Identification of novel PKD1 mutations in two Chinese families with autosomal dominant polycystic kidney disease by targeted next generation sequencing

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To the Editor: Autosomal dominant polycystic kidney disease (ADPKD) is a common inherited kidney disease with an estimated incidence of 1 in 400 to 1 in 1000. It is a late-onset systemic disorder characterized by the development and progressive enlargement of cysts in the kidney, eventually leading to end-stage renal disease. Previous studies have shown that ADPKD is a heterogeneous monogenic disorder resulting from mutations in two genes: PKD1 and PKD2. Clinical data showed that PKD1 and PKD2 mutations account for 85% and 15% of ADPKD cases, respectively. Compared to PKD2 mutations, PKD1 mutations usually indicate more severe disease, earlier onset, and poorer prognosis. There are no mutation hotspots for PKD1 and PKD2, suggesting that mutations are not only unique to a single family but also high variable. In the present study, a novel nonsense mutation, c.6491C>A (p.Ser2164Ter), and a known frameshift mutation, c.12608_12635del (p.Arg4203Profs*146), in the PKD1 gene were identified by targeted next generation sequencing in two Chinese ADPKD families.

Two three-generation pedigrees [Figure 1A] that included 14 individuals with ADPKD were recruited in this study. All patients were definitively diagnosed with ADPKD by ultrasound, magnetic resonance imaging, or computed tomography scan according to standard criteria. A brief clinical summary of these patients is shown in Supplementary Table 1, http://links.lww.com/CM9/A174.

In pedigree 1, a novel nucleotide substitution c.6491C>A in exon 15 of the PKD1 gene was identified and validated through Sanger sequencing [Figure 1B]; it was absent in 200 normal unrelated individuals and had not been reported previously in any published database, including NCBI dbSNP, HapMap, Exome Variant Server Database, 1000 Genome, and a database of 100 Chinese healthy adults. The variant was considered as a novel mutation because it was not reported in Human Gene Mutation Database (HGMD). This c.6491C>A mutation was detected in all the affected members but was absent in asymptomatic family members and displayed its co-segregation with the disease in pedigree 1 [Figure 1A]. The pathogenicity prediction by Mutation Taster (http://www.mutationtaster.org/) was demonstrated as “disease-causing.” The C to A transversion was predicted to introduce an early stop codon UAA at position 2164 (p.Ser2164Ter), creating a premature truncated protein with 2140 amino acid shorter than the wild-type protein [Supplementary Figure 1, http://links.lww.com/CM9/A174].

In pedigree 2, a 28 bp-deletion (c.12608_12635delGGCTGGGgAGGTTGTAGGCTGACGCTGACGCC) in exon 46 of the PKD1 gene was identified and validated through Sanger sequencing [Figure 1C]. The c.12608_12635del mutation also displayed its co-segregation with the disease in pedigree 2 [Figure 1A]. However, the 28bp-deletion was reported by Neumann et al. in HGMD and considered as a known mutation for ADPKD. The pathogenicity prediction by Mutation Taster was demonstrated as “disease-causing.” The 28 bp deletion was predicted to change the open reading frame, cause the loss of the original stop codon UAG at position 4304, and introduce a new stop codon UAA at position 4348 (p.Arg4203Profs*146), leading to a prolonged abnormal protein with 44 amino acid longer than the wild-type protein [Supplementary Figure 2, http://links.lww.com/CM9/A175].
The *PKD1* gene encodes polycystin-1 (PC1), which contains a large N-terminal extracellular region, eleven transmembrane domains, and a cytoplasmic C-terminal tail with a coiled-coil structure that interacts with polycystin-2 (PC2). The PC1–PC2 complex colocalizes to the primary cilium, performs mechanosensory functions, and participates in the adhesion, proliferation, and differentiation of renal tubular epithelial cells. Related researches have shown that the abnormality or absence of the PKD1 C-terminal tail affects signal transduction, intracellular location, and renal prognosis.[6] In this study, the novel nonsense mutation c.6491C>A (p.Ser2164Ter) in the *PKD1* gene was predicted to produce a truncated protein lacking transmembrane domains and the cytoplasmic C-terminal tail, while the known frameshift mutation c.12608_12635del (p.Arg4203Profs*146) in the *PKD1* gene was predicted to produce a prolonged protein with an abnormal cytoplasmic C-terminal tail. The above mentioned changes in the PKD1 C-terminal tail would lead to inappropriate C-terminal-mediated signal transduction cascades, perhaps resulting in the hyperplasia of tubular epithelial cells, hyperactive secretion, and eventually pathogenic cystogenesis.

In conclusion, a novel nonsense mutation, c.6491C>A (p.Ser2164Ter), and a known frameshift mutation, c.12608_12635del (p.Arg4203Profs*146), in the *PKD1* gene were identified in two Chinese ADPKD families. Mutation screening in the Chinese population may contribute to understanding the genetic diversity among different ethnic groups and enrich the *PKD1* mutation database.

**Declaration of patient consent**

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patients have given their consent for their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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**Conflicts of interest**

None.

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