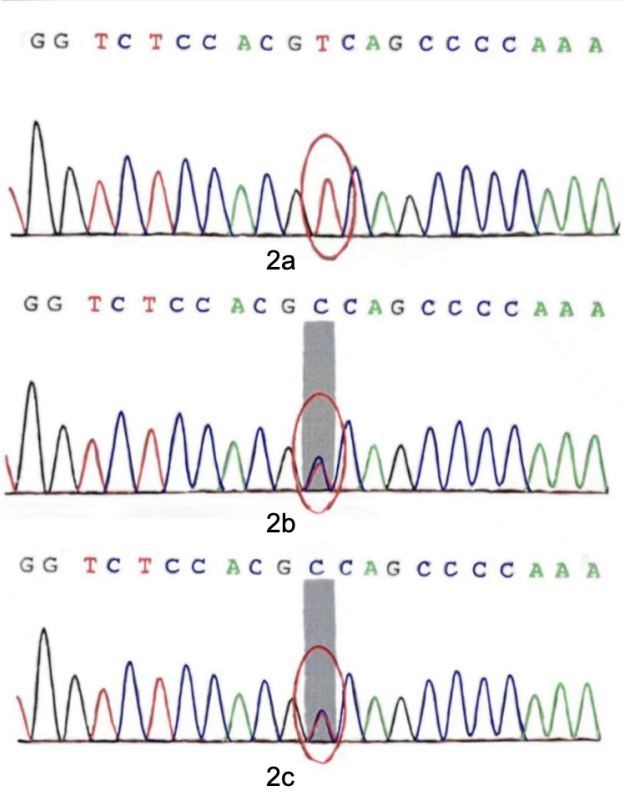

Fig. 2. Codon 908 in exon 5. (a) cytochrome P450, family 17, subfamily A, polypeptide 1 (*CYP17A1*) of the patient. (b) *CYP17A1* of the patient's father. (c) *CYP17A1* of the patient's mother.

Patients with isolated 17,20-lyase deficiency retain 17α-hydroxylase activity but lack 17,20-lyase activity. Consequently, patients with isolated 17,20-lyase deficiency typically present with hypospadias, microphallus, and scrotum malposition, while maintaining normal blood pressure and serum potassium levels [21].

In this study, the patient exhibited early signs of underdeveloped secondary sexual characteristics, hypertension, hypokalemia, and abnormal sexual development. The patient displayed male pseudohermaphroditism, Tanner I stage bilateral breasts, and external genitalia with a primitive female appearance. Serum tests also revealed decreased cortisol, renin, and aldosterone levels, accompanied by elevated ACTH levels. Moreover, testosterone, dehydroepiandrosterone sulfate, and estradiol levels were reduced, but progesterone levels increased. Additionally, increased LH and FSH levels were consistent with the manifestation of complete combined deficiency type 17OHD.

Although early screening is crucial for these diseases, most countries currently only screen for 21OHD, with insufficient emphasis on 17OHD. Moreover, diagnostic tools for 17OHD are limited. The urinary steroid profile, which measures the activity of 17α-hydroxylase and the ratio of metabolic precursors/products of 17,20-lyase activity, is highly elevated, indicative of *CYP17A1* deficiency [22]. Genetic sequencing stands as the gold standard for diagnosing *CYP17A1* deficiency. Therefore, we conducted genetic testing on the patient and her parents to confirm the diagnosis in this case. The results indicated a homozygous mutation at c.908G>A in the fifth exon of *CYP17A1* on chromosome 10. To date, The Human Gene Mutation Database (http://www.hgmd.org/) has documented 177 mutations in the P450c17 gene including nonsense mutations, missense mutations, point mutations, deletions, and insertions [11,19,23]. Genetic mutations in the fifth exon are relatively rare, with limited literature reports as of 2020. Most documented cases report homozygous mutations, including missense, nonsense, and frameshift mutations. For example, Wu *et al.* [24] reported a fifth exonic mutation in China, including a homozygous missense mutation c.796C>G (p.L266V) and a frameshift mutation, c.932_939delTTAAATGG (p.Val311Asp), which combines with an exon seven mutation (Y329fs) [25]. In addition, Xiao *et al.* [26] reported a mutation of c.916A>G (p. Thr306Ale), constituting a compound heterozygous mutation with an additional mutation in the second exon (p. Thr101Ilefs*2). According to reports from abroad, Petri *et al.* [22] highlight diverse missense and nonsense homozygous mutations in the fifth exon. c.896T>A (p.I299N) and the two cases of c.904G>C (A302P) reported by Rosa *et al.* [27], both being missense homozygous mutations. Guenego *et al.* [28] reported that c.938G>A (p. Trp313X) is a nonsense homozygous mutation. Moreover, Asirvatham's study [15] first identified c.893A>G (p. Asp298Gly) in the fifth exon as a pathogenic mutation.

Although the functional relevance of the patient's c.908G>A mutation has not been experimentally confirmed, it is speculated to have pathogenic potential based on protein modeling, clinical manifestations, and biochemical findings. Parental genetic testing revealed that both parents were heterozygous for c.908G>A in the *CYP17A1* gene, confirming the inheritance of homozygous mutations in the patient. In addition, chromosome examination indicated a 46, XY karyotype for the patient. The patient presented with a sexual development disorder, which led to inconsistencies between the genotype and phenotype. As a result, the patient was assigned female at birth and raised as such by her parents despite carrying a Y chromosome.

The congenital disorder 17OHD is currently incurable, with most cases being diagnosed during adolescence [29,30]. Treatment strategies for diagnosed patients involve comprehensive and personalized treatment approaches, including hormonal replacement therapy, psychological guidance, gender-specific interventions, and reproductive surgical treatments. Alternative treatments include glucocorticoid and sex hormone therapy [31]. Lifelong glucocorticoid intake is considered the primary treatment for this condition [32]. Glucocorticoid reduces ACTH and DOC levels, effectively inhibiting adrenal hyperplasia and facilitating the control of hypertension and hypokalemia [33].

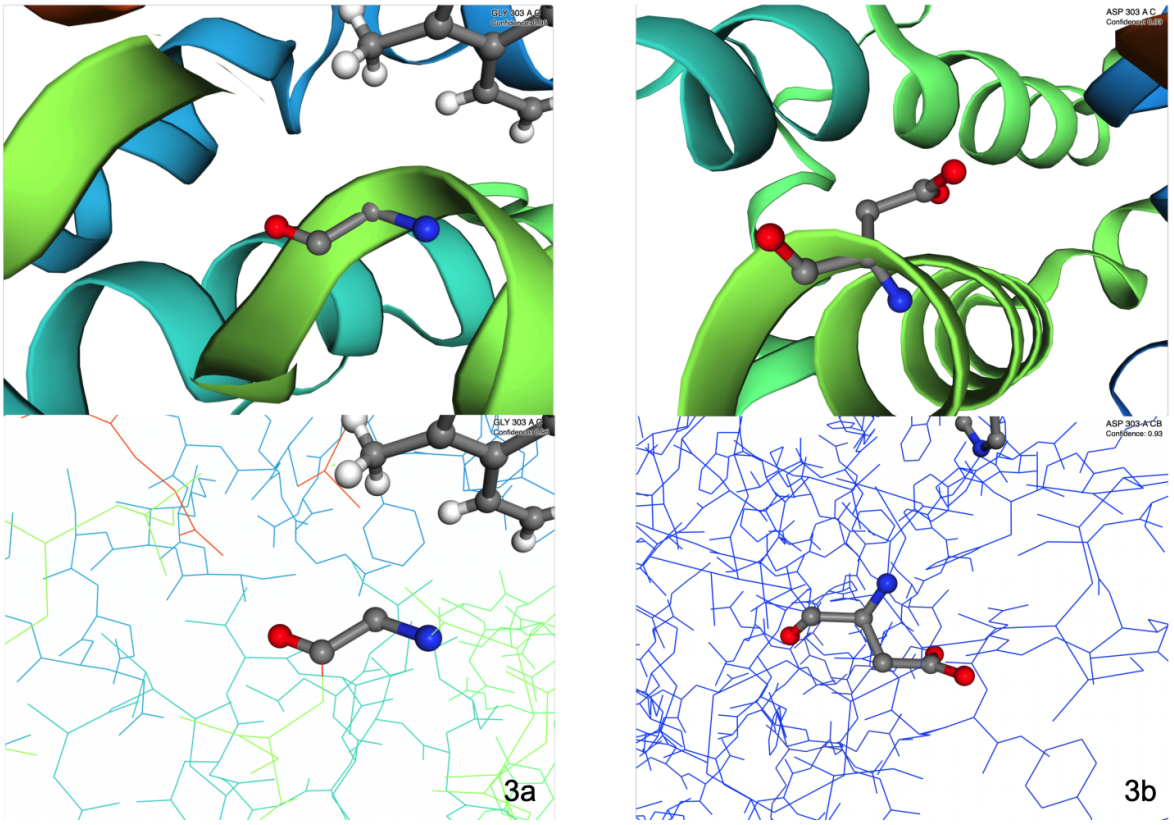

Fig. 3. Modeling of *CYP17A1*-simulated structures. (a) The wild-type structure. (b) The mutant structure (Red indicates negative charge, blue indicates positive charge, and gray indicates neutral).

If blood pressure fails to return to normal after glucocorticoid treatment, calcium channel blockers or spironolactone may be necessary to further control blood pressure [3]. Moreover, gender selection becomes imperative when the chromosomal gender does not align with societal gender identities [34]. Treatment modalities may vary depending on the chosen gender. For those opting for a female identity, early laparoscopic gonadectomy is recommended, while testosterone supplementation and genital reconstruction surgery are advised for those choosing a male identity [17,35]. For patients with a chromosome karyotype of 46, XY, diligent screening for underdeveloped cryptorchidism is essential, with timely post-puberty removal to prevent malignant transformation [36].

After diagnosing the current patient, a multidisciplinary discussion confirmed the presence of abnormal structures in the left iliac fossa, raising the possibility of testicular development. Initial interventions include hormone supplementation and antihypertensive medication. Planned laparoscopic surgery aims to investigate the foreign body noted in the iliac fossa. However, despite the administration of oral prednisone acetate (5 mg in the morning and 2.5 mg in the evening), the patient's blood pressure was not adequately controlled. Resultantly, nifedipine controlled-release tablets (30 mg/day) were added to the treatment regimen, effectively reducing the patient's blood pressure to normal levels. The current approach aims to maintain the female sexual characteristics of the patient, which has been actively communicated with the parent and her family.

Regarding the adrenal mass lesion, existing literature suggests that most patients experience no progression or reduction/disappearance of the mass following glucocorticoid treatment [19,25]. This phenomenon is thought to be attributed to the long-term stimulation from feedback-type increased ACTH levels. Therefore, immediate surgical intervention has been deferred. Surgical consideration will only be entertained if the mass fails to regress after sufficient hormone replacement therapy.

Future studies will develop cell or animal mutation models to verify the pathogenicity of the gene mutation site. Meanwhile, we will follow up with the patient.

Conclusion

In this study, we identified a novel gene mutation, a homozygous c. 908G>A (p.G303A) change in the fifth exon of *CYP17A1* on chromosome 10, expanding the *CYP17A1* mutation database. As a result, we constructed a three-dimensional model of the mutant *CYP17A1* protein to evaluate the pathogenicity of this variation. Although 17OHD is a rare condition, clinical vigilance for CAH is essential for patients with unclear genital features at birth,

delayed puberty, or early onset of hypertension and hypokalemia. We recommend conducting timely and relevant investigations, genetic testing, and chromosomal examinations. After confirmation of the diagnosis, prompt initiation of appropriate treatment is necessary. A personalized and comprehensive approach should be adopted, emphasizing the significance of early diagnosis and treatment to improve the patient's life quality.

Disclosure Statement

None of the authors have anything to disclose.

Availability of Data and Materials

The datasets used or analyzed during the current study are available from the corresponding authors upon reasonable request.

Author Contributions

HC and JSX conceived the idea of this study; MW, XJH and XYX acquired and analyzed the data; MW is responsible for illustration. All authors wrote and revised the draft. All authors contributed to the article and approved the submitted version. All authors read and agreed to the published version of the manuscript. All authors agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

This study was conducted in accordance with the Declaration of Helsinki and was approved by the Lanzhou University Second Hospital ethics committee (ethics approval number: 2023A-712). Written informed consent to participate in this study was provided by the patient and her parents.

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Conflict of Interest

The authors declare no conflict of interest.

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