CASE REPORT

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Clinical and Genetic Analyses of Two Unrelated 46,XX Girls with Combined 17α-hydroxylase/17,20-lyase Deficiency from China

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What is already known on this topic?

17α-hydroxylase/17,20-lyase deficiency (17OHD) is a rare autosomal recessive disease caused by homozygous or compound heterozygous mutations in *CYP17A1* gene. 17OHD can be classified into complete and partial forms based on the phenotypes resulting from cytochrome P450 17α-hydroxylase (P450c17) enzyme defects of different severities.

What this study adds?

For the first time, we describe a 46,XX case of complete 17OHD accompanied by nocturnal enuresis. We identified a new compound heterozygote (p.R347C and p.R362H) of *CYP17A1* gene in a 46,XX case with partial 17OHD.

Abstract

Cytochrome P450 17α-hydroxylase (P450c17) enzyme, encoded by the *CYP17A1* gene, catalyzes 17a-hydroxylation and 17,20-lyase reactions essential for cortisol and sex steroid synthesis. 17α-hydroxylase/17,20-lyase deficiency (17OHD) is a rare autosomal recessive disease caused by CYP17A1 mutations, classified into complete and partial forms based on P450c17 defect severity. We report two unrelated girls diagnosed with 17OHD at the age of 15 and 16. Both presented with primary amenorrhea, infantile genitalia, absent axillary and pubic hair, and hypergonadotropic hypogonadism. Case 1 exhibited undeveloped breasts, nocturnal enuresis, hypertension, hypokalemia, and reduced cortisol and 17α-hydroxyprogesterone. Case 2 showed a growth spurt, spontaneous breast development, elevated corticosterone, and decreased aldosterone. Both had a 46,XX karyotype. Genetic analysis revealed a homozygous p.S106P mutation in Case 1 and compound heterozygous p.R347C/p.R362H mutations in Case 2, with the latter representing a novel combination. Based on the clinical, laboratory and genetic findings, Case 1 and Case 2 were definitively diagnosed as complete and partial forms of 17OHD, respectively. Both received estrogen and glucocorticoid replacement therapy, leading to gradual development of the uterus and breasts, and the onset of first menstruation. In Case 1, hypertension, hypokalemia, and nocturnal enuresis were significantly alleviated. In conclusion, we report the first case of complete 17OHD accompanied by nocturnal enuresis and identify a novel compound heterozygote (p.R347C / p.R362H) of *CYP17A1* gene in a case of partial 17OHD.

Keywords: Congenital adrenal hyperplasia, 17α-hydroxylase/17,20-lyase deficiency, *CYP17A1* gene, mutation, nocturnal enuresis

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Introduction

Congenital adrenal hyperplasia (CAH) is a group of seven autosomal recessive diseases caused by mutations in genes encoding key enzymes involved in cortisol biosynthesis (1). The cytochrome P450 17α-hydroxylase (P450c17) enzyme, encoded by cytochrome P450 family 17 subfamily A member 1 (*CYP17A1*) gene, catalyzes both the 17a-hydroxylation and 17,20-lyase reactions required for the production of cortisol and sex steroids (2,3). 17a-hydroxylase/17,20-lyase deficiency (17OHD) is a rare type of CAH with an estimated incidence of 1:50,000 worldwide, accounting for about 1% of all CAH cases (1,4).

Various mutations in the *CYP17A1* gene cause the complete or partial loss of either or both 17a-hydroxylase and 17,20-lyase activities, which has been recognized as the molecular basis of 17OHD (3). Most mutations are associated with the classic phenotype of combined 17OHD, which results in the substantial reduction of cortisol and sex hormones, and the accumulation of mineralocorticoid precursors, such as deoxycorticosterone (DOC) and corticosterone (1). Deficiency of sex hormones causes 46,XY disorders of sex development and sexual infantilism in females. Both 46,XX and 46,XY patients have female external genitalia and usually present with absence of secondary sexual characteristics and hypergonadotropic hypogonadism during puberty (5). Elevated levels of DOC lead to hypertension and hypokalemia with suppression of aldosterone production, while excess corticosterone exhibiting glucocorticoid activity prevents patients from an adrenal crisis although cortisol production is low or absent (5). The clinical and laboratory features has been reported to be milder in patients with partial combined 17OHD due to a degree of sex hormone production (6).

Several major structural domains are necessary for the normal function of P450c17 enzyme based on the molecular modeling of enzyme structure, including the membrane attachment domain, the heme-binding site, the substrate-binding pocket, and the redox-partner binding site (2,3). *CYP17A1* mutations affecting the steroid-binding pocket [e.g., p.S106P (7), and D487_F489 deletion (8)] or heme-binding site [e.g., p.H373L (9), and p.R440H (10)] have been found to result in combined 17OHD either completely or partially, whereas mutations in the redox-partner binding site [e.g., p.R347H (11), and p.R358Q (11)] may preferentially impair 17,20-lyase activity. Thus, genetic mutation analysis is critical for making definite diagnosis and understanding the molecular mechanism of 17OHD.

Here, we report two unrelated 46,XX cases, one with complete and one with partial 17OHD. The preliminary diagnoses were made by the estimation of clinical and laboratory features, and were confirmed by the identification of *CYP17A1* mutations.

Case Reports

Clinical and Laboratory Features at Baseline

Two unrelated, phenotypic girls with combined 17OHD are described. Both were referred to the gynecological endocrinology clinic during July to October in 2021.

Case 1 was a 15-year-old girl who presented because of primary amenorrhea and absence of secondary sexual characteristics. Her parents were first-degree cousins. They reported that she has been weak and sickly since childhood, and often felt tired. She had nocturnal enuresis since childhood, once or twice a night. She denied chronic constipation, fecal incontinence, and other urinary symptoms, including frequent micturition, urgent micturition, painful micturition, dysuria, or daytime incontinence. No significant psychological or behavioral problems were observed on clinical screening. She was 153.0 cm tall and weighed 33.0 kg, both significantly below the 50th percentile reference values for 15-year-old girls (159.8 cm and 49.8 kg) in China. Physical examination revealed a blood pressure of 144/101 mmHg, Tanner stage 1 breast development, infantile external genitalia, and absence of axillary and pubic hair. The patient also showed delayed bone age of approximately 11 years, and decreased bone mineral density with a T-score between -1 and -2.5. Ultrasound imaging exhibited a low-echo strip of 4.8 cm × 0.3 cm behind the bladder without ultrasonographically evident intrauterine space, a 2.6 cm × 1.3 cm echo-free area on the left ovary and a 2.8 cm × 1.3 cm echo-free area on the right ovary with 10-12 follicles in bilateral ovaries. Spina bifida occulta was excluded by X-ray examination. No urinary tract abnormalities were detected by ultrasound examination.

Case 2 was a 16-year-old girl who sought medical advice because of primary amenorrhea. The patient was the only daughter and her parents were not consanguineous. The patient began breast development and growth spurt about two years before presentation. Physical examination showed a weight of 57.0 kg, height of 164.0 cm, body mass index of 21.2 kg/m^2, blood pressure 131/89 mmHg, Tanner stage 2 breast development, infantile female external genitalia and no axillary or pubic hair. Ultrasound imaging revealed a small uterus (1.7 × 1.2 × 1.7 cm^3) as well as 3.0 cm × 2.3 cm and 3.8 cm × 2.2 cm echo-free areas on the left and right ovaries respectively. Bilateral adrenal glands were normal in size, as assessed by color ultrasonography.

The serum hormone and electrolyte concentrations of both patients were retrieved from the electronic medical records and are shown in Table 1. Hypokalemia was detected in Case 1. With regard to the sex hormone profile, reduced levels of estradiol, testosterone and dehydroepiandrosterone sulphate and elevated levels of progesterone and luteinizing hormone (LH) were detected in both cases, indicating hypergonadotropic hypogonadism. Low cortisol and 17α-hydroxyprogesterone (17OHP) were found in Case 1. DOC, corticosterone and aldosterone were measured in Case 2, and the results showed elevated corticosterone and decreased aldosterone.

Based on the clinical presentations and laboratory findings, Case 1 was initially diagnosed as complete 17OHD while Case 2 was suspected of suffering from partial 17OHD. More laboratory tests were conducted for Case 1 to investigate the potential cause of nocturnal enuresis. Routine blood test revealed normal counts of red blood cells, white blood cells and platelets. Renal function indicators, including creatinine 55.0 umol/L, uric acid 269.00 umol/L, and urea nitrogen 4.40 mmol/L, were within normal range. Normal fasting blood glucose (4.82 mmol/L) was observed. The results of routine urine examination were normal. The urine specific gravity was 1.01, within normal limits. Through the structured history and systematic physical examination, these secondary causes of nocturnal enuresis were excluded, including urinary system diseases, spina bifida occulta, diabetes mellitus, and diabetes insipidus.

Genetic Analyses

Molecular genetic testing was conducted for definitive diagnosis of 17OHD. The chromosome karyotype for both patients was 46,XX. Clinical exome sequencing, which included coding exons for about 5000 clinically relevant disease-causing genes (12), was performed for both patients at the AmCare Genomics Lab, Guangzhou, China. The enriched DNA samples were sequenced on the Illumina HiSeq2000 (Illumina, San Diego, CA, USA) with 150 bp, single-end read length. Gene variants were annotated using population and literature databases, including GnomAD, ClinVar, OMIM, and HGMD. The pathogenicity of gene variants was classified according to the American College of Medical Genetics guidelines (13). Suspected mutations were validated by Sanger sequencing of both the patients and their parents. Case 1 harbored a homozygous mutation

Table 1. Laboratory tests for two cases with 17α-hydroxylase/17,20-lyase deficiency at presentation

Parameters	Case 1	Case 2	Normal range
FSH, IU/L	29.33	7.90	3.5-12.5
LH, IU/L	41.52	20.30	2.4-12.6
Estradiol, pmol/L	18.35	18.35	45.4-854
Testosterone, nmol/L	0.087	0.094	0.29-1.67
Progesterone, nmol/L	28.30	34.29	0.18-2.84
Prolactin, mIU/L	390.10	181.50	102-496
SHBG, nmol/L	126.10	42.60	26.1-110
DHEAS, ug/dL	12.33	12.75	15-1000
ACTH, pg/mL	49.67	-	7.0-65.0
Cortisol, nmol/L	7.80	172.60	101.2-535.7
17OHP, nmol/L	0.150	6.850	1.32-7.07
DOC, ng/mL	-	0.257	≤0.30
Corticosterone, ng/mL	-	43.644	0.18-19.70
Aldosterone, ng/mL	-	0.055	0.07-0.35 (standing)
K, mmol/L	2.75	3.84	3.5-5.3
Na, mmol/L	143.00	141.30	137-147
Cl, mmol/L	105.20	105.70	99-110
Ca, mmol/L	2.48	2.41	2.15-2.55

FSH: follicle-stimulating hormone, LH: luteinizing hormone, SHBG: sex hormone binding globulin, DHEAS: dehydroepiandrosterone sulphate, ACTH: adrenocorticotropic hormone, 17OHP: 17α-hydroxyprogesterone, DOC: deoxycorticosterone

(c.316T > C, p.S106P) in exon 2 of *CYP17A1*, and both parents were heterozygous for the p.S106P mutation (Figure 1, Table 2). Case 2 was a compound heterozygote for p.R347C and p.R362H mutations in exon 6 of *CYP17A1*, which were inherited from her mother and father, respectively (Table 2, Figure 2).

Follow-up Data During Treatment

Upon definite diagnosis of 17OHD, Case 1 was treated with dexamethasone (0.5 mg per day) and estrogen (1 mg per day), and was also given vitamin D and calcium supplementation. Case 2 was treated with estrogen (1 mg per day), followed by the addition of prednisone (5 mg per day). The follow-up data of the two cases were collected at 3 months and 9 months after treatment, as shown in Table 3. For Case 1, there was significant weight gain, blood pressure approached the normal range, and serum potassium increased to normal level. The immature uterus and breasts developed gradually. Ultrasonography showed the uterus was $2.6 \times 1.9 \times 2.7$ cm^3, the left ovary 3.0 cm × 1.4 cm, and the right ovary 2.8 cm × 1.4 cm in size. First menstruation occurred after nine months of treatment. The nocturnal enuresis improved greatly, and had almost resolved after six months. Case 2 had her first menstruation after 4 months of treatment. Thereafter, menstrual flow gradually became regular, which occurred every 25-30 days and lasted 3 to 5 days. Her breasts and uterus continued to develop. The latest ultrasonography showed the uterus was $2.6 \times 1.7 \times 2.2$ cm^3, the left ovary 2.9 cm × 1.5 cm, and the right ovary 3.2 cm × 1.8 cm in size.

Written informed consents were obtained from the two patients and their parents to publish this study.

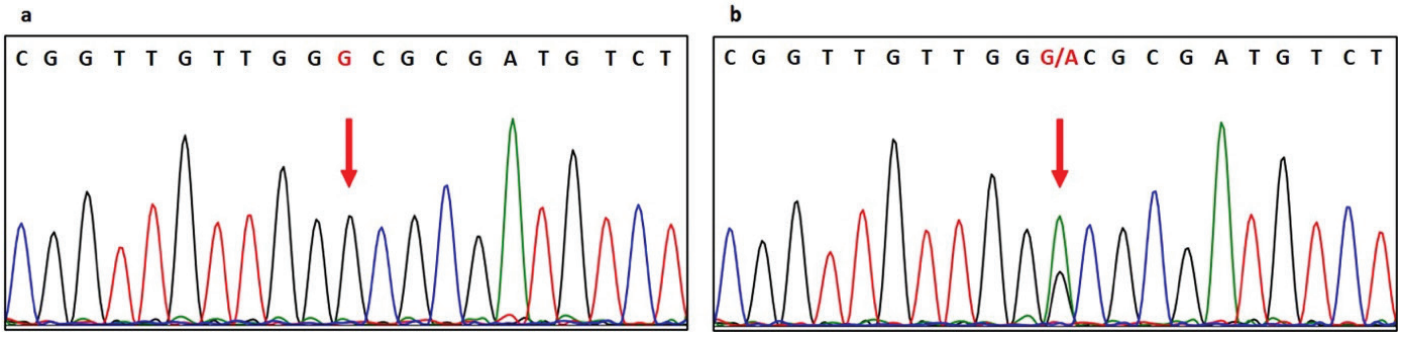

Figure 1. The *CYP17A1* gene mutation analysis for Case 1 and her parents. A) A homozygous missense mutation (A > G) at position 316 in exon 2 was detected in the patient. B) A heterozygous mutation (A > G) at position 316 in exon 2 was detected in both her mother and father

Table 2. Genetic analyses for two cases with 17α-hydroxylase/17,20-lyase deficiency (17OHD)

Parameters	Case 1	Case 2
Karyotype	46,XX	46,XX
Mutant gene	*CYP17A1* gene	*CYP17A1* gene
Mutation	c.316T > C (p.S106P)	c.1039C > T (p.R347C)/ c.1085G > A (p.R362H)
Zygosity	Homozygote	Compound heterozygote
MAF[a]	0.000008	0.000008/0.000032
Location	Exon 2	Exon 6
ACMG classification	Pathogenic	Pathogenic
Disease (OMIM)	17OHD	17OHD
Mutation inherited from mother	c.316T > C (p.S106P)	c.1039C > T (p.R347C)
Mutation inherited from father	c.316T > C (p.S106P)	c.1085G > A (p.R362H)
Loss of P450c17 enzyme acitivity[b]	Complete (7)	Partial (26)/complete (4)

[a]From gnomAD-Exomes, [b]From references.
MAF: Minor Allele Frequency, ACMG: the American College of Medical Genetics and Genomics

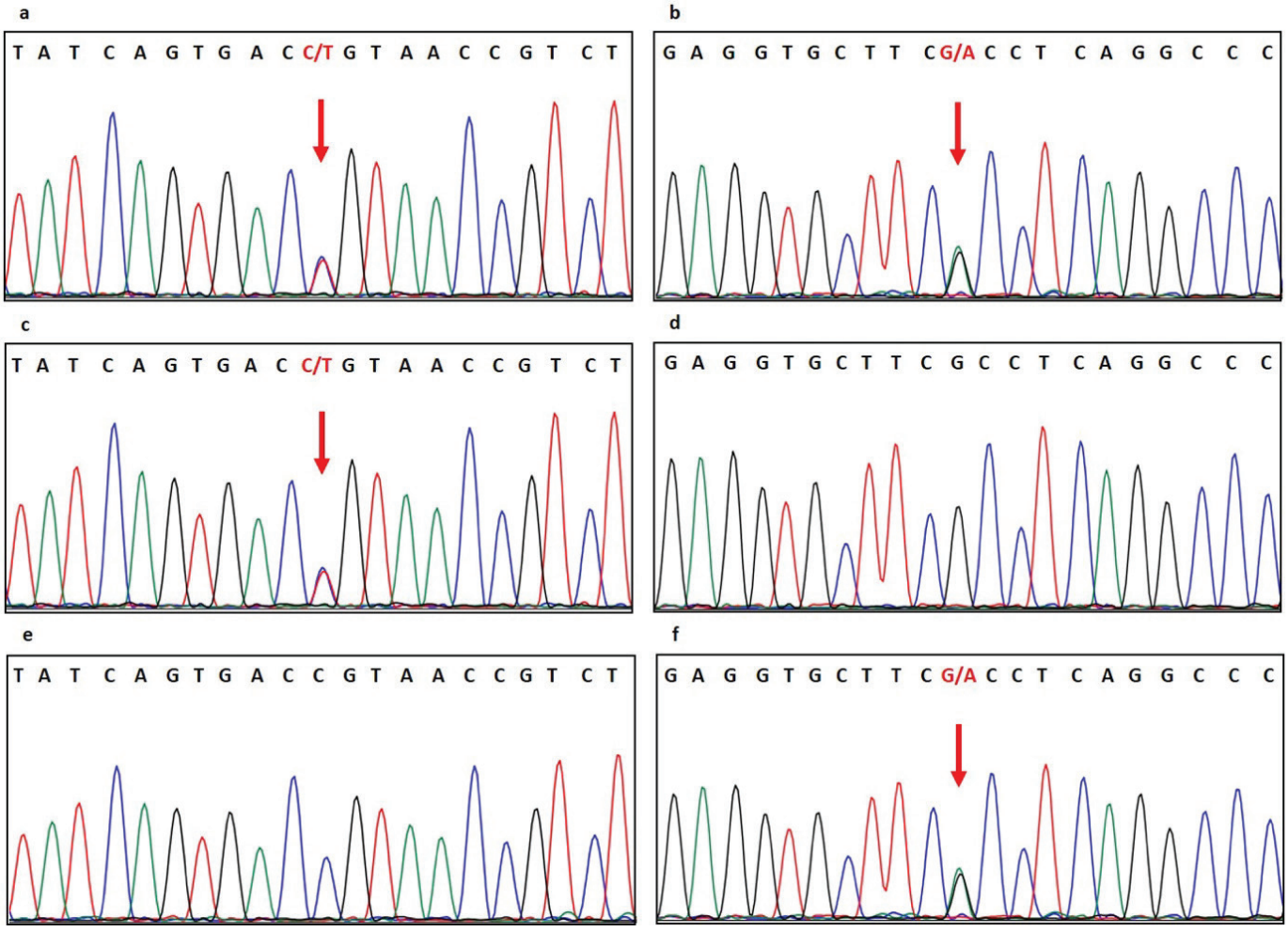

Figure 2. The *CYP17A1* gene mutation analysis for Case 2 and her parents. A) A heterozygous mutation (C > T) at position 1039 in exon 6 was detected in Case 2. B) A heterozygous mutation. (G > A) at position 1085 in exon 6 was detected in Case 2. C) A heterozygous mutation (C > T) at position 1039 in exon 6 was detected in her mother. D) A wild type at position 1085 in exon 6 was detected in her mother. E) A wild type at position 1039 in exon 6 was detected in her father. F) A heterozygous mutation (G > A) at position 1085 in exon 6 was detected in her father

Discussion

CAH due to 17OHD was firstly described in 1966 by Biglieri et al (14). To date there have been at least two hundred cases published. Notably, 46,XX cases are much rarer than 46,XY cases (15). The diagnosis of combined 17OHD in genetic females is generally made at puberty, when patients exhibit absent or delayed puberty development, and hypergonadotropic hypogonadism (16). This phenomenon was also observed in the two 46,XX cases in the current presentation.

Case 1 presented with the typical clinical and laboratory manifestations of complete deficiency of P450c17 enzyme, including primary amenorrhea, infantile external genitalia, no axillary or pubic hair, absent breast development, hypertension, hypokalemia, extremely low levels of cortisol and sex hormones but elevated progesterone, FSH and LH. It was not difficult to make a clinical diagnosis of complete 17OHD. However, Case 2 had a growth spurt and spontaneous breast development as well as normal levels of cortisol, 17OHP and DOC in spite of reduced serum estradiol and testosterone, indicating a less severe estrogenic and androgenic deficit caused by partial loss of both 17a-hydroxylase and 17,20-lyase activities.

In addition to the classic manifestations, Case 1 also showed delayed bone age, decreased bone density and long-lasting nocturnal enuresis. Research has found that bone age retardation and osteoporosis were relatively frequent in 17OHD patients and closely related to the reduced production of sex steroids (17). It is worth noting that this is the first report of nocturnal enuresis in 17OHD patients.

Table 3. The follow-up data of two cases with 17α-hydroxylase/17,20-lyase deficiency during treatment

Parameters	Case 1		Case 2	
	At 3 months	At 9 months	At 3 months	At 9 months
Height, cm	153.0	153.0	166.0	166.0
Weight, kg	38.0	41.5	59.0	61.0
BMI, kg/m^2	16.2	17.7	21.4	22.1
BP, mmHg	110/67	98/79	120/70	112/75
Tanner stage	B2P1	B3P1	B3P1	B4P1
FSH, IU/L	22.25	19.82	10.39	7.69
LH, IU/L	27.67	37.16	13.78	25.59
Estradiol, pmol/L	77.61	31.26	18.35	22.42
Testosterone, nmol/L	-	-	0.09	0.09
Progesterone, nmol/L	17.91	18.17	22.30	20.52
Prolactin, mIU/L	-	-	319.50	303.60
ACTH, pg/mL	36.29	5.90	-	122.71
Cortisol, nmol/L	0.10	38.30	-	133.50
K, mmol/L	3.52	5.17	4.18	-
Na, mmol/L	145	138.50	143	-
Cl, mmol/L	107.10	103.80	105.5	-
Ca, mmol/L	2.40	2.51	2.58	-

BMI: body mass index, BP: blood pressure, FSH: follicle-stimulating hormone, LH: luteinizing hormone, ACTH: adrenocorticotropic hormone

Nocturnal enuresis is intermittent involuntary voiding during sleep in the absence of physical disease in a child aged 5 years or more, which is the most common type of urinary incontinence in children (18). The prevalence of nocturnal enuresis decreases with age, affecting only about 1% of adolescents by age 15 years (19). The etiology of primary enuresis is not completely understood. It is presumed that long-lasting nocturnal enuresis in Case 1 may be linked to her elevated blood pressures, which was thought to cause suppression of vasopressin and sodium regulating hormones secretion resulting in increased renal excretion of solutes and water (20). Another possible explanation is that estrogen deficiency may affect the normal function of the female lower urinary tract, affecting urine storage and elimination. The bladder and urethra, which originate from the urogenital sinus, are under the influence of estrogen, just like the vagina (21). Evidence suggested that estrogen treatment can improve or even cure urinary incontinence, especially urge incontinence (22). Interestingly, the symptom of nocturnal enuresis in Case 1 improved greatly after six months of estrogen and dexamethasone treatment. Of course, coincidence cannot be ruled out because primary enuresis has a spontaneous disappearance rate of around 15% per year (18).

Using molecular diagnostics, a homozygous p.S106P and a compound heterozygous p.R347C/p.R362H mutation in *CYP17A1* were identified in Case 1 and Case 2, respectively. The findings confirmed the diagnosis of 17OHD, which has been recognized as an autosomal recessive disease caused by the homozygous or compound heterozygous mutations of *CYP17A1* gene. The *CYP17A1* gene, located on chromosome 10q24.3, consists of 8 exons and 7 introns encoding a 508 amino acid protein P450c17 (17). More than 100 mutations have been reported since the *CYP17A1* gene was first cloned in 1987 (23). The majority appear to be random, while several mutations reoccur in certain ethnic groups, suggesting a founder effect, such as p.W406R and p.R362C mutations in Brazilians (4), and D487_F489 deletion and p.Y329fs in Chinese (24,25). Here, though, the three variants identified in the present study are not prevalent in Chinese but they all have been identified in 17OHD cases previously. In addition, the enzymatic activities of these mutants have been reported and explained in the literature (4,7,26,27).

Homozygous S106P mutation was first reported in two unrelated Guamanian genetic males with the complete form of 17OHD in 1991 (7). Afterwards, two Chinese 17OHD patients were found to be compound heterozygotes for S106P and other mutations in *CYP17A1* gene (28,29). Site-

directed mutagenesis experiment showed that the mutant S106P had neither 17α-hydroxylase nor 17,20-lyase activity (7). According to molecular modeling of the human P450c17 sequence, the mutant S106P destroys all P450c17 enzyme activity by altering the positioning of I112 which is a highly conserved residue that forms one edge of the substrate-binding pocket (3).

There have been several previously reported patients carrying the c.1039C>T (p.R347C) mutation (25,26,30,31,32). The majority were compound heterozygotes (25,26,30), while only two cases were homozygote, a 67-year-old Japanese woman with partial combined 17OHD (31) and a 46,XY case with isolated 17,20-lyase deficiency (32). The arginine of codon 347 lies in the redox-partner binding site and contributes positive charges to the proximal surface of P450c17, at which cytochrome b5 interacts with the P450c17-oxidoreductase complex to promote electron transfer (2,3). Though it was found that normal functioning of the redox-partner binding site is essential for the 17α-hydroxylase/17,20-lyase activities of P450c17, the mutations affecting a cluster of basic residues usually lead to subtle defect in electron transfer and selectively disrupt 17,20-lyase activity without substantial reductions in 17α-hydroxylase activity, such as p.R347H and p.R358Q (11). Remarkably, R347C disrupts the function of the whole protein more seriously than p.R347H probably because of the formation of abnormal cysteine dimers (26). An *in vitro* study found that the R347C mutation had 13.6% and <1% of 17α-hydroxylase and 17,20-lyase activities, respectively (26). Nevertheless, some 17,20-lyase activity may be retained due to the accumulation of cytochrome b5 and oxidoreductase, resulting in the development of secondary sexual characteristics (11).

With regard to the other *CYP17A1* mutation in Case 2, p.R362H has been identified in a Mexican mestizo, a Turkish, and a Chinese previously, all with complete 17OHD (25,27,33). The R362 residue comprises part of the highly conserved ExxR motif at the C-terminus of the K helix, a motif present in all known cytochrome P450 enzymes (3,23). The hydrogen bonding between the adjacent E and R residues in this motif stabilizes the structure of the K helix, and helps to form the redox-partner binding site (3). Studies suggested that Arg362His replacement weakens hydrogen bonding within the ExxR motif and completely impaired the enzymatic activities (4,27).

Although the p.R347C and p.R362H mutations of *CYP17A1* gene have been reported separately before, their compound heterozygote was firstly described in Case 2 in the present study. This new compound heterogenous mutation leads to partial 17OHD, which may result from the affected function of the redox-partner binding site. Further cases or functional analyses are needed to draw a conclusion on genotype-phenotype correlations of the compound heterogenous mutation.

Conclusion

17OHD is a rare cause of CAH, and arises from the homozygous or compound heterozygous mutations of *CYP17A1*. The present study identified two unrelated 46,XX cases with complete and partial 17OHD respectively. The homozygous p.S106P mutation detected in the case with complete 17OHD has been reported previously. Although the p.R347C and p.R362H mutations of *CYP17A1* gene have been reported separately before, their compound heterozygote was firstly identified in Case 2 with partial 17OHD. Moreover, we describe a case of complete 17OHD accompanied by nocturnal enuresis for the first time.

Ethics

Informed Consent: Written informed consents were obtained from the two patients and their parents to publish this study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: Ting Han, Yingxia Wang, Yinglan Wu, Concept: Yamei Li, Yinglan Wu, Design: Yamei Li, Yinglan Wu, Data Collection or Processing: Yamei Li, Ting Han, Yingxia Wang, Analysis or Interpretation: Yamei Li, Jie Gao, Jianglin Zhang, Yinglan Wu, Literature Search: Yamei Li, Ting Han, Writing: Yamei Li, Jie Gao.

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