Clinical Characteristics and Molecular Aetiology of Cytochrome P450 Oxidoreductase Deficiency Diagnosed in 46 XX Patients

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Research Article

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Abstract

Background

P450 oxidoreductase deficiency (PORD) affects cytochrome enzyme activities, causing various symptoms, such as adrenal insufficiency, disorders of sex development and skeletal malformations. This study aims to elucidate the clinical manifestations, genotype characteristics, diagnosis and management of 46 XX karyotype patients with PORD in China.

Method

The patients' clinical characteristics were summarized based on manifestations, hormone profiles, and responses to treatments. Seven patients aged between 11 and 19 years were included in the series from 2004 to 2022 in a tertiary medical centre.

Result

All patients presented ovarian multilocular cysts and different manifestations of skeletal malformation. Patients after puberty all suffered from abnormal menses. Five patients' external genitalia exhibited virilizing patterns, and three had received perineoplasty. The hormone analyses of six patients indicated hypergonadotropic hypogonadism, while all patients' progesterone and deoxycorticosterone levels were elevated. The most frequent *POR* mutation, c.1370G > A, is located on exon 11 and appears in all seven patients with an allele frequency of 92.9% (13/14). One case was a carrier of a novel variance (c.1684dupG), situated within exon 14, encoding a nonsense mutation in the NADPH binding area.

Conclusion

Therefore, c.1370G > A could be a dominant mutation type of PORD in China. Female patients with PORD have a vulnerable ovarian reserve, and their ovarian macrocysts can be managed conservatively for fertility preservation. This study specifically focuses on PORD in 46 XX Chinese individuals, which implies its genetic causes with novel genetic findings and summarizes patients' puzzling spectrum of clinical manifestations.

Introduction

Cytochrome P450 oxidoreductase (POR) serves as a flavoprotein that transfers electrons from the primary electron donor (e.g., nicotinamide adenine dinucleotide phosphate hydrogen (NADPH)) to all microsomal cytochrome P450 enzymes. POR deficiency (PORD) pertains to rare congenital adrenal hyperplasia (CAH), contributing to varying degrees of compromised activity of a broad array of steroidogenic enzymes, such as P450c17, P450c21 (21-hydroxylase), P450aro (aromatase) and P450 51A1 (sterol 14α-demethylase), leading to corresponding clinical phenotypes [1–3]. PORD is caused by pathological variations in the *POR* gene on chromosome 7q11.23[1]. Distinguished from other CAHs, PORD affects bone development, and it was first reported as a CAH subtype of Antley–Bixler syndrome (ABS) combined with urogenital defects in 2004[1]. Since then, more than 100 cases have been published around the world[4]. Due to the combination of pathophysiological mechanisms in 21-hydroxylase deficiency (21OHD), 17α-hydroxylase deficiency (17OHD) and 14α-demethylase deficiency, the clinical manifestations of PORD span from steroid deficiency in CAH to, disorders of sex development (DSD) to skeletal malformations.

When referring to 46XX DSD, the deprivation of normal oestrogen synthesis will spur gonadotropin secretion and prompt recurrent multilocular ovarian cysts, which are commonly found among PORD patients [5]. In addition, damage to POR function may impair sex steroid metabolism, resulting in ambiguous genitalia and infertility in 46 XX females[1, 2]. From these two aspects, these patients will have special gynaecological problems, and the symptoms and signs need to be carefully distinguished from other forms of DSD or CAH.

Here, we retrospectively summarized seven 46 XX female patients with PORD over the past 18 years since 2004 in our department and analysed their clinical presentations, hormone changes, gene mutations, treatments, and prognosis. Due to their puzzling manifestations, PORD patients with the 46 XX karyotype are often misdiagnosed and received inappropriate medical or operational treatments. Due to a founder effect, Japanese people are thought to have a higher prevalence of PORD[6]; however, data involving the genotype–phenotype characteristics of the Chinese ethnicity are limited, and no reports have focused on a specific karyotype. To our knowledge, this is the first study to specifically address Chinese PORD patients with 46 XX. We hope to illustrate their endocrinological characteristics, clarify the genetic basis and guide the management of PORD, especially those interventions relevant to preservation of fertility.

Materials And Methods

Patients and clinical data

Patients with PORD were included if the peripheral blood karyotype was 46 XX and if clinical and biochemical manifestations confirmed PORD, with medical histories being completely documented. The study was approved by the Ethics Committee of Peking Union Medical College Hospital (PUMCH) (IRB Number: JS-2510). Written consent was obtained from all adults or legal guardians of minors under 18 years old.

The clinical presentations of patients with PORD with 46 XX included irregular menses, primary or secondary amenorrhea, underdeveloped breast, sparse axillary and pubic hair, virilizing genitalia, and skeletal malformation.

The laboratory results of PORD were increased serum adrenocorticotropic hormone (ACTH) with increased 17α-hydroxy progesterone (17OHP) and 11-deoxycorticosterone (DOC). Sex hormones usually presented as hypergonadotropic hypogonadism—the oestradiol (E2) level remained at the early follicular stage level with a luteal-phase progesterone (P) level [6].

Medical data, including age, social sex, chief complaint, clinical investigation, management, menstrual history and family history from 2004 to 2022, were retrospectively collected from medical records. Sequencing of the *POR* gene is crucial for final validation, but clinical diagnosis depended primarily on the patients' manifestations and laboratory results.

Physical examination was recorded at their very first visits. Abnormal skeletal morphology was recorded. Breast, axillary and pubic hair development were assessed using the Tanner rating scale, while the external genitalia were allocated to the proper Prader stage. Laboratory investigations included (1) gonadal function: anti-Müllerian hormone (AMH), follicle-stimulating hormone (FSH), luteinizing hormone (LH), E2, P and T and pelvic sonography for the internal reproductive organs; (2) adrenal function: ACTH, 17OHP, cortisol (F), aldosterone (ALDO), androstenedione, dehydroepiandrosterone (DHEA), dehydroepiandrosterone sulfate (DS), 11-deoxycorticosterone (DOC), serum sodium (Na+), and serum potassium (K+). Peptide hormone tests were performed via an automated Elecsys Immunoanalyzer (Beckman Coulter UniCel DXI800, Beckman Coulter; Brea, CA, USA), and the mass spectrometric method (LC—MS/MS, Quest, USA) was used for the comprehensive analysis of steroid metabolism. The follow-up time ranged from two months to more than 11 years.

Mutation analysis of the POR gene by Sanger sequencing

Blood samples were collected for sequencing of the *POR* gene (NM_000941.3). Genomic DNA from peripheral blood was extracted using a Lab-Aid 820 Automatic DNA Extraction Kit (Xiamen Zhishan Biotechnology Co., Ltd., China) according to the manufacturer's instructions. Exons and flank areas of *POR* were tested through Sanger sequencing.

Results

General clinical characteristics

Seven patients were eligible for analysis (Table 1). They all presented as females with a 46 XX karyotype. Their first visits were between 11 and 19 years old. The majority camewere due to abnormal menses (5/7, 71.4%), and the second most common complaints were ovarian cysts (3/7, 42.9%). All patients experienced spontaneous but less-developed breast development (Tanner stage II-V), while the axillary and pubic hair were almost in line with their ages (Tanner stage II-IV). Five patients' external genitalia exhibited virilizing patterns, staged as Prader I-IV, and three (Cases 2, 3 & 6) had received perineoplasty to correct the clitomegaly and/or labial fusion. No patient complained of retardation of height growth or hypertensive disorder.

Table 1
e 1 General characteristics of 7 patients with PORD

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7
Age at first visit (years)	12	14	19	17	17	16	11
Current age (years)	16	24	22	18	18	17	13
Chief complaint	Recurrent ovarian cysts	Pelvic mass Irregular menses	Primary amenorrhea	Primary amenorrhea	Bone deformity Irregular menses	Secondary amenorrhea	Recurrent ovarian cysts
Menses cycle	Before menarche	2–6 months	Amenorrhea	Amenorrhea	2–3 months	1–2 months	Before menarche
Height (cm)	155	146	169	168	157	172	168
Weight (kg)	52	47	56	51	34	55	70
Blood pressure (mmHg)	106/63	108/70	121/67	111/69	101/61	107/72	110/70
Breast (Tanner stage)	II	II	III	V	III	IV	II
Pubic/axillary hair (Tanner Stage)	III/II	IV/III	III/III	II/II	IV/II	II/II	I/II
External genitalia (Prader Stage)	Female	III	IV	Female	I	III	Female
Skeletal system	Scoliosis	Midface hypoplasia, Metatarsus adductus	Radiohumeral synostosis	Joint contraction of limbs	Arachnodactyly, Scoliosis	Midface hypoplasia	Midface hypoplasia
Previous medical history	-	Ovarian cystectomy twice, and pathology confirms luteinized cyst clitoroplasty	Clitoroplasty Plasty of labia majus	-	-	Ovarian cystectomy once, and pathology confirms luteinized cyst Plasty of labia majus	Ovarian cystectomy once, and pathology confirms luteinized cyst

Gonadal axis function

Their serum E2 levels followed an early-follicular-stage pattern. Specifically, serum P levels were abnormally elevated (6.60-14.78 ng/mL), serum T levels ranged from normal to slightly higher, and gonadotropins (FSH and LH) were moderately to severely elevated (Table 2). All seven patients had bilateral enlarged multilocular ovaries. Cases 2, 6 & 7 had received ovarian cystectomy, and their pathologies confirmed the diagnosis of luteinized cysts. All patients were prescribed combined oral contraceptives (COC) after diagnosis of PORD, and no relapse of ovarian cysts occurred thereafter. They were negative for ovarian tumour markers, including CA12-5, CA19-9, HE4, CEA, and AFP.

Adrenal axis function

For impaired glucocorticoid metabolism, four patients (Cases 2, 3, 6 & 7) had significantly high ACTH, but only Cases 2 & 7 presented reduced serum F levels (Table 2). The 17OHP level was exclusively above the upper limit, and those of Cases 2, 5, 6 & 7 were even higher than 10 ng/mL. The mineralocorticoid axis was also involved. The serum DOC level extended beyond the reference range, compared to patients' shortage of ALDO (except for the unavailable data of Case 1). However, all patients' blood pressure was normal, and the serum interference with Na^+ and K^+ levels was not observed. No case reported an abnormal DS or androstenedione level in circulation.

Table 2
Gonadal and adrenal axes of 7 patients

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Reference range
AMH (ng/mL)	-	-	-	1.66	0.14	0.06	0.57	0.65–9.98
FSH (IU/L)	13.3	6.56	42.7	10.4	26.70	80.87	26.8	<10.00
LH (IU/L)	4.45	1.29	31.5	22.8	28.4	28.27	10.5	2.12–10.89
E2 (pg/mL)	40.7	32.9	31.2	26.0	37.8	28.2	21.7	22–115
P (ng/L)	11.07	8.55	6.06	6.10	14.78	11.03	12.39	0.38–2.28
T (ng/mL)	0.31	0.72	0.32	0.38	0.13	0.07	0.25	<0.41
17OHP (ng/mL)	9.57	14.96	6.65	9.41	16.61	17.72	14.93	0.3–2.34
DS (ng/mL)	105.6	22.0	68.3	24.1	69	163.6	175.71	12–133
DHEA (ng/mL)	-	1.2	1.8	2.2	< 0.5	2.9	< 0.5	< 6.6
Androstenedione (ng/mL)	-	1.21	0.74	1.84	0.55	0.32	0.93	0.12–2.25
ALDO (ng/mL)	-	0.041	0.060	0.065	<0.02	0.039	<0.02	0.065–0.220
DOC (ng/mL)	-	0.286	0.143	0.381	0.201	0.414	0.702	<0.100
ACTH (pg/ml)	36.7	55.5	110	33.3	35.2	65.9	218	0–46
Cortisol (μg/dl)	10.99	3.73	13.78	12.3	6.6	16.2	3.5	4.0-22.3
K (mmol/l)	4.3	4.9	4.6	4.9	3.97	4.5	4.4	3.5–5.5
Na (mmol/)	142	137	141	140	142.4	143	141	135–145
Pelvic ultrasound	Infantile uterus, Left ovary: 4.5 cm×2.6 cm, multilocular cysts Right ovary: 5.2 cm×3.0 cm, the largest one is 3.1 cm in diameter, multilocular cysts	Infantile uterus, Left ovary: 8.9 cm*7.3 cm, multilocular cysts Right ovary: 9.2 cm*6.3 cm, multilocular cysts	Infantile uterus, Left ovary: 5.4 cm*4.3 cm, multilocular cysts Right ovary: 3.5 cm*3.3 cm	Infantile uterus, Left ovary: 4.1 cm×2.3 cm, multilocular cysts Right ovary: 4.9 cm×1.8 cm, the largest one is 4.3 cm in diameter, multilocular cysts	Normal uterus, Left ovary: not evident Right ovary: 10.0 cm*6.3 cm, multilocular cysts	Normal uterus, Left ovary: 3.1 cm×2.7 cm, multilocular cysts Right ovary: 12.0 cm*7.7 cm, multilocular cysts	Infantile uterus, ovary: nothing abnormal detected Right ovary: 10.3 cm×6.3 cm, multilocular cysts, Doppler: resistance index 0.48	-

Note: 17OHP (17α-hydroxy progesterone); ACTH (adrenocorticotropic hormone); AMH (anti-Müllerian hormone); ALDO (aldosterone); DHEA (dehydroepiandrosterone); DOC (11-deoxycorticosterone); DS (dehydroepiandrosterone sulfate); E2 (oestradiol); FSH (follicle-stimulating hormone); LH (luteinizing hormone); T (testosterone).

Detection of genetic mutations

The detected *POR* mutations are summarized in Table 3. Cases 4 & 7 were originally diagnosed as isolated 17,20-lyase deficiency (a rare form of 17OHD) according to their clinical manifestations. However, Sanger sequencing revealed no mutation in *P450c17A1*. Therefore, a further analysis of the *POR* gene was arranged. Cases 1 to 6 carried accordant mutations, which were uniformly c.1370G > A (p. Arg457His) for two alleles, while case 7 was a carrier of two heterozygous allele mutations, including this prevalent mutation and a novel mutation (c.1684dupG, p. Glu562Gly fs*13). This newly discovered variance was situated within exon 14, encoding a nonsense mutation in the NADPH binding area. The most frequent mutation, c.1370G > A, was located on exon 11 and belonged to the missense category. This variation appeared in all seven patients, with an allele frequency of 92.9% (13/14).

Table 3
Summary of *POR* gene mutations in 7 patients

	Genotype	Amino acid changes	Exon	Coding effect	Functional domain	ACMG classification	Previous reports	dbSNP	Scores of SIFT prediction	Prediction (cut-off = 0.05)
Case 1 to Case 6	c.1370G > A	p.Arg457His	11	Missense	NADPH-binding	pathogenic	Yes	rs28931608	0.00	Deleterious
Case 7	c.1370G > A	p.Arg457His	11	Missense	NADPH-binding	pathogenic	Yes	rs28931608	0.00	Deleterious
	c.1684dupG	p.Glu562Glyfs*13	14	Frameshift	NADPH-binding	pathogenic	New	N/A	-	Loss of function

Note: dbSNP (single nucleotide polymorphism database); N/A (not available); NADPH (nicotinamide adenine dinucleotide phosphate); rs (reference SNP); SFIT (sorts intolerant from tolerant).

Discussion

A compromised function of POR will disrupt the cytochrome P450 system, leading to failures in steroid synthesis, skeletal development and ambiguous genitalia. PORD is rare but usually exhibits a variety of clinical manifestations, such as oligomenorrhea and ovarian cysts that resemble polycystic ovary syndrome (PCOS), elevated 17OHP that resembles 21-OHD, and skeletal deformities that resemble ABS. Notably, PORD does not reveal hyperandrogenism, which is a departure from PCOS and 21-OHD. These seven 46 XX patients in this cohort exhibited consistent clinical hormone profiles, mimicking combinations of 21OHD and 17OHD. In addition, their masculinized genitalia, malformation of the skeleton and classical genetic mutations also correspond to the signature PORD.

Genotype-Phenotype Analysis

Although we describe cases particularly in 46 XX females, PORD involves both chromosomal sexes at a roughly equal rate, and the majority are of European or Japanese descent[7]. In line with the autosomal recessive pattern of inheritance, biallelic mutations in the POR gene were detected in all seven cases. The *POR* gene contains 16 exons. Exons 1 to 15 encode the POR enzyme containing 680 amino acids, while an extra exon does not encode any protein[8]. Spread is the flavin mononucleotide domain of POR directly transferring electrons for P450 enzymes, while most mutations are clustered in the NADPH-binding domain serving as the electron donor. Nevertheless, data from three large PORD cohorts have reached only a poor genotype–phenotype correlation[9–11]. Among all seven patients, exon 11 of *POR* harbours at least one mutation (c.1370G > A), which leads to a conversion of arginine at amino acid position 457 to histidine. This *POR* mutation, p.Arg457His, is most widely reported in Japanese people [4, 7], and it is also the most prevalent in our cohort, present in 13 out of 14 alleles. However, in patients of Caucasian origin, the p.Ala287Pro is the most frequently reported[10]. Previously, an in vitro study found that p.Ala287Pro does not impair aromatase activity but that p.Arg457His abolishes it; both mutations lead to 46 XX virilization if present in the homozygous state[12]. Therefore, the p.Arg457His is reported to be associated with virilization in 46,XX patients but likely results in normal male genital development[6]. In addition, because cholesterol production in skeletal tissues occurs in a simple one-way manner without alternative reactions, the skeletal phenotype is supposed to depend obviously on the p.Arg457His dosage, reflecting the residual activity of POR[6]. As a result, the threshold for the development of severe skeletal phenotypes resides between a single copy and two copies of the p.Arg457His residual activity. In Case 7, we reported a newly discovered null mutation c.1684dupG (p. Glu562Gly fs*13). Since the frameshift variance contributes to a premature termination of peptide chain, leaving almost 100 amino acids unattached, the mutated enzyme is presumably to be loss-of-function. No PORD-affected live-born individual has been found to carry this kind of null mutation on both alleles thus far. This suggests that such a genotype is incompatible and lethal to postnatal life, which is in accordance with the observation of early intrauterine foetal death in the *Por* deletion murine model[13].

Endocrine characteristics

Most newly discovered PORD cases are infants or even foetuses, while adolescents and adults account for only 24%[7]. The most prevalent clinical manifestations were an aberrant hormonal profile at birth or developmental delay since puberty (89.2%), ABS-like skeletal deformity (82.7%), disorders of sex development or hermaphroditism (75%), nonclassical CAH-related symptoms (74.6%), ovarian multilocular morphology in females (46.7%) and maternal virilization during pregnancy (40.8%)[7]. These figures refer to PORD as a typical endocrinological issue. The low serum E2 levels (21.7–40.7 pg/mL) of our seven cases are attributed to decreased ovarian androgen production (except Case 2) and its subsequent aromatization[14]. The hypogonadism is partially responsible for the negative feedback of high FSH. This could be mixed with ovarian insufficiency, particularly when patients have menstrual problems and low AMH (Cases 5, 6 & 7). Low-to-normal AMH can exist in these patients, and this scenario is commonly seen in other CAH subtypes, such as 17 OHD[15]. Since patients with severe *POR* mutations suffer from severe P450 enzymatic defects,

their follicular reservoir can undergo premature failure due to impaired granular cell steroid metabolism; mild forms of mutation that leave partial secretive function of follicles contribute to the residual ovarian follicles' response to the persistent stimulation of raised FSH. Interestingly, regardless of the level of AMH or FSH, all patients are found to have ovarian multilocular cysts, and these cysts are frequently seen in compromised function of POR[16]. The underlying cause is that the relatively young age of these patients is distinguished from the postmenopausal exhaustion of the ovarian reserve. Even a limited number of remaining follicles will respond to FSH recruitment and grow into a multilocular ovarian morphology. In addition to the accumulation of P as a steroid precursor, excessive LH will mediate luteinization of these cysts and further promote P production in these PORD-CAH patients[17]. All affected individuals from our cohort exhibited a simultaneous increase in serum 17OHP and P, which misleadingly suggested nonclassical (NC) 21OHD. Moreover, impaired catalytic activity of 17,20-lyase is responsible for decreased circulating androgen levels, which mimics the isolated 17,20-lyase (ILD) form of 17OHD, but differs from 21OHD and PCOS[16]. Surprisingly, 75% of PORD patients with 46 XX are commonly accompanied by ambiguous genitalia[7]. Four of our cohorts (4/7, 57.1%, Cases 2, 3, 5 & 6) underwent virilization of external genitalia. This is an apparent dichotomy, given that DHEA and androstenedione production in the foetus should be disturbed due to impaired 17,20-lyase activity. Even the modest amount of androgens produced could be accumulated due to the deficiency of placental aromatase affected by PORD[18]. In addition, elevated 17OHP, which cannot be efficiently metabolized via P450c21 or P450c17 activities, seeks an alternative pathway via 5α-reduction and is ultimately converted to DHT[19].

Skeletal deformities are associated with lanosterol 14α demethylase (CYP51A1), which is involved in cholesterol biosynthesis[20] and retinoic acid metabolism by microsomal CYP26 enzymes[21]. Compound heterozygous and homozygous mutations in the *POR* gene are associated with more serious skeletal deformities, resulting from the effect of various mutations on the activity of related enzymes[10]. Cases 1 to 6 harbour the same homozygous mutation but have various skeletal deformities, illustrating the heterogeneity of this symptom in PORD.

Ovarian cysts and fertility outcomes

Ovarian cysts can trigger significant morbidity ranging from mild abdominal tenderness to acute ovarian cyst rupture or torsion. All patients from our cohort had fluid-filling luteinized cysts of at least one ovary. Cases 2, 6 & 7 have even previously undergone ovarian cystectomy, and their pathologies confirmed the diagnosis of luteinized cysts. All patients are prescribed COC after the operation, and this provides effective conservative management for this type of recurrent cyst. Large cysts shrink soon after COC administration in most patients by suppressing gonadotropin stimulation from the hypophysis; however, ovarian cysts may reappear after the cessation of COC treatment, and it is still effective to use it again to repress the cyst[22]. Their ovarian tumour markers were negative at the beginning. However, if ovarian cysts persist after COC intervention, the possibility of nonfunctional tumours should be excluded. In addition, recurrent functional ovarian cysts in 46XX PORD must be differentiated from other endocrine-related diseases, such as 46 XX partial 17OHD, Van Wyk–Grumbach (VWG) syndrome, and functional gonadotroph adenomas (FGAs) [23].

Fertility preservation is a challenging issue for 46 XX patients with PORD. Natural conception has not been reported in these females, and almost all patients of reproductive age encounter primary infertility[16]. PORD will implicate CYP51A1, an enzyme responsible for the conversion of lanosterol to meiosis-activating sterols, which in turn cause defective oocyte maturation[24]. For patients with severe mutations of *POR* leading to the complete loss of enzymatic function, the premature depleted ovarian reservoir offers them a rare chance to conceive[16]. For patients still equipped with remaining primordial follicles and diagnosed with a partial loss of POR activity, endocrinological elements lead to a barrier to natural fertility. The main contributing factor is excessive P levels without cyclic change, which in turn exert an anti-gonadotropic effect on the hypothalamus and pituitary gland. Without the physical periodic fluctuation of gonadotropin, even in those cases with oligomenorrhea, ovulation seldom occurs spontaneously. This is presumably due to the blockage of LH positive feedback on rising E2 by high P levels. Persistently high circulating P levels reverse the endometrial receptivity synchronized with embryo development[25] and alter the cervical mucus. Moreover, anovulation could also be blamed for defective follicular maturation due to steroidogenesis failure, particularly androgen deficiency[26]. Thanks to the advancement of assisted reproductive technology (ART), pregnancy can be achieved by controlled ovarian stimulation (COS) and in vitro fertilization[22] while suppressing P with potent corticosteroids and creating an artificial menstrual cycle with hormone replacement for frozen-thawed embryo transfer[27]. Bosch *et al* revealed that serum P levels < 1.5 ng/ml over COS are associated with higher live pregnancy rates[28]. Consequently, pregnancy can be achieved in females through ART if PORD is correctly diagnosed as early as possible and if the ovaries are well protected by avoiding unnecessary operation due to the spontaneous disappearance of cysts following the commencement of COC[22]. This is essential for dealing with multilocular cysts and protecting the diminished ovarian reserve in 46 XX PORD patients, maximizing their chance for future ART.

Limitations

Several limitations exist in our study. Primarily, since PORD is a rare type of CAH, the sample size is very limited, but we are working on the collection and updating of new cases. Second, some laboratory studies can be modified without consideration of cost and accessibility in our hospital. The pathogenicity of the newly identified mutation (c.1684dupG) was not evaluated by an in vitro functional study. The skeletal evaluation was based on physical examination and plain radiographs in some cases; peripheral quantitative computed tomography for the study of bone lesions might be a better option. In addition, the assessment of adrenal function by serum steroid variation with ACTH stimulation is more precise and solid[29]. Given that PORD affects multiple systems, its management is challenging and should encompass transdisciplinary cooperation, including paediatric endocrinologists and orthopaedists. Herein, we provide management experience dominantly from the perspectives of gynaecological endocrinology and reproduction and hope to promote patients' sexual-developmental and fertility outcomes.

Conclusion

We present a whole picture of the clinical manifestations, genotype characteristics, diagnosis and treatments of 46 XX female patients with PORD in Chinese patients. According to our series, c.1370G > A (p. Arg457His) is possibly the most prevalent mutation of *POR* in Chinese people due to the same founder effect as that of the Japanese ethnicity. In addition, a novel nonsense mutation (c.1684dupG) is reported. PORD in 46 XX can be misdiagnosed as 17OHD, especially the ILD form. Bone malformation is the key to the differential diagnosis, but it may not be recognized or not very signature. Recurrent ovarian cysts in females with PORD can be effectively suppressed using COCs instead of repeated ovarian cystectomy. Early diagnosis, timely steroid supplements, and ART may make it possible for these patients to retain their fertility and have their own biological children.

Declarations

Ethics approval: This study was approved by the Ethics Committee of PUMCH.

Consent to participate: Written consent was obtained from each individual or legal guardian if underage.

Consent for publication: Written consent was obtained from each individual or legal guardian if underage.

Availability of data and material: All data generated or used during the study appear in the submitted article.

Competing interests: There were no conflicts of interest.

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Author contributions: Conceptualization: Qinjie Tian, Fengxia Yao; Data curation: Zhan Duoduo, Fengxia Yao; Data collection: Shan Deng, Min Luo; Funding acquisition: Qinjie Tian; Investigation: Zhang Duoduo Fengxia Yao; Methodology: Fengxia Yao; Writing – original draft: Duoduo Zhang; Writing – review & editing: Qinjie Tian, Fengxia Yao

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