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CLINICAL REPORT

A novel heterozygous *PKD1* variant causing alternative splicing in a Chinese family with autosomal dominant polycystic kidney disease

Qianying Zhao[1,2,3] | **Yu Tan**[1,2,3] | **Xiao Xiao**[1,2,3] | **Qinqin Xiang**[1,2,3] | **Mei Yang**[1,2,3] | **He Wang**[1,2,3] | **Shanling Liu**[1,2,3]

[1]Department of Medical Genetics, West China Second University Hospital, Sichuan University, Chengdu, China

[2]Department of Obstetrics and Gynecology, West China Second University Hospital, Sichuan University, Chengdu, China

[3]Key Laboratory of Birth Defects and Related Diseases of Women and Children (Sichuan University), Ministry of Education, Chengdu, China

Correspondence
Yu Tan and Shanling Liu, Department of Medical Genetics, West China Second University Hospital, Sichuan University, No. 20, Section 3, Renminnan Road, Chengdu, Sichuan 610041, China.
Email: ty131419@hotmail.com and sunny630@126.com

Abstract

Background: Autosomal dominant polycystic kidney disease (ADPKD) is mainly caused by pathogenic variants of *PKD1* and *PKD2*. Compared to *PKD2*-related patients, patients with *PKD1* pathogenic variants have more severe symptoms, present a gradual decline in renal function, and finally progress to end-stage kidney disease with an earlier mean onset age.

Methods: In this study, trio exome sequencing (ES) was performed to reveal the genetic etiology in a Chinese family clinically diagnosed with polycystic kidney, followed by validation through Sanger sequencing on both genomic DNA and cDNA levels. Subsequently, targeted preimplantation genetic testing was provided for the family.

Results: A novel heterozygous *PKD1* variant (c.1717_1722+11del) was detected in the proband and other clinically-affected relatives. Interestingly, cDNA sequencing demonstrated that the variant, despite being annotated as non-frameshift within exon 8, impacted the splicing of *PKD1*. Two abnormal transcription products were formed: one induced frameshift, while the other caused 133 amino acids to be inserted between exon 8 and exon 9.

Conclusions: Our study revealed a novel *PKD1* variant using ES as the cause of ADPKD in a Chinese family with multiple affected members. The variant at the exon-intron boundary would induce alternative splicing, which should not be excluded from genetic analysis. Validated on the cDNA level could provide more comprehensive genetic information for disease stratification. And the novel variant expands the spectrum of *PKD1* variants in ADPKD. The recurrent risk could be blocked accordingly for the families' offspring.

KEYWORDS

alternative splicing, autosomal dominant polycystic kidney disease (ADPKD), exome sequencing (ES), *PKD1*

Yu Tan and Shanling Liu contributed equally to this work.

1 | INTRODUCTION

Autosomal dominant polycystic kidney disease (ADPKD) is a common inherited disorder characterized by multiple renal cysts and is generally late-onset. Though slowly progressive, approximately 50% of ADPKD patients have end-stage kidney disease (ESKD) by 60 years old with multisystem involved (e.g., liver cysts) (Gabow et al., 1992; Johnson & Gabow, 1997).

Most ADPKD is genetically heterogeneous, resulting from pathogenic variants in *PKD1* (OMIM: 601313) and *PKD2* (OMIM: 173910) (Chang et al., 2013; Torres et al., 2009). The encoding proteins interact with each other in kidney primary cilia and are critical for maintaining normal tubular structure and promoting tubular epithelial cell adhesion, proliferation, and differentiation (Bertuccio et al., 2009; Newby et al., 2002; Torres & Harris, 2009).

Genetic testing is valuable, since the traditional diagnostic approach based on renal ultrasound usually identifies ADPKD patients till their middle age, due to late-onset symptoms (Chang et al., 2013). Yet there are no hot spots of mutation in *PKD1* and *PKD2*, patients with *PKD1* variants usually have an earlier average age at the onset of ESKD (Harris & Rossetti, 2010; Kurashige et al., 2015; Robinson et al., 2012). Disease in patients with *PKD1* truncating mutations could progress more rapidly than in patients with non-truncating mutations (Chang et al., 2013; Cornec-Le Gall et al., 2013). Once the disease-causing pathogenic variant has been identified, tailored treatment can be arranged for the ADPKD family, while prenatal and preimplantation genetic testing (PGT) are available for offspring as a means of prevention.

To date, 3042 variants in *PKD1* gene have been reported in Human Gene Mutation Database (HGMD® Professional 2023.1), with 2426 variants classified as "DM". Some exonic variants located at exon-intron boundaries, though synonymous, would disrupt normal splicing and thus induce diseases (Deng et al., 2021).

Herein, we identified a novel heterozygous *PKD1* variant, located at the end of exon 8, as the genetic cause of a Chinese ADPKD family. Our study showed that on the cDNA level, the variant caused alternative splicing: one product with an insertion of 188 bases around the splice site, inducing frameshift of *PKD1*; and another adding 133 amino acids. After validation with co-segregation analysis, the genetic results were applied in PGT for the female proband.

2 | CLINICAL SUMMARY

In our study, a female patient (III8), clinically diagnosed with PKD, was tested for genetic pathogenesis after counseling. The polycystic kidney was initially detected using an ultrasound examination at her 10 years old, without any symptoms, a relatively early diagnostic age because of positive family history. Regular monitoring of the urinary system with ultrasound was carried out thereafter, and bilateral kidneys were gradually involved with multiple cysts. At the age of 29, multiple small hepatic cysts as well were detected using computerized tomography (CT) (Figure 1a). Till now, the patient complained of no discomfort, with normal renal function and urine protein. Eight other family members (II3, II5, II7, II9, II11, III1, III2, III5) were also diagnosed with PKD, while her grandma (I2) was clinically

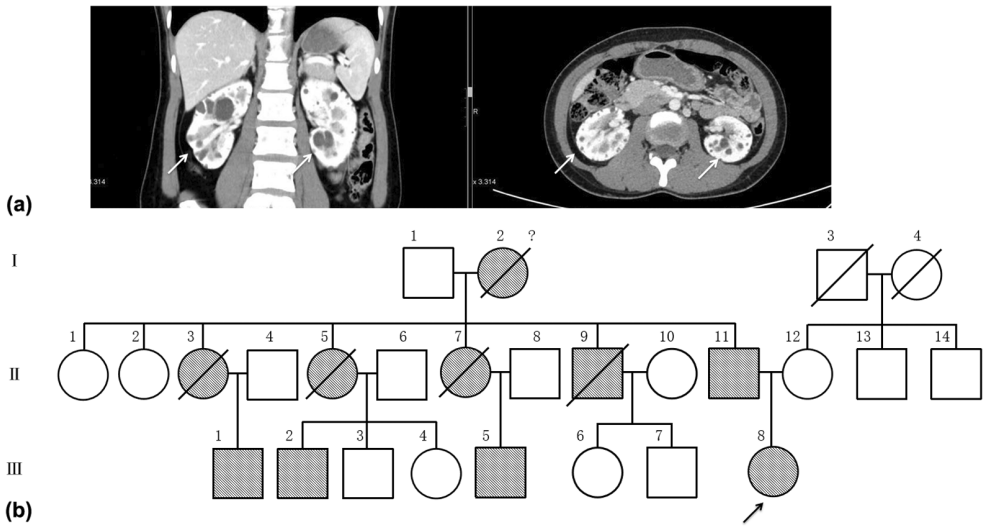


FIGURE 1 (a) Abdominal CT images of the proband, with polycystic kidneys indicated by arrows. (b) The pedigree of the present family, with the proband indicated by an arrow;"?" indicates that the proband's grandma was clinically suspected of PKD.

suspected (Figure 1b). The family history indicated an autosomal-dominant inheritance model, and the PKD members deceased for undefined reasons around their 60s. To identify if phenotype co-segregates with genotype in the family, samples of II1 and III1 were additionally tested with informed consent.

3 | METHODS

3.1 | Ethical compliance

Experiment on human subjects was approved by the Ethical Review Board of West China Second University Hospital, Sichuan University. Informed consent for participation in this study was obtained from all individuals.

3.2 | Trio exome sequencing and analysis

Genomic DNA (gDNA) was extracted from the subjects' (III8, II11, II12, II1, and III1) peripheral blood leukocytes using QIAamp DNA Blood Mini Kit, according to the manufacturer's instruction.

Trio exome sequencing (ES) was performed using gDNA from III8, II11, and II12. Exome capture sequencing was performed using NanoWES Human Exome V1 (Berry genomics) following the manufacturer's protocol. The exon-enriched libraries were sequenced through Illunima NovaSeq6000 platform (Illunima). Next, all reads were aligned to the reference human genome GRCh38/hg38 with Burrows—Wheeler Aligner software. Local alignment and recalibration of base quality of the Burrows—Wheeler aligned reads were conducted by GATK Indel Realigner and the GATK Base Recalibrator (broadinstitute.org/), respectively. After that, single-nucleotide variants (SNVs) and small insertions or deletions (InDels) were identified by GATK Unified Genotyper (broadinstitute.org/). ANNOVAR and the Enliven Variants Annotation Interpretation System (Berry genomics) were used for functional annotation.

Public databases, such as gnomAD (http://gnomad.broadinstitute.org/) and 1000 Genomes Project (http://browser.1000genomes.org), were used for excluding high-frequency variants from the general population. Pathogenicity of SNVs was evaluated based on related 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), Mayo ADPKD Variant Database (https://pkdb.mayo.edu/), etc. Genetic pathogenicity and significance of SNVs were systematically evaluated according to American Society for Medical Genetics and Genomics (ACMG) guidelines (Richards et al., 2015).

3.3 | Validation of gDNA and cDNA level

Finally, candidate variants related to PKD were validated by bidirectional Sanger sequencing: polymerase chain reaction (PCR) amplification was performed using pair primers (Table 1) designed to cover candidate variants identified by ES. To figure out if the variant impact splicing, total RNA of the trio (III8, II11, and II12) was isolated through RNApure Blood Kit (CWBIO, CW0582S) using fresh peripheral blood samples. After being reversed to cDNA using a synthesis Kit (Thermo Scientific, K1622), target fragments were amplified using PCR primers in the flanking sequence of *PKD1* from exon 7 to exon 9 (Table 1). Then PCR products were electrophoresed in 2% agarose gel, and bands were extracted using a gel cleanup kit (Axygen). Direct Sanger sequencing was conducted afterward by ABI 3500 Genetic Analyzer (Thermo Fisher Scientific) and the results were analyzed using Chromas software (version 2.6.5; Biosoft).

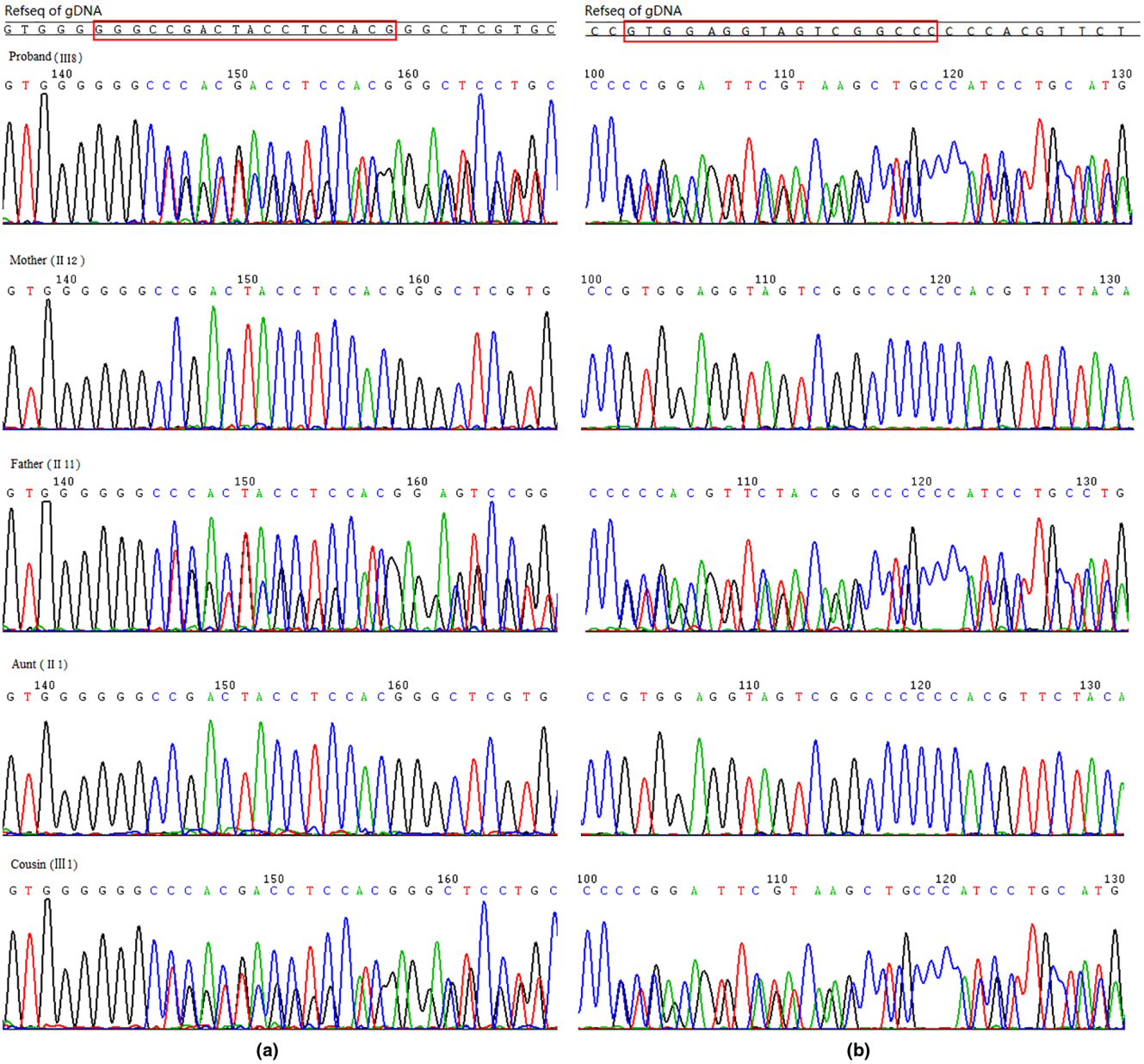
4 | RESULTS

4.1 | Novel *PKD1* heterozygous variant in a Chinese ADPKD family

After trio ES, we identified a heterozygous variant (NM_001009944.3, c.1717_1722+11del) in *PKD1* as the candidate genetic cause of PKD for the Chinese family. The average sequencing depth of trio-ES on *PKD1* gene was 218×. This heterozygous variant was identified in the proband (III8) and her clinically-affected father (II11), but not in the mother (II12). The presence of the variant was further validated by Sanger sequencing. Samples from a healthy relative (II1) and an affected cousin (III1) were also tested (Figure 2). The results revealed that the candidate variant co-segregated with phenotype in this family: the proband, her father, and cousin clinically diagnosed with PKD had the variant, while the variant was detected neither in the proband's mother nor her aunt's denial of PKD.

TABLE 1 Primers used in the current study.

Primers	Forward	Reversed
gDNA primers	GCCTGGAGGTAATG TGAGT	TCACTGTGCAC TCGCCACC
cDNA primers	GAGCCTAGACGTGT GGAT	GAACGGAGAAG AGGAACTC



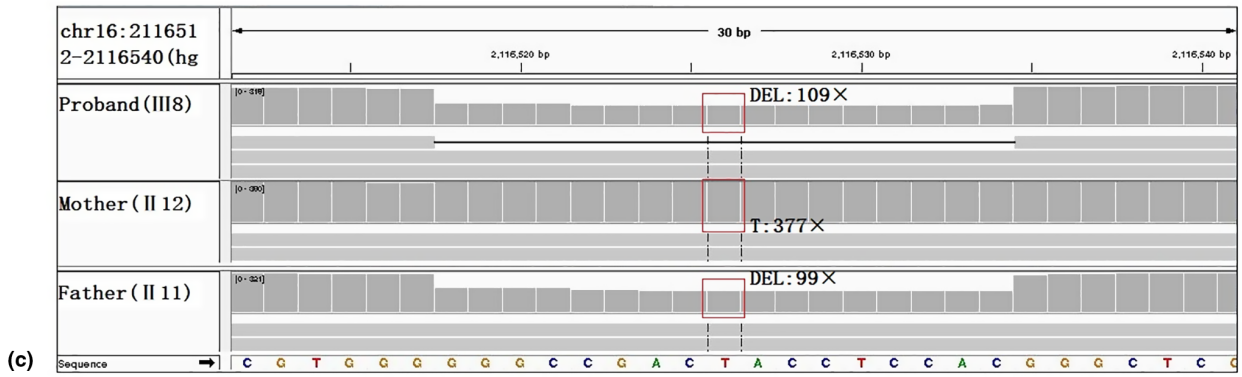


FIGURE 2 Validation of the candidate variant (*PKD1*, c.1717_1722+11del) of genomic DNA (III8, II12, II11, III1) by Sanger sequencing: (a) Forward sequencing; (b) Reverse sequencing; the red rectangle indicates where the variant occurs on the reference sequence. (c) IGV result of the variant detected by trio-ES.

Till then, this variant has not been reported in the general population as indicated in ExAC browser, 1000 Genome Project, gnomAD or described in disease databases such as HGMD, Clinvar, or Mayo ADPKD Variant Database. This deletion variant covers the last six nucleotide sequences of exon 8 and the following 11 bases of intron 8. Since located at exon-intron boundary, we assumed *PKD1* c.1717_1722+11del, though annotated as non-frameshift for exonic function, may impact splicing. Therefore, cDNA from the family was obtained and target PCR products were sequenced. Three bands (marked as Band 1, 2, and 3 in Figure 3) were uncovered after electrophoresis for the proband and her father, while only one band (Band 1) was shown on the mother's gel lane.

Direct sequencing of these cDNA PCR products with both forward and reverse primers (Figure 3b) revealed that Band 1 correlates to the classic transcription sequence, while Band 2 and 3 sequences indicated alternative splicing around the end of exon 8 in *PKD1* gene. Instead of the classic transcription product shared by the trio, the distinct splicing products, presented only in the proband and her clinically-affected father, would indicate dysfunction of *PKD1* inducing the disease. After blating, we confirmed the deletion from the last 6 bases of exon 8 to the first 11 bases of intron 8 occurred. Interestingly, another 188 bases aligned to the 5′-end sequences of *PKD1* intron 8 were inserted between exon 8 and exon 9 (Figure 3c), causing frameshift (Band 2). Similarly, cDNA sequencing result of Band 3 demonstrated that a total of 399 bases from the 5′-end of *PKD1* gene intron 8 were inserted into exon 8 and exon 9 (Figure 3d). This 399-bp insertion combined with c.1717_1722 + 11del would be silent via nonsense-mediated mRNA decay (NMD) with the predicted occurrence of stop codon before exon 9.

Based on the above results, the novel variant c.1717_1722+11del in *PKD1* was categorized as "pathogenic" (PVS1, PM2, PP1) according to the ACMG criteria.

4.2 | Preimplantation genetic testing targeted at the pathogenic variant causing ADPKD

Based on the results of trio ES and Sanger sequencing, we presumed the novel pathogenic variant in *PKD1* (c.1717_1722+11del) as the genetic cause of PKD in the Chinese family. Because the affected relatives deceased around their 60s, a relatively short life span, the proband expressed a desire for preventing her familial genetic disease when preparing for pregnancy. Her offspring has a likelihood of 50% to possess the deleterious genotype, leading to ADPKD. Subsequently, PGT was provided for the proband's couple with informed consent.

5 | DISCUSSION

To date, 3042 variants of *PKD1* gene have been reported in the HGMD database, 220 of which were found to have effect on mRNA splicing. And 123 splice variants are submitted to Mayo ADPKD Variant Database. In our study, we uncovered c.1717_1722+11del for the first time, which expands the spectrum of *PKD1* gene in ADPKD and contributes to the global references for genetic counseling of ADPKD patients. Of note, there is increasing evidence that silent variants including inframe variants could be deleterious, and almost 50 diseases afflicting most organ systems have been associated with synonymous variants (Sauna & Kimchi-Sarfaty, 2011). Especially, variants located at exon-intron boundaries should not be excluded from disease-causing analysis (Deng et al., 2021). Variants can disrupt splicing or splicing regulation by altering either cis or trans-acting factors, which is one of the common mechanisms for synonymous variant causing disease (Buratti et al., 2006). In the current study, the deletion at the exon-intron site disrupts the classic transcription of *PKD1*, inducing two alternatively spliced transcripts, and the heterozygous variant co-segregates with the PKD phenotype in the Chinese family. No other PKD or polycystic liver disease-related variants have been identified, nor digenic ADPKD was revealed with trio-ES data, indicating the pathogenic role of the novel *PKD1* variant collectively.

Pathogenic variants in *PKD1* and *PKD2* account for most ADPKD, less common associated genes identified by molecular genetic testing included *ALG9*, *DNAJB11*, *GANAB*, etc. (Harris & Rossetti, 2010; Huynh et al., 2020; Porath et al., 2016). There is substantial variability in the renal and other extra-kidney manifestations; therefore, ES or multi-gene panel is usually suggested to identify the genetic cause of ADPKD, especially when the phenotype is indistinguishable from other inherited disorders. Variants in *PKD1* have been demonstrated to induce a more progressive renal phenotype than in *PKD2*-related ADPKD (Cornec-Le Gall et al., 2013; Hateboer et al., 1999; Kurashige et al., 2015). The proband's gradually progressed to bilateral kidney manifestation till her 30s and relatively short life span of PKD members accord with the genetic cause of the family (*PKD1*-related).

The renal function of affected individuals carrying truncating variants declines significantly more rapidly than other variant types, suggesting that a proportion of inframe changes are likely to result in partial loss of gene function (Cornec-Le Gall et al., 2013; Hwang et al., 2016). Incompletely penetrant non-truncating *PKD1* variants are associated with less severe disease (Pei et al., 2012; Rossetti et al., 2009). The proband and her affected relatives carry the same deletion, which covers the boundary of exon 8 and intron 8. cDNA sequencing results indicated the

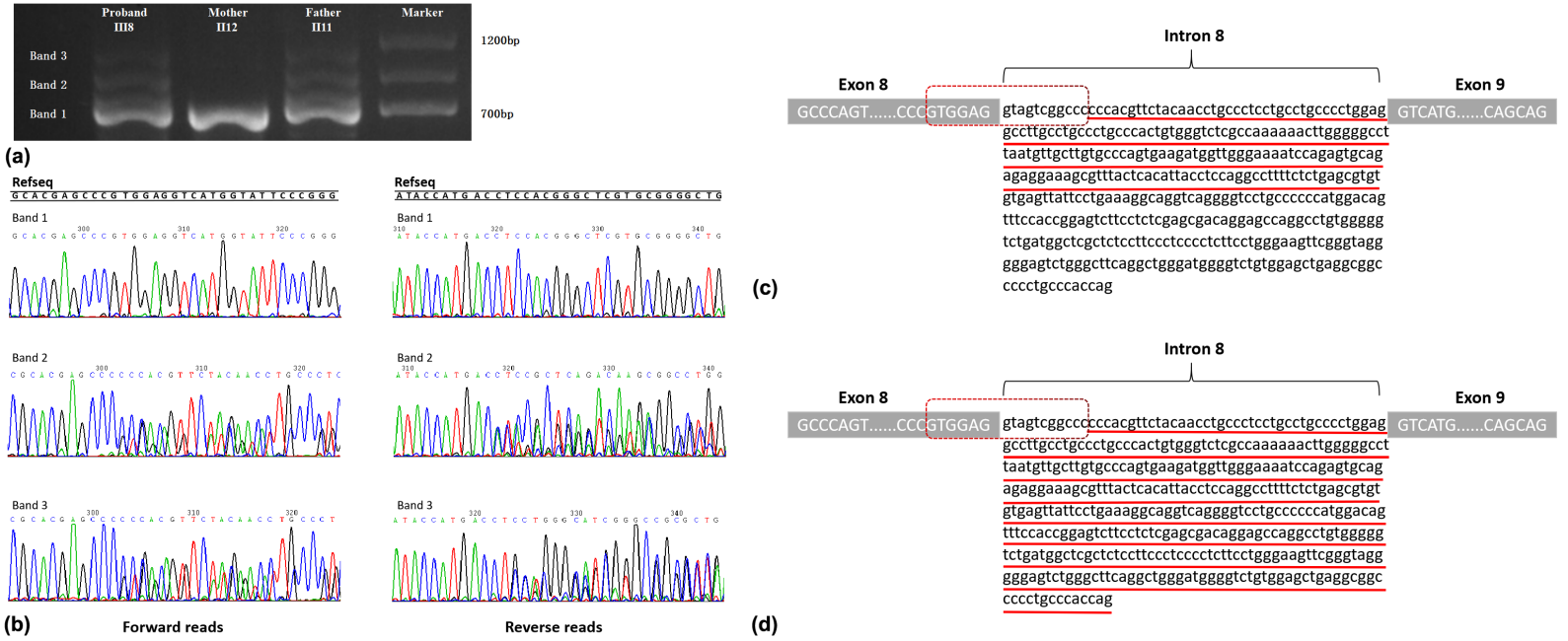


FIGURE 3 (a) Gel electrophoresis of targeted cDNA fragments; (b) Sanger sequencing results of cDNA polymerase chain reaction products (Band 1, 2, and 3) using forward and reverse primers, respectively; (c) and (d) schematic diagrams of splicing products of Band 2 and 3, respectively. The red dashed box marks the deleted sequences (*PKD1*, c.1717_1722+11del), and the red solid line underlines the inserted bases from intron 8 of *PKD1*.

variant induced alternative splicing and assumed to cause truncating of *PKD1* via NMD. Our results demonstrated that validation on the RNA level could provide more comprehensive genetic information in addition to gDNA alteration. Alternative splicing consequences may explain the intrafamilial variability in disease severity. Subsequently, more accurate stratification of patients could be achieved.

In addition, the affected relatives from the paternal line diagnosed or suspicious of PKD had shorter life span compared to their siblings without PKD. Several researches demonstrated that family history aid in clinical risk stratification and careful history-taking of ADPKD family provides a simple means to predict mutated gene and verify the genetic results (Chang et al., 2013; Chang & Ong, 2012; Robinson et al., 2012; Torres et al., 2012). Especially when the economic factor is considered in genetic testing for affected individuals, targeted *PKD1/PKD2* testing would be a choice after comprehensive clinical analysis. Collectively, the family history and genetic results suggested a reduced level of functional protein due to the identified *PKD1* variant, which would be valuable to clarify the disease status and predict the prognosis for the family. ES was applied to our proband with a need of fertility, for additional consideration such as carrier screening of monogenic disease. No secondary findings were reported according to ACMG guidelines and current laboratory consensus.

Based on the genotype, tailored management and surveillance could be arranged. The benefit and side effects of potential treatment should be balanced especially for long-term use. Many clinical trials of various mechanism-based drugs for ADPKD are currently undergoing, it would be interesting to figure out whether patients with distinct genotype would respond differently to these novel treatments (Chang & Ong, 2012).

ADPKD, though late-onset, multisystem would be involved: approximately half ADPKD patients would progress to ESKD by age 60 years; the prevalence of liver cysts increases with age and occasionally results in clinically significantly severe polycystic liver disease, most often in females. Therefore, the proband had an eagerness to prevent the pathogenic *PKD1* variant from passing on to her offspring. Subsequently, PGT is discussed during genetic counseling and employed with informed consent.

6 | CONCLUSIONS

To sum up, genetic testing should be timely recommended for PKD patients and their clinically-affected relatives as valuable means of primary and secondary prevention for the family. ES or multigene panel is preferable for genetic diagnosis to exclude other hereditary disorders with overlapping clinical manifestations. Variants at exon-intron boundaries of related genes though presumed to be non-frameshift should be analyzed with caution. Validation on RNA level could provide more comprehensive information about the functional impact of splicing, thus reaching more precise disease stratification for the ADPKD family.

AUTHOR CONTRIBUTIONS

Qianying Zhao and Yu Tan collected and analyzed the data and was a major contributor in writing the manuscript. Shanling Liu and He Wang edited the manuscript. Qianying Zhao was a major contributor in formatting the manuscript. Qianying Zhao, Yu Tan, Mei Yang, Xiao Xiao, and Qinqin Xiao conducted the experiments.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

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No funds have been received.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ORCID

Qianying Zhao https://orcid.org/0000-0003-3026-4827
Yu Tan https://orcid.org/0009-0000-9258-993X
Mei Yang https://orcid.org/0000-0002-6200-5865

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