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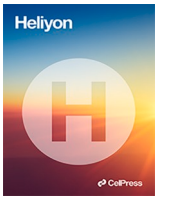

Case report

Genetic analysis and counseling of ADPKD caused by novel heterozygous mutations of *PKD1* in two Chinese families: Case report

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ABSTRACT

Autosomal dominant polycystic kidney disease (ADPKD) is the most common hereditary kidney disease, characterized by the progressive formation of multiple cysts in both kidneys, destruction of the renal structure, changes in renal function and eventually leading to end-stage renal failure and renal transplantation. In our study, Whole-exome sequencing (WES) was used to identify the responsible mutation of ADPKD in two unrelated Chinese PKD families. The WES revealed three variants in the *PKD1* gene, c.9857T > C in family 1, c.9860T > G and c.3496G > A in family 2. The comprehensive analysis of population frequency, conservation, structural prediction, and pathogenicity prediction by multiple software suggests that c.9857T > C and c.9860T > G in the *PKD1* gene are the primary causes of occurrence and inheritance of ADPKD in family 1 and family 2, respectively. Due to the significant genetic heterogeneity of ADPKD, it's necessary to understand molecular mechanisms further and collect more data on gene mutations that cause ADPKD. The newly discovered *PKD1* variant in this study can expand the database of gene variants and understanding of ADPKD, and provide valuable information for accurate diagnosis and genetic counseling of ADPKD families.

1. Introduction

Polycystic kidney disease (PKD) is a common autosomal genetic disease, which is a group of diseases characterized by fluid-filled renal cyst hyperplasia. These cysts can cause progressive damage to normal renal parenchyma and eventually lead to progressive renal failure. It is also the most common reason for end-stage renal disease in adults and children. According to different genetic patterns, PKD can be divided into autosomal recessive polycystic kidney disease (ARPKD) and autosomal dominant polycystic kidney disease (ADPKD). ADPKD is the most common monogenic genetic disease, and the prevalence of ADPKD is reported to be between 1 in 400 and 1 in 1000 live births [1–3], ranking first in hereditary nephropathy. Symptoms typically manifest in adulthood; however, approximately 2–5% of cases present before 15 years of age. The renal phenotype ranges from patients in advanced age with preserved kidney function to rare cases of enlarged kidneys detected in utero. In addition to the clinical manifestations caused by impaired renal function such as low back pain, hematuria, repeated urinary tract infections, proteinuria, hypertension, abdominal masses, and renal failure, ADPKD can also cause extrarenal lesions such as hepatopancreatic cysts, colonic diverticulum, cardiac valvular disease, and

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intracranial aneurysms [2,4]. At present, the proposed pathogenesis mainly includes a two-hit mechanism [5], cilia pathogenesis hypothesis [5,6], helix zone-helix zone interaction theory, and so on.

Most ADPKD is genetically heterogeneous and is caused by pathogenic mutations of *PKD1* (OMIM:173900) and *PKD2* (OMIM:173910) (*PKD1* gene mutation accounts for about 85 %, *PKD2* gene mutation accounts for about 15 % [7]). Other rare pathogenic genes include the glucosidase II alpha subunit gene (*GANAB*), DNAJ source B subfamily 11 gene (*DNAJB11*), etc. involved in the maturation and trafficking of the polycystin [3,8]. *PKD1* is located in 16p13.3, which is composed of 46 exons and encodes a 4303 amino acid protein. The coding product, polycystin-1 (PC-1), is a receptor protein for cell-cell/matrix interaction and regulates cell proliferation and apoptosis. *PKD2* is located in 4q22.1 and contains 15 exons, which encode polycystin-2 (PC-2) with 968 amino acids. Its function is a transient receptor potential ion channel, regulating intracellular calcium concentration. PC-1 interacts with PC-2 to form a functional complex, which acts as a flow-dependent mechanical sensor for regulating the differentiation state of renal tubular epithelial cells [9–11]. In the primary cilia of the kidney, the interaction between the two coding proteins is essential for maintaining normal renal tubular structure and promoting the adhesion, proliferation, and differentiation of renal tubular epithelial cells [12].

In the latest version of the ADPKD Variant Database (https://pkdb.mayo.edu/variants), 2322 *PKD1* mutations involving 2077 families and 278 *PKD2* mutations involving 462 families were described. The mutations were spread over almost all exons, without hot spot regions [3]. And new pathogenic mutations have been found and confirmed constantly, as well as mutations of uncertain significance, which brings difficulties and challenges to the diagnosis and genetic counseling of ADPKD. In this study, we performed WES testing on two ADPKD families in China to clarify the etiology of patients in these families and provide genetic counseling and fertility guidance strategies for them.

2. Case presentation

Case 1: Proband 1 is a 30-year-old married man with asthenospermia who did not give birth half a year after marriage. At the age of 24, he was diagnosed with adult bilateral polycystic kidney and polycystic liver by computerized tomography (CT) (Fig. 1A). The proband 1 received a comprehensive physical examination, imaging examination, laboratory examination, medical history, and family history inquiry. We learned that he had hypertension, proteinuria, and no history of hematuria and cerebrovascular disease.

Pedigree investigation: the proband's elder brother (III1), fourth aunt (II6), and cousin (III4) were all diagnosed clinically with polycystic kidney disease. The age of onset was 28, 40, and 41 years old, respectively. His father (II1) and aunts (II4 and II5) were healthy, and his mother (II2) and uncles (II3 and II7) died of illness (Fig. 1B). According to the proband's recollection, his mother and uncles had polycystic kidneys though their medical history was unknown clearly.

Case 2Proband 2 is a 32-year-old woman, diagnosed with adult polycystic kidney by CT when she was 25 years old (Fig. 1C). At present, her renal function is within the normal range, without hypertension, hematuria, proteinuria, and kidney stones.

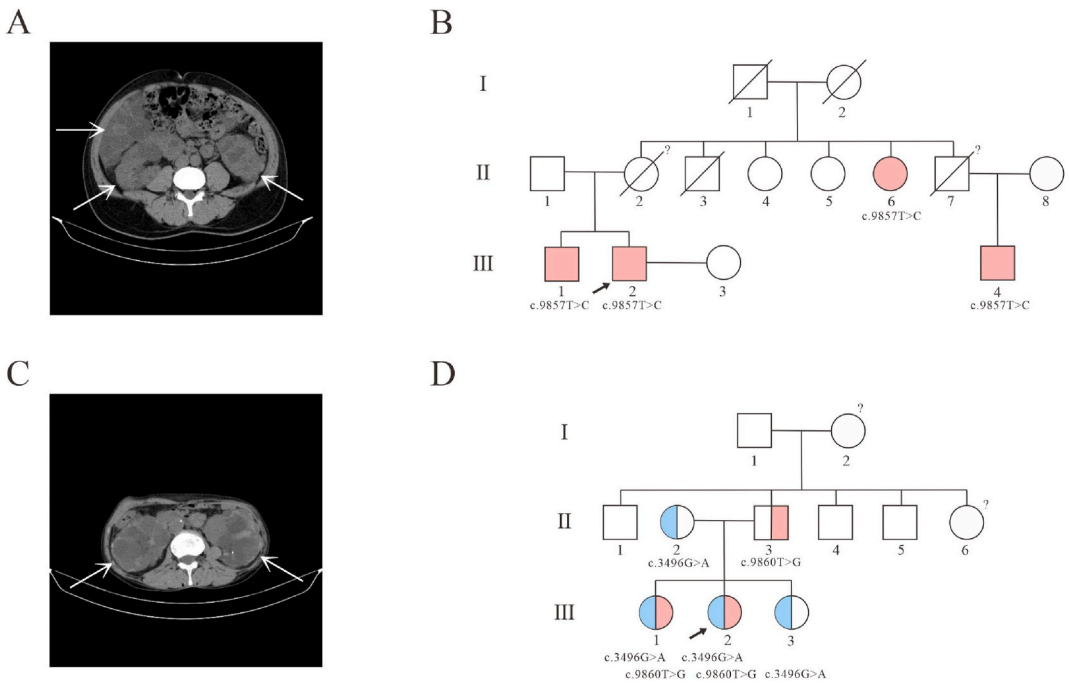

Fig. 1. (A) and (C) CT images of the probands, with polycystic kidneys and polycystic liver indicated by white arrows. (B) and (D) The pedigrees of the families, with the probands indicated by a black arrow; "?" indicated that the probands' relatives were clinically suspected of PKD but not identified by sequencing.

Pedigree investigation: the proband's elder sister (III1), father (II3), aunt (II6), and grandmother (I2) were all diagnosed clinically with polycystic kidney disease. The age of onset was 24, 35, 30, and 46 years old, respectively. Her mother (II2) and younger sister (III3) were healthy (Fig. 1D).

3. Materials and methods

3.1. Ethical compliance

This study was approved by the Ethics Committee (LYFY-YCCZ-2023012) and the informed consent of the patients.

3.2. Whole-exome sequencing (WES) and analysis

According to the manufacturer's instructions, genomic DNA (gDNA) was extracted from EDTA peripheral blood leukocytes of probands and their relatives using a TIANamp genomic DNA extraction kit from Tiangen Biotechnology, China. WES was performed using gDNA from III2 and III3 in family 1 and III2 in family 2 by Annaroad Gene Technology (Beijing) Co. using SureSelect (V5+UTR; Agilent) for target capture (100bp Pair End mode and 100x coverage). The quality of the data was assessed by FastQC and the data was processed following Broad Institute's best practice guidelines for GATK v3.4 (https://www.broadinstitute.org/).

Public databases such as gnomAD (http://gnomad.broadinstitute.org/) and 1000 Genomes Project (http://browser.1000genomes.org) are used to exclude high-frequency variants from the general population. The pathogenicity of SNV was evaluated according to relevant scientific literature and disease databases, including ClinVar (http://www.ncbi.nlm.nih.gov/clinvar), PubMed (https://www.ncbi.nlm.nih.gov/pubmed/), OMIM (http://www.omim.org), HGMD (http://www.hgmd.org), and Mayo ADPKD Variant database (https://pkdb.mayo.edu/) etc. The genetic pathogenicity and significance of SNV were systematically evaluated according to the guidelines of the American College of Medical Genetics and Genomics (ACMG) and the Association for Molecular Pathology (AMP) [13].

3.3. Sanger sequencing verification

Polymerase chain reaction (PCR) amplification was performed using pair primers designed to cover candidate variants identified by WES. The products were recovered and purified by agarose gel electrophoresis, and sequenced by an ABI3730xl genetic analyzer. Chromas software was used to analyze the sequencing results. (The primer sequence is as follows: PKD1-chr16-2149928-F:

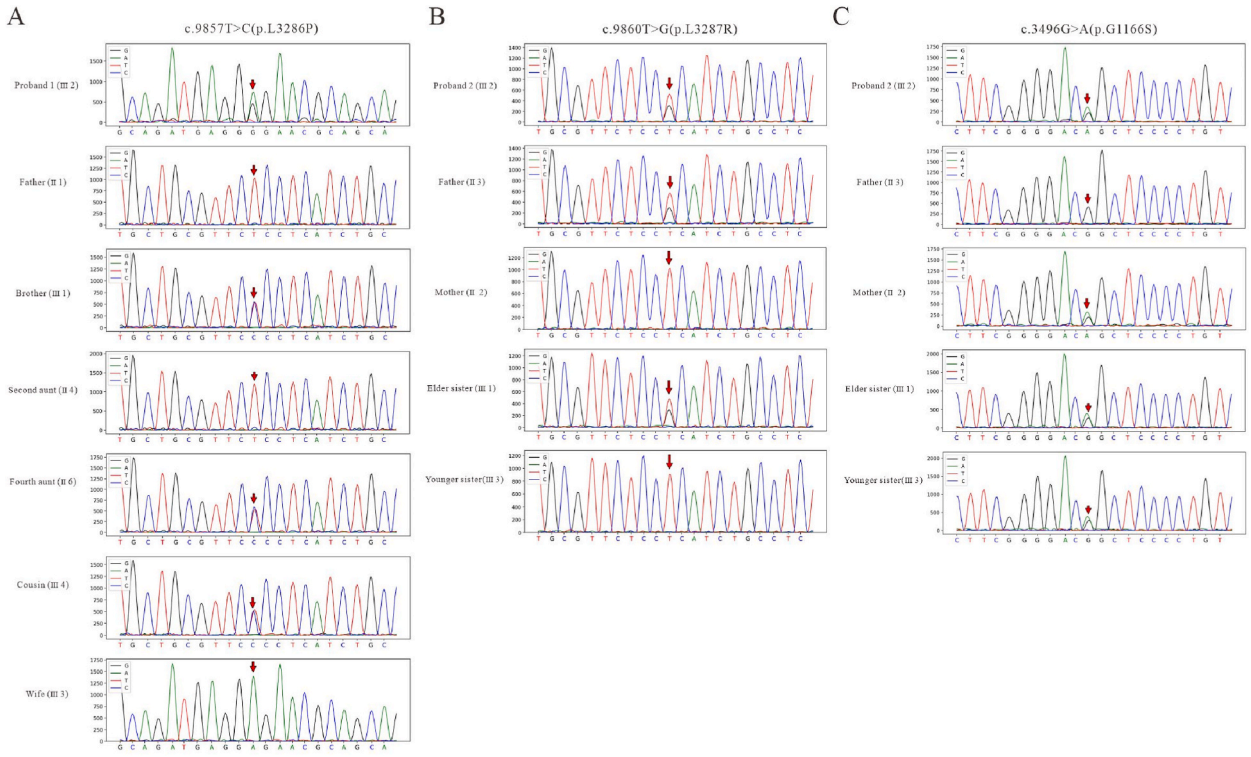

Fig. 2. Validation of the candidate variants (c.9857T > C, c.9860T > G, and c.3496G > A) of genomic DNA in probands and their relatives by Sanger sequencing.

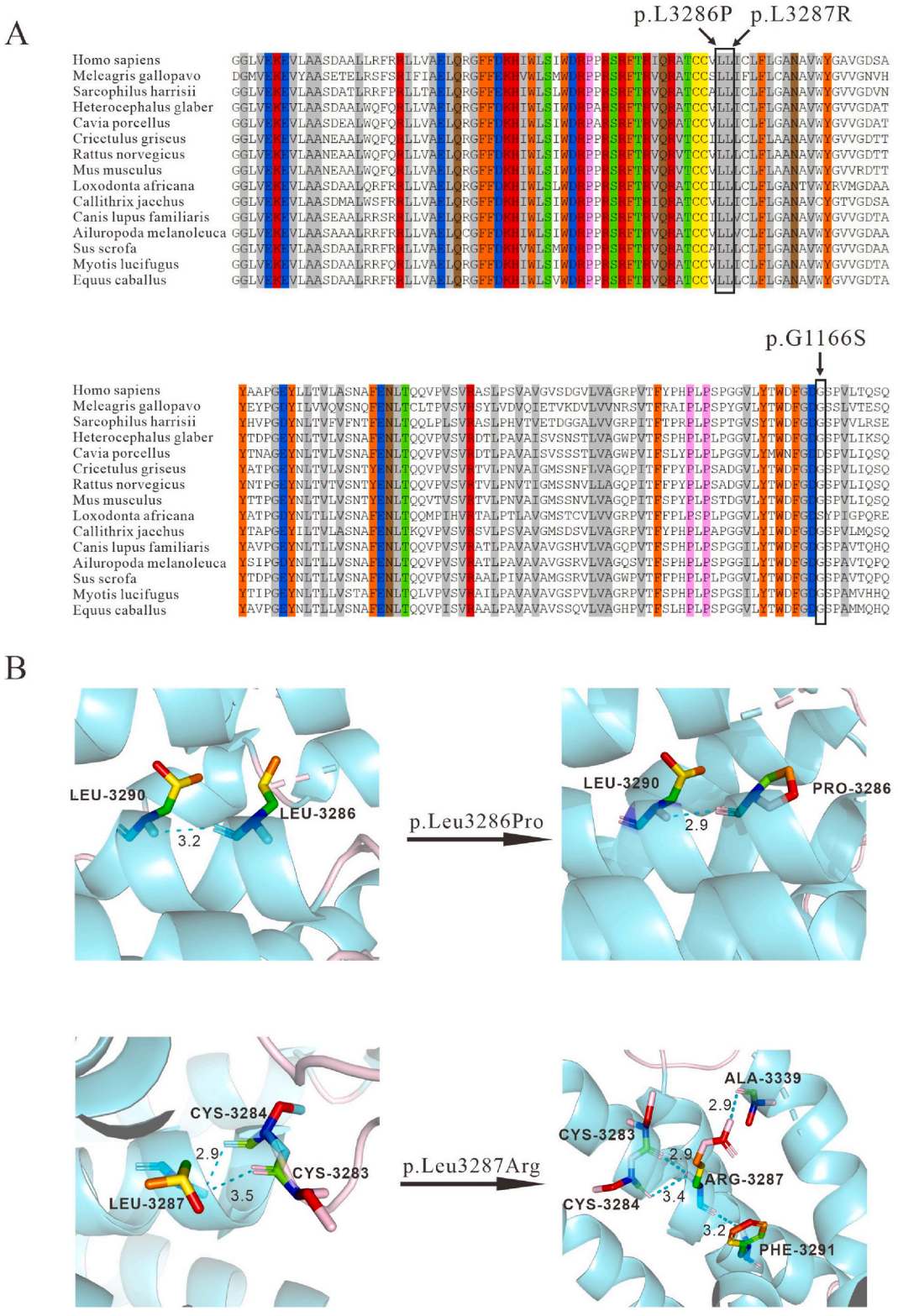

Fig. 3. (A) Conservation of mutant amino acids in different species. (B) PC-1 structure prediction of missense variations of *PKD1* gene (by SWISS-MODEL software).

CCCAGGCTCCATTCCCAGTAC; PKD1-chr16-2149928-R: CCTCCCTGCCTTCTAGGCG; PKD1-chr16-2149925-F: CCCAGGCTCCATTCCCAGTAC; PKD1-chr16-2149925-R: CCTCCCTGCCTTCTAGGCG; PKD1-chr16-2161672-F: TGCTCCACTGTTGCCTCCG; PKD1-chr16-2161672-R: CTGTCCCCACAGGTGAGTACC).

3.4. In silico predictions

The software RDDC^{SC} and SpliceAI were used to predict whether *PKD1* candidate mutations affected the splicing of mRNA. PolyPhen-2(http://genetics.bwh.harvard.edu/pph2/), PROVEN(https://www.jcvi.org/research/provean), Mutation Taster(https://www.mutationtaster.org/), SIFT(http://sift-dna.org) and so on were used to predict the pathogenicity of the mutations.

3.5. Protein modeling

The amino acid sequence of the human *PKD1* gene was obtained from the NCBI (NP_001009944.3). The initial protein structure was taken from PDB ID: 6a70 (PDB DOI: https://doi.org/10.2210/pdb6A70/pdb) [14], the structure of human PC-1/PC-2 complex, which consists of the truncated constructs of PC-1 (residues 3049–4169) and PC-2 (residues 185–723). The variant structures of the PC-1/PC-2 complex were built using the SWISS-MODEL server(https://swissmodel.expasy.org/). PyMOL software was used to represent structural figures.

4. Results

4.1. Novel PKD1 heterozygous variants in two Chinese ADPKD families

Three heterozygous mutations of *PKD1* gene, c.9857T > C (p.L3286P) in family 1 and c.9860T > G (p.L3287R) and c.3496G > A (p.G1166S) in family 2 were found by WES. The average sequencing depth of WES and the proportion of the average depth of the target area greater than 20 × met the quality control requirements of WES.

In family 1, the candidate variant c.9857T > C (p.L3286P) was co-segregated with the polycystic kidney phenotype through pedigree analysis and Sanger sequencing validation (Fig. 2A). Alignment with NCBI database(https://www.ncbi.nlm.nih.gov/) revealed that this variation was located in exon 29, and its absolute coordinate was chr16:2149928 (genomic version: hg19), and the affected transcript was NM_001009944. After a comprehensive analysis, the variant has not been reported in population frequency databases such as ExAC browser, 1000 Genome Project, gnomAD, ESP6500, and has not been described in the Clinvar and Mayo ADPKD Variant databases. It was included as DM [3] in the HGMD professional version database. Both RDDC^{SC} and SpliceAI revealed that variant c.9857T > C did not affect mRNA splicing. PolyPhen-2 analysis showed that the amino acid of the variant site was leucine in all 15 species, which was highly conserved (Fig. 3A). On the other hand, this missense variant of *PKD1* was predicted to be highly damaging to the function of PC-1 using multiple online prediction tools including SIFT, PolyPhen2, PROVEAN, and MutationTaster, etc (Table 1). Referring to the ACMG gene mutation interpretation guidelines [13], this variation meets three piece of evidence (PM2_Supporting + PP1+PP3+PP4) and is graded as Uncertain significance.

In family 2, pedigree analysis and Sanger sequence (Fig. 2B and C) indicated that the variant c.9860T > G (p.L3287R) was paternal and was co-segregated with the polycystic kidney phenotype, while the variant c.3496G > A (p.G1166S) was maternal and was not co-segregated with the polycystic kidney phenotype based the fact of her healthy mother and younger sister. Alignment with the NCBI database suggested that the paternal mutation c.9860T > G was located in exon 29, and its absolute coordinate was chr16:2149925 (genomic version: hg19). Through synthetic analysis, this variant has not been reported in the general population as indicated in the ExAC browser, 1000 Genome Project, gnomAD, ESP6500, or described in disease databases such as HGMD, Clinvar, or Mayo ADPKD Variant Database. Conservation analysis (Fig. 3A) and prediction results (Table 1) based on multiple software demonstrated that variant c.9860T > G has a harmful effect on the function of PC-1. Referring to the ACMG gene mutation interpretation guidelines [13],

Table 1
Pathogenicity prediction of the identified mutations (c.9857T > C, c.9860T > G, and c.3496G > A) using multiple online in silico tools.

No.	In silico analysis tools	PKD1: c.9857T > C, p.L3286P chr16:2149928		PKD1: c.9860T > G, p.L3287R chr16:2149925		PKD1: c.3496G > A, p.G1166S chr16: 2161672	
		Prediction	Score	Prediction	Score	Prediction	Score
1	SIFT	Damaging	0.001	Damaging	0.001	Tolerable	0.095
2	Polyphen-2	Probably_damaging	1.0	Probably_damaging	1.0	Probably_damaging	0.964
3	MutationTaster	Disease_causing	1.000	Disease_causing	1.000	Disease_causing	0.991
4	FATHMM-MKL	Damaging	0.979	Damaging	0.982	Tolerable	0.319
5	CADD	Damaging	24.8	Damaging	24.5	Damaging	21.1
6	PROVEAN	Damaging	−4.73	Damaging	−5.48	Tolerable	−2.3
7	DANN	Damaging	0.997	Damaging	0.997	Tolerable	0.970
8	VEST3	Damaging	0.828	Damaging	0.898	Damaging	0.69
9	M-CAP	Damaging	0.771	Damaging	0.758	Damaging	0.590
10	ClinPred	pathogenic	0.7353	pathogenic	0.9904	pathogenic	0.7147
11	REVEL	Damaging	0.456	Damaging	0.701	Damaging	0.584

this variation meets three pieces of evidence (PM2_Supporting + PP1+PP3+PP4) and is graded as Uncertain significance.

However there, the maternal c.3496G > A (p.G1166S) was located in exon 15, and its absolute coordinate was chr16:2161672 (genomic version: hg19). After analysis, the population frequency of this variant site is 0.0006 (the maximum values of ESP6500, 1000 Genome Project, and EXAC_ALL), and the East Asian population frequency in the gnomAD database is 0.0002. Further, it was reported as DM [15] in the HGMD professional database and has been recorded in the Clinvar database, Mayo ADPKD Variant Database. According to the ACMG gene mutation interpretation guidelines [13], there is no available pathogenic evidence at this locus, and it is graded as Uncertain significance. Based on the conservation analysis (Fig. 3A) and prediction results (Table 1), we speculated that maternal c.3496G > A was not the primary cause of ADPKD in family 2.

4.2. The change of the conformation of PC-1 induced by PKD1 c.9857T > C (p.L3286P) and c.9860T > G (p.L3287R)

Missense3D software was used to analyze whether the mutation c.9857T > C (p.L3286P) in the *PKD1* gene caused changes in the spatial structure of PC-1. The results indicated that this substitution, from leucine to proline, introduced a buried proline, destroying the PC-1 structure. Meanwhile, the residue substitution report from another online software, VarSite, pointed out that the residue at 3286th in the PC-1 sequence was leucine with aliphatic side chains (containing only carbon and hydrogen atoms), which was hydrophobic; while the variant residue is proline with a rigid side chain, which restricts the conformation of the PC-1 at this point. Furthermore, the variant identified using DynaMut server predictions resulted in a decrease in molecular stability and flexibility:$\Delta\Delta G = -1.559$kal/mol (Destabilizing). (The difference in the Gibbs free energy between mutant (ΔGm) and WT protein (ΔGw) provided by the web server, $\Delta\Delta G = \Delta Gm - \Delta Gw$, indicates the effect of the substituted mutation on protein stability. They classified $\Delta\Delta G \geq 0$ kcal/mol as stabilizing and $\Delta\Delta G < 0$ kcal/mol as destabilizing [16].) Additionally, the structure of this missense mutation, predicted by SWISS-MODEL software, suggests that Leu3286 is located in the α-helix of the secondary structure of PC-1 and forms hydrogen bonds with Leu3290. Compared with the wild type, the mutant has a change in the size of the hydrogen bond (Fig. 3B), resulting in a change in the protein spatial structure, which may destroy the protein function.

For the variant c.9860T > G (p.L3287R) in *PKD1* gene, both Missense3D and VarSite revealed that the variant residue is an arginine that has a positively charged side chain, making it hydrophilic. The substitution arginine for leucine replaced a buried hydrophobic residue with a hydrophilic residue, a buried uncharged residue with a charged residue. This change is a very large one, and might well result in a change to the function of PC-1. DynaMut predicted an increase in molecular stability and flexibility:$\Delta\Delta G = 0.964$kal/mol (Stabilizing). Moreover, from the 3D structure of PC-1 with p.L3287R mutation predicted by SWISS-MODEL, we found that Leu3287 is also located in the α-helix of the secondary structure of PC-1 and forms hydrogen bonds with Cys3283 and Cys3284. After mutation, the number of hydrogen bonds increases. Arg3287 forms hydrogen bonds with Ala3339 and Phe3291 additionally (Fig. 3B), which may have a great influence on the function of PC-1.

5. Discussion

In the absence of renal replacement therapy (RRT), ADPKD is the most common potentially lethal disease [17] (because it can lead to renal failure and death). It is also the most common hereditary progressive nephropathy, characterized by the development and progressive enlargement of cystic lesions in the kidney, in which renal cyst development begins in utero, although cyst initiation and enlargement continue throughout the patient's life. Though slowly progressive, cyst enlargement leads to an exponential increase in total kidney volume, and approximately 50 % of ADPKD patients have end-stage kidney disease (ESKD) before the age of 60 with multisystem involvement [12,18].

ADPKD is genetically heterogeneous, with two genes identified mainly: *PKD1* and *PKD2* [19]. Previous studies have shown that the severity of ADPKD is directly related to genetic mutations. Diseases associated with *PKD1* mutations appear to be more severe, with earlier-onset renal failure (fifth decade), than those associated with *PKD2* (seventh decade) [20]. Most individuals with *PKD1* mutations have renal failure by age 70 years, whereas more than 50 % of individuals with *PKD2* mutations have adequate renal function at that age (mean age of onset of ESRD 54.3 years with *PKD1*; 74.0 years with *PKD2*) [20]. Furthermore, among some people, clinical symptoms may lag behind imaging, and that is, even if CT imaging indicates the presence of a polycystic kidney, the patients may have no clinical symptoms. Therefore, to some extent, early diagnosis of AKPKD can prevent complications and protect renal function. Before the high-risk group (the patient's immediate family members) has no clinical symptoms, it can be clear whether they are ADPKD patients. In addition, early diagnosis is also of great significance for genetic counseling and prenatal diagnosis of the fetus.

In our study, based on the results of WES, pedigree, and bioinformatics analysis, we speculated that two heterozygous mutations, c.9857T > C and c.9860T > G, were the cause of PKD occurrence and inheritance in two Chinese ADPKD pedigrees, although a functional assay would be needed to prove the involvement of these variants beyond doubt. Expression studies of PC-1 trafficking have been difficult owing to the large size of the ~14kb transcript. Of course, this is one of the limitations of this study, that is, only in silico predictions rather than functional experiments in vivo or in vivo to confirm that these variants lead to impaired function of PC-1; on the other hand, the follow-up time is too short, and these two probands have not yet progressed to the ESRD stage. Third, the DNA from the deceased mother and uncle of the proband 1 and aunt and grandmother of the proband 2, could not be available for further examination so that the final source of genetic variation in the two families could not be determined. Further, to strengthen the understanding of the molecular mechanism of ADPKD and provide substantial contributions to this field, it is necessary to collect more medical records of ADPKD patients and conduct extensive analysis of the relationship between genotype and phenotype.

In summary, we identified two variants of *PKD1* gene in Chinese ADPKD families, of which c.9857T > C (p.L3286P) was only mentioned in an Italian cohort study [3], while c.9860T > G (p.L3287R) has not been reported yet, and it is considered to be a de novo

mutation. The clinical significance of this study lies in the discovery of the genetic factors leading to polycystic kidneys in two Chinese families by WES, which has unraveled the mystery of the disease that has been plaguing two families for many years, and provided a theoretical basis for their genetic counseling and fertility guidance.

Given that the diagnosis of ADPKD is established in a proband with age-specific kidney imaging criteria and either an affected first-degree relative with ADPKD or a heterozygous pathogenic variant in *PKD1*, *PKD2*, or one of the less common associated genes (*ALG5*, *ALG9*, *DNAJB11*, *GANAB*, *IFT140*) identified by molecular genetic testing. The benefit of our study to clinical practice lies in that ADPKD should be suspected in individuals with the following: multiple bilateral kidney cysts and absence of manifestations suggestive of different cystic kidney disease; cysts in other organs (especially the liver); enlargement of the kidneys or liver on physical examination; hypertension in an individual younger than age 35 years; an intracranial aneurysm; family history consistent with autosomal dominant inheritance (e.g., affected males and females in multiple generations). Moreover, 10%–20 % of individuals diagnosed with ADPKD have the disorder as the result of a de novo pathogenic variant, so the absence of a known family history does not preclude the diagnosis. It is appropriate to consider testing symptomatic individuals with PKD, including suspected ADPKD, regardless of age or family history.

Since ADPKD is a completely explicit autosomal genetic disease, according to the typical Mendelian inheritance law, it's speculated that both men and women carrying the dominant pathogenic gene can be affected and pass it on from generation to generation. If one of the parents is affected, the incidence of the offspring is 50 %; if both parents are affected, the incidence of offspring is 75 %, and the probability of inheritance is very high. The existing treatments can only delay the deterioration of renal function, but cannot reverse the trend of deterioration. Therefore, early detection of presymptomatic genes, monitoring of clinical-related indicators, and timely symptomatic treatment in ADPKD family members can effectively delay the progress of ADPKD. For families with fertility needs, such as proband 1 and his wife in this study, who expressed a strong desire to prevent his familial genetic disease, we recommend a prenatal or preimplantation genetic diagnosis of high-risk fetuses or embryos as soon as possible to avoid the birth of children with ADPKD.

6. Conclusion

In this study, we found two heterozygous mutations c.9857T > C (p.L3286P) and c.9860T > G (p.L3287R) in *PKD1* gene in two unrelated probands, diagnosed clinically with PKD. These mutations were also detected in the probands' clinically affected relatives, but not in their healthy relatives.

The most important factor in determining whether a missense change was likely pathogenic was the degree to which the corresponding sequence of amino acids was conserved. Conservative analysis showed that the amino acids at these two adjacent positions were highly conserved among species, indicating that this region plays an important role in protein function. The predictions of multiple online software programs and the 3D structure prediction by SWISS-MODEL showed that although these two variations did not cause changes in splicing patterns or change the secondary structure of PC-1, due to the high conservation of amino acids at these two sites, the substitutions from leucine to proline and from leucine to arginine affected the length or the number of hydrogen bonds, which may limit the spatial structure of PC-1, thus affecting the function of *PKD1* and leading to the occurrence of disease.

CRediT authorship contribution statement

Yanan Wang: Writing – review & editing, Validation, Supervision, Resources, Data curation, Conceptualization. **Jiapei Jin:** Writing – original draft, Visualization, Software, Investigation, Formal analysis, Data curation. **Yuqiong Chai:** Methodology, Formal analysis, Data curation. **Pai Zhang:** Validation, Formal analysis, Data curation. **Weiwei Zang:** Validation, Resources.

Ethics statement

Two probands and their family members were informed and agreed with the study. The corresponding ethics committee approved the current study (LYFY-YCCZ-2023012). This study complies with the relevant guidelines and ethical regulations.

Date and code availability statement

The raw sequence data reported in this paper have been deposited at the Genome Sequence Archive (Genomics, Proteomics & Bioinformatics 2021) in the National Genomics Data Center (Nucleic Acids Res 2022), China National Center for Bioinformation/ Beijing Institute of Genomics, Chinese Academy of Sciences with accession numbers HRA006672 and HRA006968 that are publicly accessible at https://ngdc.cncb.ac.cn/gsa-human.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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