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The genetic spectrum of polycystic kidney disease in children

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SUMMARY

OBJECTIVE: Autosomal dominant polycystic kidney disease is an inherited kidney disorder with mutations in *polycystin-1* or *polycystin-2*. Autosomal recessive polycystic kidney disease is a severe form of polycystic kidney disease that is characterized by enlarged kidneys and congenital hepatic fibrosis. Mutations at *PKHD1* are responsible for all typical forms of autosomal recessive polycystic kidney disease.

METHODS: We evaluated the children diagnosed with polycystic kidney disease between October 2020 and May 2022. The diagnosis was established by family history, ultrasound findings, and/or genetic analysis. The demographic, clinical, and laboratory findings were evaluated retrospectively.

RESULTS: There were 28 children (male/female: 11:17) evaluated in this study. Genetic analysis was performed in all patients (*polycystin-1* variants in 13, *polycystin-2* variants in 7, and no variants in 8 patients). A total of 18 variants in *polycystin-1* and *polycystin-2* were identified and 9 (50%) of them were not reported before. A total of eight novel variants were identified as definite pathogenic or likely pathogenic mutations. There was no variant detected in the *PKDH1* gene.

CONCLUSION: Our results highlighted molecular features of Turkish children with polycystic kidney disease and demonstrated novel variations that can be utilized in clinical diagnosis and prognosis.

KEYWORDS: Next-generation sequencing. Polycystic kidney disease. Polycystic kidney and hepatic disease 1. PKD1 protein. PKD2 protein.

INTRODUCTION

Autosomal dominant polycystic kidney disease (ADPKD) is the most common inherited renal disorder, with a prevalence between 2.4 and 9.0 per 10,000[1,2]. ADPKD is caused by disease-causing variants in the *polycystin-1* (*PKD1*) and *polycystin-2* (*PKD2*) genes[3]. The clinical diagnosis of ADPKD is based on the patient's age, a positive family history, and the number of kidney cysts on ultrasound imaging[4,5]. Autosomal recessive polycystic kidney disease (ARPKD) is an inherited polycystic kidney disorder characterized by the development of bilateral renal cystic and congenital hepatic fibrosis[6]. ARPKD is associated with pathogenic variants in the *PKHD1* gene. The liver abnormalities consist of hepatomegaly, increased echogenicity, portal hypertension, or dilated intrahepatic bile ducts[7,8]. Genetic tests may be essential to obtain a definitive diagnosis when the diagnosis cannot be established by imaging-based methods[9]. In this study, we evaluated demographic, clinical, and genetic results of children with polycystic kidney disease. However, until now, there has been limited information about the genetic spectrum of Turkish children with ADPKD or ARPKD. In addition, we evaluated the pathogenic effects of novel variants through protein prediction tools.

METHODS

We evaluated 28 children from 26 families with polycystic kidney disease between October 2020 and May 2022. ADPKD was diagnosed by a family history, renal ultrasound findings, and/or genetic results. Demographic, clinical, and laboratory test results were evaluated retrospectively (Table 1). The genetic study was performed after obtaining the informed consent of the parents. The study protocol was approved by the ethics committee of the Eskisehir Osmangazi University (Protocol No: 2022-152). Genomic DNA was obtained from patients' peripheral venous blood using the QIAamp DNA Blood Mini QIAcube Kit (Qiagen, Hilden, Germany) following the manufacturer's instructions. The next-generation sequencing panel provided good coverage of exon-flanking intronic regions of *PKD1* (except for exon 1 of *PKD1*), *PKD2*, and *PKDH1* were analyzed by Illumina NovaSeq platform using the Agilent SureSelect V5 kit. QIAGEN Clinical Insight (QCI) Interpret data analysis platform was used for the analysis of raw data. Several in silico prediction programs were used to evaluate the pathogenic effect of the mutation and its function on the biological processes of the protein such as SIFT, Mutation Taster, and Polyphen2. The American College of Medical Genetics and Genomics (ACMG) guidelines was used

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for variant classification[8]. We evaluated the pathogenicity of the variants taking into account by using the population allele frequency data from different population databases (1000 Genome, gnomAD, and ExAC). The statistical analyses were performed using the SPSS 10.0 software. In this analysis, clinical data were expressed in percentages.

RESULTS

A total of 28 children from 26 families diagnosed with polycystic kidney disease during the period in question were enrolled in the study. Of those patients, 11 (39.3%) were males and 17 (60.7%) were females (Table 1). The mean age of patients was 10.75 (4.85) years ranging from 3 to 18 years. The family history of polycystic kidney disease was discovered in 78.6% of cases (22/28). Notably, 13 patients (46.5%) had a maternal family history, and 9 patients (32.1%) had a paternal family history. Table 1 summarizes the demographic data and clinical outcomes of patients. Renal cysts were bilateral in 18 (67.9%) patients. Only two patients (7.1%) had hepatic cysts, and none of them had hepatic fibrosis. A total of four patients had cardiac findings such as patent foramen ovale (two patients), atrial septal defect (one patient), and ventricular septal defect (one patient). Recurrent urinary tract infections were detected in six (21.4%), hypertension was observed in one (3.6%), urolithiasis was defined in two (7.1%), proteinuria in four (14.3%), pyuria in two (7.1%), and hematuria in five (17.9%) patients. None of them had chronic renal failure during their follow-up. Among 28 children, we identified 18 variants, including 12 *PKD1* (66.7%) variants and six *PKD2* (33.3%) variants (Table 2). The mutation detection rate and PKD1 and PKD2 mutation rates are presented in Table 3. No variant was detected in the *PKDH1* gene in any of the patients. A pathogenic or likely pathogenic variant was determined in 15 patients (11 *PKD1* variants and 3 *PKD2* variants). Among the 12 *PKD1* variants, 7 mutations were novel, including 5 frameshift, 1 nonsense, and 1 missense. Additionally, one novel *PKD1* (c.10364T>G; p.Leu3455Arg) variant of uncertain significance (VUS) was also identified. Among the six *PKD2* variants, two variants were novel. These variants have not been previously found in major variant databases such as ExAc, gnomAD, dbSNP, and ClinVar. Three variants were predicted as pathogenic or likely pathogenic (*PKD2*:c.1180G>C, *PKD2*:c.965G>A, and *PKD2*:c.1906C>T) and three were also predicted as VUS (*PKD2*:c.198C>A, *PKD2*:c.83G>C, and *PKD2*:c.2186T>A) (Table 2).

Table 1. Demographic, clinical, and laboratory findings of patients with polycystic kidney disease.

Characteristics	PKD (28 patients)
Age	Mean±[SD] (min-max) 10.75±[4.85] (3-18)
Sex	Male: 11 (39.3%) Female: 17 (60.7%)
Family history Maternal history Paternal history	22/28 (78.6%) 13 (46.5%) 9 (32.1%)
Renal cyst (bilateral) Renal cyst (unilateral)	19/28 (67.9%) 9/28 (32.1%)
Hepatic cyst	2/28 (7.1%)
Cardiac abnormalities	4/28 (14.3%)
Recurrent urinary tract infections	6/28 (21.4%)
Hypertension	1/28 (3.6%)
Urolithiasis	2/28 (7.1%)
Proteinuria	4/28 (14.3%)
Pyuria	2/28 (7.1%)
Hematuria	5/28 (17.9%)
A positive genetic result	20/28 (71.4%)
A negative genetic result	8/28 (28.6%)

PKD: polycystic kidney disease.

DISCUSSION

ADPKD is the most commonly seen inherited renal disease characterized by the development and progressive enlargement of cysts in the renal, eventually resulting in end-stage renal disease[5]. ADPKD is a monogenic disease caused by mutations in *PKD1* and *PKD2* genes[6]. Mutations in *PKD1* and *PKD2* are not hotspot mutations, suggesting that pathogenic variants of *PKD1* or *PKD2* are often unique[7]. Previous studies showed that *PKD1* and *PKD2* mutations are responsible for 85 and 15% of ADPKD cases, respectively[8,9]. ARPKD is a rare inherited infantile form of polycystic kidney disease, characterized by bilaterally enlarged echogenic kidneys and congenital hepatic fibrosis secondary to malformation of the biliary ducts[10]. The *PKHD1* gene mutations can cause ARPKD[11,12].

In this study, we used a target gene panel search for *PKD1* and *PKD2* (ADPKD) and *PKDH1* (ARPKD) genes in 28 children with a variant detection rate of 71.4% (20/28). However, we could not detect any *PKDH1* gene variant in patients. Kinoshita et al. detected the mutations in 89.1% of the patients[13]. The demographic characteristics of this study group were similar to another Turkish cohort study enrolling 69 ADPKD patients. The mean age of patients in the study was 10.75 years, whereas it was 9.3 years in their Turkish cohort study. In our study, the female to male (17:11) ratio was similar to the other study

Table 2. Details of *polycystin-1* and *polycystin-2* gene variants in this study.

Patient ID	Gene	Exon	cDNA	Protein change	Variant effect	Novelty	ACMG classification	SIFT/Polyphen2/ Mutationtaster
PKD1 gene								
P2	PKD1	10	c.2048G>A	p.Trp683Ter	Nonsense	Reported	PVS1, PM2, and PP5	Pathogenic
P3	PKD1	27	c.9547C>T	p.Arg3183Ter	Nonsense	Reported	PP5, PVS1, and PM2	Pathogenic
P5 and P6	PKD1	46	c.12664dupC	p.Leu4222ProfsTer6	Frameshift	Novel	PM2 and PVS1	Pathogenic
P13	PKD1	11	c.2226C>G	p.Tyr742Ter	Nonsense	Novel	PVS1 and PM2	Pathogenic
P15	PKD1	1	c.165_171del	p.Leu56ArgfsTer15	Frameshift	Reported	PVS1, PP5, and PM2	Pathogenic
P16	PKD1	23	c.8314_8316del	p.Glu2772del	Frameshift	Novel	PM1 and PM2	Pathogenic
P18	PKD1	46	c.12664dup	p.Leu4222ProfsTer6	Frameshift	Novel	PM2 and PVS1	Pathogenic
P19	PKD1	11	c.2534T>C	p.Leu845Ser	Missense	Reported	PP5 and PM2	Pathogenic
P20	PKD1	15	c.6649del	p.Val2217CysfsTer25	Frameshift	Novel	PVS1 and PM2	Likely pathogenic
P21	PKD1	5	c.974A>G	p.Tyr325Cys	Missense	Reported	PM2, PP5, and PP2	Likely pathogenic
P22	PKD1	33	c.10364T>G	p.Leu3455Arg	Missense	Novel	PM2 and PP2	VUS
P25	PKD1	43	c.11716dup	p.Cys3906LeufsTer55	Frameshift	Novel	PVS1 and PM2	Likely pathogenic
PKD2 gene								
P9	PKD2	1	c.198C>A	p.Asp66Glu	Missense	Reported	PP2 and BP4	VUS
P10	PKD2	5	c.1180G>C	p.Asp394His	Missense	Novel	PM2 and PP2	Pathogenic
P11 and P12	PKD2	1	c.83G>C	p.Arg28Pro	Missense	Reported	PP2	VUS
P24	PKD2	4	c.965G>A	p.Arg322Gln	Missense	Reported	PM1, PM2, and PP5	Pathogenic
P27	PKD2	9	c.1906C>T	p.Gln636Ter	Nonsense	Novel	PVS1 and PM2	Likely pathogenic
P28	PKD2	11	c.2186T>A	p.Leu729Gln	Missense	Reported	BS2	VUS

ACMG: American College of Medical Genetics and Genomics; SIFT: Sorting Intolerant From Tolerant.

Table 3. Genetic results of different studies with autosomal dominant polycystic kidney disease cohort.

Authors	Number of patients	Mutation detection rate (%)	PKD1 (%)	PKD2 (%)
Kim et al.[11]	542	81.4	348 (82.3%)	75 (17.7%)
Audrézet et al.[12]	42	90.4	36 (94.7%)	2 (5.3%)
Kinoshita et al.[13]	101	89.1	82 (87.2%)	12 (12.8%)
Tutal et al.[14]	69	66.6	40 (86.9%)	6 (13.1%)
Kasap Demir et al.[15]	29	75.8	22 (95.4%)	1 (4.6%)
Reed et al.[18]	24	58	12 (85.7%)	2 (14.3%)
Audrézet et al.[19]	519	91.6	392 (80.5%)	95 (19.5%)
Carrera et al.[20]	440	80	301 (85.5%)	51 (14.5%)
Eo et al.[21]	188	84.5	131 (69.7%)	57 (30.3%)
Hoefele et al.[22]	93	64.5	52 (86.7%)	8 (13.3%)
Heyer et al.[23]	1,119	92.4	869 (77.7%)	165 (14.7%)
Rossetti et al.[24]	202	89.1	153 (85.0%)	27 (15.0%)
Xu et al.[25]	120	81.7	85 (91.4%)	8 (8.6%)
This study	28	71.4	12 (66.7%)	8 (33.3%)

(38:31)[14]. In a previous study conducted in Turkey, the diagnosis rate was 66.6% with direct sequencing of *PKD1* (86.9%) and *PKD2* (13.1%). The reason of the lower diagnosis yield in their study was the lack of genetic testing in some patients[15]. In our study, the frequencies of mutation in *PKD1* and *PKD2* genes were 66.7 and 33.3%, respectively. Also, the frequency of *PKD1* mutations was higher, the frequency of *PKD2* mutations was lower, and it was compatible with the medical literature (80–90% for *PKD1* and 15–20% for *PKD2*)[16,17]. In another study from Turkey, 3.8% of the patients with ADPKD had *PKD2* gene mutation[18]. The findings show that the main gene responsible for ADPKD in the Turkish population, as in other populations, is the *PKD1* gene. In this study, we found that the mutation rates of *PKD1* and *PKD2* were similar to previous studies (Table 3). A positive family history is not present in approximately 10–20% of individuals with ADPKD[15-18]. Notably, 21.4% of our patients had no family history of the disease, which was consistent with previously reported results. In a recent study on 24 patients suspected of having ADPKD with no apparent family history, 9 patients were retrospectively found to have pathogenic *PKD1* mutations[19]. It should be kept in mind that patients with de novo mutations may develop the disease without a family history. A positive family history should not be necessary for genetic research in patients. Among the 18 variants, we found that in *PKD1* and *PKD2*, 50% (9/18) are novel variants. Genetic analysis results showed that 11 variants in *PKD1* gene and 3 variants in *PKD2* gene were predicted as pathogenic/likely pathogenic. Furthermore, subcategorization of *PKD1* variants showed 6 truncation/frameshift, 3 nonsense, and 3 missense variants. After evaluation of variants for *PKD2*, two missense and one nonsense variants were detected as pathogenic or likely pathogenic. Notably, seven of the *PKD1* variants and two *PKD2* variants were novel. We identified four variants of VUS in *PKD1* (one variant) and *PKD2* (three variants) (Table 2). We identified a novel duplication variant, PKD1:c.12664dupC (p.Leu4222ProfsTer5) in two siblings who suffer from ADPKD. The family history showed a paternal origin. The variant was not identified in the dbSNP, ClinVar, or *PKD1*-LOVD databases. The p.Leu4222ProfsTer5 variant is expected to lead to an early stop codon at position 4222 and it results in a deficient and nonfunctional protein. Loss-of-function variants of the *PKD1* gene are accepted as the type of variant that constitutes the mechanism of the ADPKD. The duplication variant is considered to be the pathogenic factor for ADPKD in that family. We found a novel nonsense mutation c.2048G>A (p.Trp683Ter) was located in the 10th exon of *PKD1*. The variant was not observed in the gnomAD and 1000 genomes. It was predicted to result in a truncated protein with reduced or aberrant function. This variant was predicted to be pathogenic according to the recommendation of the ACMG guidelines. We suggested that the variant could be associated with ADPKD. For the first time, we report two missense variants of the *PKD2* gene, namely, c.198C>A (p.Asp66Glu) and c.1180G>C (p.Asp394His). These variants have not been previously identified in population databases such as 1000 genomes and gnomAD. Fathers of patients carrying these mutations were also diagnosed with ADPKD. Although previous studies have identified other variants of *PKD1* and *PKD2* in the Turkish population, here in this study, we report seven novel variants as follows: c.9547C>T, c.165_171del, c.2534T>C, c.974A>G, and c.974A>G (*PKD1*) and c.83G>C and c.965G>A (*PKD2*). The variants have been previously detected in European, Asian, and Middle Eastern populations[20-25]. *PKD1* or *PKD2* variants were not detected in any of the eight patients with typical features of PKD (8/28; 28.6%). According to the literature, the most common genetic cause of ADPKD is still *PKD1* and *PKD2* gene mutations (18, 19, 20-24). Whole exome sequencing can be used to detect other rare variants that have the potential to contribute to the ADPKD phenotype in patients with a negative result[23,25].

This study has some limitations. First, it was a retrospective, single-center study with a small sample size. In this study, a targeted panel sequence test including *PKD1*, *PKD2*, and *PKDH1* genes was used to identify polycystic kidney disease. Therefore, we could not have the opportunity to examine other genes causative of rarer forms of the disease, including *GANAB*, *DNAJB11*, and *ALG9*.

CONCLUSION

In our study group of patients with polycystic kidney disease, 12 variants were detected in *PKD1* and 6 variants were detected in *PKD2*. Six variants have previously been described in different populations. Notably, 9 out of 18 mutations are not reported before and probably unique. The six frameshift variants detected in the *PKD1* gene are novel and appear to be associated with ADPKD, and two novel missense mutations in *PKD2* can also be associated with ADPKD. This study will enrich the *PKD1* and *PKD2* mutation database and make an important contribution to the genetic counseling of ADPKD patients. Prospective studies are needed in patients with genetically diagnosed ADPKD to detect such a relationship.

AUTHORS' CONTRIBUTIONS

AK: Conceptualization, Investigation, Methodology, Supervision, Validation, Visualization, Writing – original draft, Writing

– review & editing. **YÖA:** Conceptualization, Formal Analysis, Investigation, Writing – original draft, Writing – review & editing. **MS:** Conceptualization, Investigation, Supervision, Writing – review & editing. **TK:** Conceptualization, Formal Analysis, Investigation, Methodology, Project administration, Writing – original draft, Writing – review & editing.

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