

A novel frameshift PKD1 mutation in a Chinese patient with autosomal dominant polycystic kidney disease and azoospermia: A case report

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Abstract. Autosomal dominant polycystic kidney disease (ADPKD) is primarily caused by mutations in polycystin 1, transient receptor potential channel interacting (PKD1) and PKD2, and characterized by numerous cysts in various organs, primarily the kidneys and liver. The present case report is on a 33-year-old Chinese male patient who suffered from abdominal pain and hypertension, and presented with long-term infertility. Laboratory tests indicated that the patient had a normal renal function, while abdominal computed tomography demonstrated that the patient had enlarged kidneys with a volume of 1,127.21 cm³. In a semen analysis, no sperm was detected, while a subsequent testicular biopsy analysis demonstrated numerous mature sperms with progressive motility which suggests that the cysts of the epididymis and the dilated seminal vesicles may have obstructed the ejaculation of semen. Genetic testing identified that a novel missense mutation (c.9053delT) that was responsible for the disease. ADPKD has various disease severities, which depend on whether there is a PKD1 or PKD2 mutation and whether the mutation impairs the function of the polycystin protein. Therefore, genetic testing is important for the clinical diagnosis and prognosis of ADPKD patients, as well as prenatal diagnosis.

Introduction

Autosomal dominant polycystic kidney disease (ADPKD) is the most frequently inherited kidney disease; its incidence has been reported to be 1/400 to 1/2,500 worldwide and

1.5 million individuals are affected in China (1-4). A common cause of ADPKD is a mutation in polycystin (PC)-1, a transient receptor potential channel which interacts with (PKD1) and/or PKD2, and accounts for 85 and 15% of all detectable cases of ADPKD, respectively. Approximately 10% of patients with ADPKD have no detectable PKD1 or PKD2 mutation, which may be attributed to the current lack of effective testing methods or to similar kidney cysts caused by other gene mutations (5,6). ADPKD is characterized by numerous enlarged cysts in the bilateral kidneys and liver, in addition to specific rare manifestations in other organs, including the pancreas, cerebral vasculature, aortic arch and seminal vesicles (7-10). In the case of the present study, a novel frameshift PKD1 mutation was identified in ADPKD, which additionally caused epididymal cysts and azoospermia.

Case report

In September 2017, a 33-year-old male patient presented at the outpatient department of the First Affiliated Hospital of Anhui Medical University (Hefei, China) and sought medical advice due to the complaint of abdominal pain and azoospermia. He was first diagnosed with ADPKD in 2014 by magnetic resonance imaging, which identified numerous cysts in the kidneys and liver, based on the standard of diagnosis established by Pei *et al* (11). In 2016, the patient was diagnosed with azoospermia by semen analysis following long-term infertility and he additionally developed hypertension with a peak blood pressure of 150/100 mmHg, which was controlled with Valsartan tablets.

The patient had a height of 180 cm, weight of 75 kg and body mass index of 23.1 kg/m². Mild pain with a pain score of 1 was determined using a visual analog scale, as previously described (12). The latest laboratory investigations demonstrated a normal serum creatinine concentration (81.7 μmol/l; normal range: 61.9-114.9 μmol/l), blood urea nitrogen concentration (6.31 mmol/l; normal range: 2.5-7.1 μmol/l) and estimated glomerular filtration rate (eGFR; 106.78 ml/min/1.73 m²; normal range: 90-120 ml/min/1.73 m²), and an increased uric acid concentration (506 μmol/l; normal range: 214-494 μmol/l). By analyzing the patient's previous laboratory results, it was identified that the eGFR was within

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Key words: polycystic kidney disease, total kidney volume, polycystin 1, azoospermia, transient receptor potential channel interacting, frameshift mutation

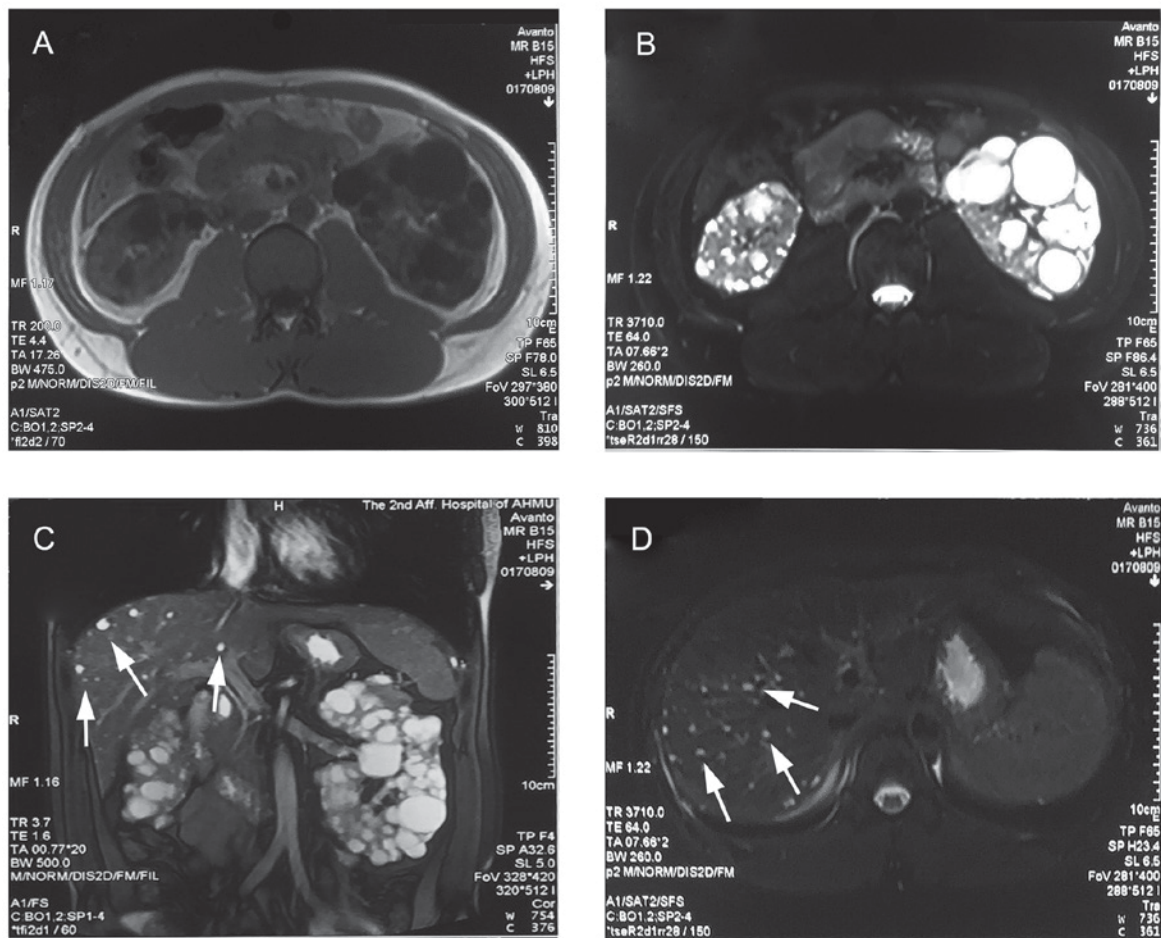


Figure 1. Abdominal CT imaging revealed enlarged kidneys with fluid-filled cysts. (A) CT scan revealed bilateral renal enlargement (transverse plane). (B) CT contrast enhancement of bilateral renal enlargement (transverse plane). (C) CT scan of the isolated liver cysts (coronal plane). (D) CT scan of the isolated liver cysts (transverse plane). The white arrows indicate the isolated liver cysts. CT, computed tomography.

the normal range from July 2015 to March 2018, without any abnormal result in December 2016 (86.91 ml/min/1.73 m²). The most recent abdominal computed tomography performed on the 14th of February 2016, demonstrated that the kidneys were significantly enlarged with numerous cysts of varying sizes with a total kidney volume of 1,127.21 cm³, while there were some isolated small cysts present in the liver (Fig. 1). In the semen analysis in July and August 2017, no sperm was detected, along with a low volume of ejaculate (2 and 2.3 ml, respectively). In the subsequent ultrasound examination, cysts were identified in the bilateral epididymis, with a size of 6 mm on the left and 4 mm on the right, in addition to dilated seminal vesicles. Of note, the subsequent testicular biopsy identified numerous mature sperms with progressive motility.

In order to make a definitive diagnosis of ADPKD, the patient was subjected to genetic sequencing analysis of the PKD1 and PKD2 genes. No mutation in the PKD2 gene was identified, whereas the coding region of PKD1 in the patient exhibited a c.9053delT frameshift mutation (p.Phe3018Serfs*56; Fig. 2), which has not been previously reported, to the best of our knowledge, in the 1,000 Genomes project, the Exome Aggregation Consortium or the PKD mutation database (13-15). Prediction regarding the effects of this mutation with Mutation Taster (www.mutationtaster.org) and PolyPhen-2 (genetics.bwh.harvard.edu/pph2) software

indicated that the protein variant is 'disease-causing' and 'probably damaging', respectively, which is in line with the situation of the present case. Sanger sequencing of the mother of the patient revealed no mutations in PKD1 or PKD2; renal function was in the normal range and there were no kidney cysts observed. The father of the patient died in a motor vehicle collision in 2005 at the age of 50 years, and therefore, it was not possible to perform Sanger sequencing, however he had normal kidney function and no family history of kidney disease.

Discussion

ADPKD is a prevalent inherited kidney disease, commonly caused by a mutation of PKD1 and/or PKD2 in the majority of cases. The mutation in the remaining 10% of patients is undetectable, which may be attributed to the current lack of effective testing methods, or to similar kidney cysts caused by other gene mutations (5,6); the glucosidase II α subunit gene, which serves a role in protein folding and quality control, may be another potential causal gene that induces ADPKD phenotypes (16). Due to the advantages of low cost and high-throughput, the technology of next-generation sequencing is widely applied in the diagnosis and study of hereditary disease, including ADPKD (17-20). However, its short-read sequencing approaches

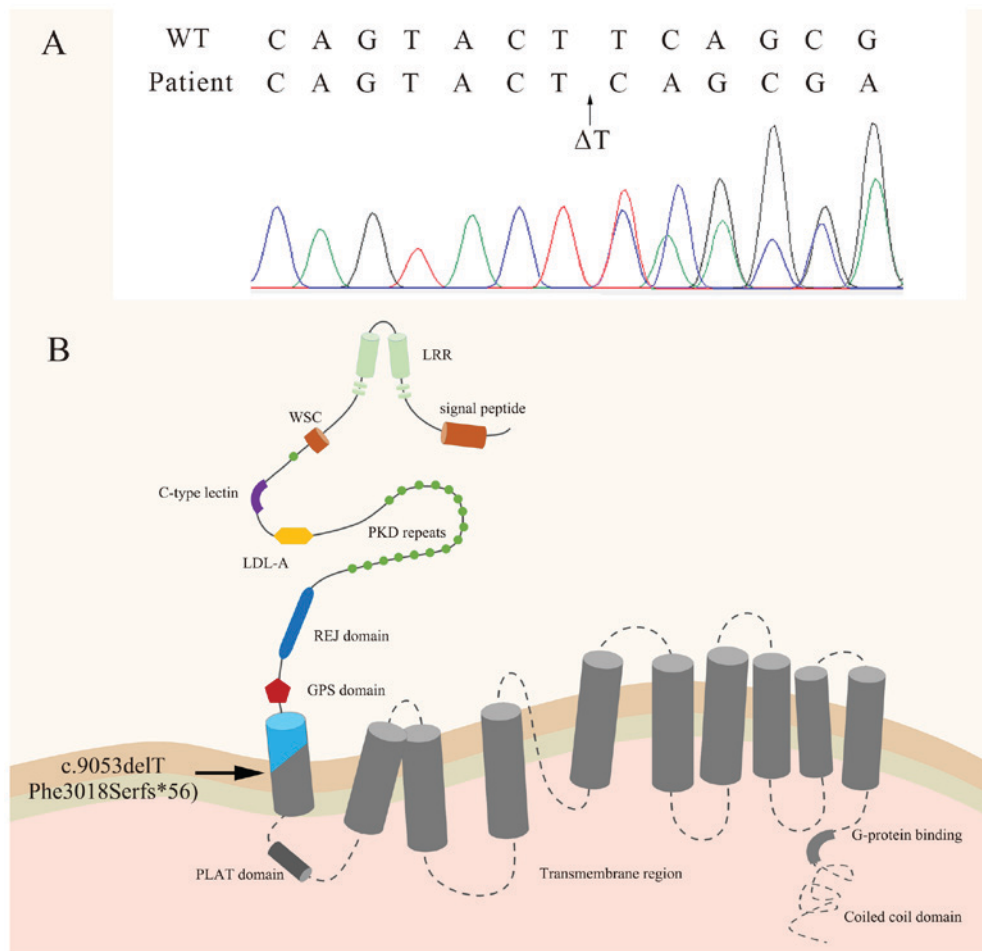


Figure 2. DNA sequencing revealing the c.9053delT mutation and aberrant PC-1 structure. (A) Direct sequence analysis of exon 25 identified c.9053delT in a heterozygous state. (B) The structure of the pathogenic PC-1 of the 33-year-old patient. WT, wild-type; PC, polycystin; LRR, leucine-rich repeats; WSC, wall stress-responsive component domain; LDL-A, low-density lipoprotein-A; REJ, receptor for the egg jelly; GPS, G protein-coupled receptor proteolytic site; PLAT domain, polycystin-1, lipoxigenase and α -toxin; PKD1, polycystin 1, transient receptor potential channel interacting.

are not able to precisely recognize complex regions, including segmental duplications, extreme GC content and gaps (21,22). The PKD1 gene is ~50 kb long, contains 46 exons and encodes an open reading frame of 12,909 bp, whereas the PKD2 gene is ~68 kb long, contains 15 exons and encodes an open reading frame of 2,904 bp. The sequencing of PKD1 is complex due to the six duplicated pseudogenes adjacent to it, which are highly homologous with exons 1-33 of PKD1 (23). Due to the long range and the six pseudogenes, single-molecule long-read sequencing is more suitable for the detection of genetic variants in patients with ADPKD (24-26). In the present study, long-range PCR (LR-PCR) amplification and targeted next-generation sequencing, as described previously (27), was used to detect the variants of PKD1 and PKD2 in the 33-year-old male patient. No PKD2 mutation was identified; however, a T-allele deletion causing a frameshift mutation was identified at the 9,053th position of PKD1 complementary DNA. Subsequent to comparing this alteration with the wild-type PKD1 gene, it was identified that this frameshift mutation not only causes the 3,018th amino acid of PC-1 to change from phenylalanine to serine, but also leads to an early termination of protein translation. PC-1 is a membrane protein composed of an N-terminal extracellular portion, 11 transmembrane (TM) domains and a short intracellular C-terminal tail, which is able to directly bind PC-2 and

G proteins to initiate multiple signaling pathways (28-31). The c.9053delT is a frameshift mutation, which leads to the formation of a stop codon downstream of c.9053delT. This truncated polypeptide consists of 3,017 intact and 56 unique amino acids, without the TM region or the intracellular C-terminal tail. Therefore, the c.9053delT mutation may be disease-causing.

For patients with ADPKD, the predominant manifestation is numerous enlarged cysts in the bilateral kidneys. However, the disease severity and renal survival times are different between patients with mutant PKD1 and PKD2: Patients with PKD1 mutations frequently have a shorter renal survival time and suffer from end-stage renal disease (ESRD) ~20 years earlier compared with patients with mutant PKD2 (32,33). The greater disease severity associated with the PKD1 mutations is caused by the earlier onset of cyst formation, not the faster cyst growth (34). The additional renal manifestations vary among patients; furthermore, cyst formation in the liver is the most common sign associated with the disease, detected in ~83% of patients with ADPKD (35). Intracranial aneurysms are additionally associated with the disease, with a prevalence of 9-12%, and raise the risk of cerebrovascular accident (36). In the present study, the 33-year-old patient sought medical advice for abdominal pain and azoospermia. Chronic abdominal pain is a common complaint, and a study from the HALT-PKD Trial

documented complaints of abdominal fullness and pain which were severe in patients with advanced disease, possibly due to organ enlargement (37). The total kidney volume (TKV) was identified as a critical biomarker to predict the progression of ADPKD in recent studies; according to a clinical evaluation model, an eGFR of <50 ml/min/1.73 m² and a TKV of the bilateral kidneys of >1,000 cm³ is associated with an estimated median disease course of ESRD of 4 years (38-40). Therefore, the 33-year-old patient was advised to maintain good renal function to prolong the renal survival time, by having a low sodium diet, drinking more water and avoiding strenuous exercise. In patients with ADPKD, seminal vesicle cysts represent a common additional renal manifestation with a prevalence of 39-60%, as opposed to a prevalence of 5% in the general population; however, these cysts are rarely associated with infertility in male patients with ADPKD (41,42). A number of previous case reports regarding infertility and azoospermia in patients with ADPKD have been published, which suggest that the lack of PC-1 or PC-2 may result in the obstruction or atonicity of seminal vesicles or ejaculatory duct cysts and lead to ejaculation failure (43-47). In the present study, the ultrasound examination detected the presence of epididymis cysts and dilated seminal vesicles; however, the testicular biopsy identified mature sperm. This suggested that the cysts of the epididymis and the dilated seminal vesicles may obstruct the ejaculation of semen. May result in the obstruction or atonicity of seminal vesicles or ejaculatory duct cysts and lead to ejaculation failure.

In summary, the patient presented in this case study suffered from ADPKD and azoospermia due to a novel mutation in the PKD1 gene, c.9053delT. Assisted reproductive technology coupled with pre-implantation genetic diagnosis of ADPKD may be used to eliminate the inheritance of this mutation to produce a healthy embryo (48,49).

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Availability of data and materials

The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

CZL performed the clinical examination and diagnosed the patient with ADPKD, as well as reviewed the manuscript. JLM recorded and analyzed the results from the clinical examinations.

JLM and SXF obtained the blood samples, extracted the total DNA, completed the long-range PCR (LR-PCR) amplification and the targeted next-generation sequencing. JLM and YCX recorded and analyzed the results from the clinical examinations. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Informed consent for participation in the study was obtained.

Patient consent for publication

The patient provided written informed consent regarding the publication of his data and images.

Competing interests

The authors declare that they have no competing interests.

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