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Original Article

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Analysis of PKD1 and PKD2 Gene Mutations for Autosomal Dominant Polycystic Kidney Disease Cases in Turkish Population

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Abstract

Objective: Autosomal dominant polycystic kidney disease (ADPKD), one of the most common causes of end-stage renal disease, is a monogenic, multisystemic disease characterized by renal cysts and various extrarenal findings. ADPKD is caused by mutations in the polycystic kidney disease 1 (PKD1) (16p13.3) and PKD2 (4q22.1) genes. The genetic analysis of the PKD1 gene is complex because of its large size, the presence of 6 pseudogenes, and allelic heterogeneity. In this study, we aimed to identify the mutations of the PKD1 gene in patients with ADPKD in Sivas, Turkey.

Materials and Methods: A total of 27 patients who were diagnosed with ADPKD were included in this study. Their mean age and body mass indices were determined. The gene variants were analyzed by targeted next-generation sequencing method.

Results: In 17 (64.3%) of the 27 patients, the variants were detected in PKD1 and/or PKD2 genes. There were 13 patients (48.1%) with PKD1 gene variants and 5 (18.5%) with PKD2 gene variants. Of the 17 patients, 1 had both PKD1 and PKD2 gene variants. We observed that 16 patients with ADPKD (66.6%) had hypertension, and liver cysts were detected in 9 (33.3%) patients.

Conclusion: PKD1 gene mutations were found in a significant number of patients with ADPKD, and hypertension is a frequently observed finding in them. In some patients, liver cysts may accompany the clinical picture of ADPKD. Our findings provide important insights for the genetic counseling of these patients.

Keywords: Autosomal dominant polycystic kidney disease, mutation, polycystic kidney disease 1 gene, polycystic kidney disease 2 gene

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INTRODUCTION

Autosomal dominant polycystic kidney disease (ADPKD) is an inherited disease characterized by multiple cysts causing end-stage renal disease (1). The frequency of the disease is 1/400-1/1,000. In patients with ADPKD, kidney stones, cerebral aneurysm, cardiac problems, colonic diverticulum, and male infertility could also be present (2). Although ADPKD may be seen at any age, the presence of these findings increases with age and the disease usually presents with symptoms in the third or fourth decade (3). Cardiovascular events and end-stage renal failure are responsible for the morbidity and mortality in ADPKD (2). ADPKD shows clinical and genetic heterogeneity, and the clinical findings and severity of the disease are variable even in the same family (4). In ADPKD, polycystic kidney disease 1 (PKD1) gene (16p13.3) mutations are responsible for 80%-85% of the cases, PKD2 (4q22.1) for 15%-20%, and glucosidase II alpha subunit (GANAB) (11q12.3) for 0.3%. GANAB mutations are associated with a milder clinical course and autosomal dominant polycystic liver disease (5, 6).

ADPKD is diagnosed by physical examination and imaging. However, these cannot exclude the disease in

individuals at risk up to the age of 40 years (7). The use of mutation-based diagnostic methods is increasing in individuals who are at risk for ADPKD and cannot be diagnosed accurately with imaging modalities. Genetic analysis may be useful for the definitive diagnosis of patients with no family history or early onset of the disease. In addition, preimplantation genetic diagnosis (PGD) can provide diagnostic and prognostic information for the next generation in patients with ADPKD (8).

The clinical manifestations of ADPKD may be similar to those of ciliopathic diseases, such as nephronophthisis or Bardet-Biedl syndrome. Hence, besides the analysis of PKD1 and PKD2 genes, polycystic kidney etiology can be revealed by comprehensive genetic screening using gene panels formed for the next-generation sequencing (NGS) method. Quantitative polymerase chain reaction, multiplex ligation-dependent probe amplification (MLPA), and array-comparative genomic hybridization methods can be used to detect wide genomic variations in patients in whom mutations cannot be detected by sequencing methods (9).

In this study, we aimed to investigate the mutation types and mutation frequency of PKD1 and PKD2 genes in patients with ADPKD in Sivas, Turkey. Through the insight gained from these studies, it could be possible to reduce the frequency of mutant genes in the next generations and to form healthy generations via genetic counseling of the patients with ADPKD.

MATERIALS AND METHODS

Study Population

A total of 27 patients with a diagnosis of ADPKD admitted to the outpatient clinic of Nephrology Department of Cumhuriyet University, Faculty of Medicine, Sivas, Turkey, had no acute renal failure and older than 18 years of age were included in this study. Patients with liver failure, acute coronary syndrome, malignancy, and signs of acute infection were excluded from the study. This study was performed in accordance with the principles of the Declaration of Helsinki. This study was approved by the Ethics Committee of Sivas Cumhuriyet University School of Medicine (Approval Date: June 28, 2016; Approval Number: 2016-06/03). Oral and written consents were obtained from all the participants.

Main Points

- In 17 (64.3%) of the 27 patients, variants were detected in polycystic kidney disease 1 (PKD1) and/or PKD2 genes.
- There were 13 (48.1%) patients with PKD1 gene variants, 5 (18.5%) with PKD2 gene variants, and 1 with both PKD1 and PKD2 variants.
- Of these, 10 of the variants detected in the PKD1 gene and 3 of the variants in the PKD2 gene have not been previously reported in the literature and databases.

Demographic (age, sex, and so on) and clinical characteristics and laboratory findings (biochemical and hematologic) of the participants were taken from their epicrisis and reports in the hospital database. Data on hepatic cysts, cerebral vascular aneurysms, and cardiac diseases were collected retrospectively. The estimated glomerular filtration rate (eGFR) was calculated by the 4-variable Modification of Diet in Renal Disease formula and normalized to body surface area. Proteinuria was calculated in the spot urine specimens as gram protein/gram creatinine. The last data on the patients with end-stage renal disease were gathered in August 2019 (~3 year follow-up).

DNA Isolation

The peripheral blood samples of 2 mL were taken into ethylene diamine tetraacetic acid tubes from all of the participants and stored at -20°C until the time of analysis. Genomic DNA isolation was performed with 200 µL of blood sample using MagNAPure LC DNA isolation kit (Roche Diagnostics; Mannheim, Germany). Density (ng/µL) and absorbance ([A260/280] [1.80-2]) of the DNA samples were measured by a spectrophotometer (Nanodrop 2000c, Thermo Scientific; Waltham, MA, USA). Samples with A260/280 values less than 1.80 were manually isolated by column method. Double-stranded DNA was quantified using Qubit fluorimeter (Qubit® dsDNA HS Assay Kit, Life Technologies; Carlsbad, California, USA).

Library Preparation and NGS

NGS technique was performed using the Custom Bundle Solution kit for nephropathies (Sophia Genetics Nephropathy Panel® Saint-Sulpice, Switzerland). This panel allows for the analysis of PKD1 and PKD2 genes as well as other genes associated with a wide variety of nephropathies (Table 1). Sophia Genetics Nephropathy Panel is a genomic application that bundles a capture-based target enrichment kit. MiSeq V3 reagent (Illumina®, CA, USA) was used, and the resultant FASTQ data at the end of 50 hours were analyzed using the Sophia Genetics DDM® bioinformatics software. The clinical importance of the detected variants was determined according to 2015 criteria of American College of Medical Genetics and Genomics. The PKD1 gene contains regions identical to the pseudogene region. However, the kit and Sophia DDM® data analysis platform are designed to differentiate between the pseudogene variants and PKD1 variants. The variants can be analyzed in the warnings section or variant basis on the analysis platform. The controls of these regions can be controlled on the platform via the Integrative Genomics Viewer connection.

Statistical Analysis

The IBM Statistical Package for Social Sciences version 22 (IBM SPSS Corp.; Armonk, NY, USA) was used for all statistical analyses of this study. Descriptive statistics were shown as frequencies and percentages for categorical variables and as median (interquartile range [IQR]) for continuous variables. The continuous variables were tested for normality by one-sample Kolmogorov-Smirnov test and Shapiro-Wilk test.

RESULTS

A total of 27 patients from the Sivas Cumhuriyet University School of Medicine, Sivas, Turkey were included in this study. The patients who underwent mutation analysis had been diagnosed before by using ultrasonography and/or computed tomography. Demographic and clinical characteristics and laboratory findings of the patients with ADPKD are shown in Table 2. Of the participants, 13 (48.1%) were women and 14 (51.9%) were men. The mean age of the patients was 52.6±15.8 years; the mean body mass index was 27.6±5.1 kg/m^2. A positive family history was found in 19 patients (70.3%). In a family of 12 patients, some had undergone hemodialysis. Radiologic evaluation revealed liver cysts in 9 (33.3%) patients. When the patients were evaluated for systemic disease, we detected 16

Table 1. List of genes included in the nephropathy panel

Gene	
PKD1	SLC12A3
PHEX	ATP6V1B1
COL4A3	FOXC1
PKD2	NR3C2
CASR	CRB2
COL4A	DSTYK
PKHD1	AVPR2
CTNS	CUBN
COL4A5	PAX2
WT1	AQP2
SLC12A1	EMP2
FN1	EYA1
HNF1b/TSC2	AGXT
KCNJ1	KANK2
NPHS2	SIX1
CEP290	GRHPR
BSND	SLC4A1
LAMB2	CLCN5
UMOD	SLC34A1
CLCNKB	SLC4A4
ATP6V0A4	OCRL
TTC21B	CYP24A1

Table 2. Demographic and clinical characteristics and laboratory findings of patients with ADPKD

Characteristics	ADPKD (27)
Age (years)	52.6±15.8
Sex (male)	14 (51.9)
Family history of ADPKD	19 (70.3)
End-stage renal disease	4 (14.8)
Hepatic cyst	9 (33.3)
Coronary artery disease	
(20 cases available)	4 (14.8)
Hypertension	16 (59.3)
Systolic blood pressure (mm Hg)	143.5±15.0
Diastolic blood pressure (mm Hg)	86.1±7.6
Antihypertension drugs	
Angiotensin II receptor blockers	8 (29.6)
Calcium channel blockers	7 (25.9)
Diuretics	6 (22.2)
ACE inhibitors	5 (18.5)
Beta blockers	2 (7.4)
Glomerular filtration rate (mL/min/1.73 m^2)	68 (40-108)
Proteinuria (g/g creatinine)	0.13 (0.07-0.26)
Blood glucose (mg/dL)	91 (82-100)
Blood urea nitrogen (mg/dL)	19.8±8.1
Blood creatinine (mg/dL)	1.2 (0.7-1.7)
Blood uric acid (mg/dL)	5.8±1.9
Total protein (g/dL)	7.2 (6.8-68.7)
Serum albumin (g/dL)	4.8 (4.3-44.7)
Alanine aminotransferase (IU/L)	17 (11-21)
Aspartate aminotransferase (IU/L)	16.5 (15.3-18)
Sodium (mEq/L)	139.9±2.5
Potassium (mEq/L)	4.5±0.5
Phosphorus (mg/dL)	2.8±0.7
Calcium (mg/dL)	9.2±0.5
White blood cell count (10^9/L)	7.5±2.2
Hematocrit (%)	43±6.1
Hemoglobin (g/dL)	14.4±2.1
Platelet count (10^9/L)	224 (203-273)
25-hydroxyvitamin D (ng/mL)	14.7 (10.8-22.9)
Parathyroid hormone (pg/mL)	48.4 (37.8-94.9)
Erythrocyte sedimentation rate (mm/h)	8.5 (5-30)
C-reactive protein (mg/L)	4.0 (1.7-8.3)

Data are presented as mean±standard deviation or median (interquartile range) or frequency and percentages
ADPKD: autosomal dominant polycystic kidney disease; ACE: angiotensin-converting enzyme

(59.3%) with hypertension. End-stage renal failure was present in 4 (14.8%) patients.

After genetic screening with NGS, 17 (85.2%) of the 27 patients were found to have 23 variants of PKD1 and/or PKD2 genes. Of these, 18 (78.2%) of the variants were in the PKD1 gene, and 5 mutations (21.7%) were in the PKD2 gene. In 1 (3.7%) patient, mutations were detected in both the genes. In the other 10 (37%) patients, pathogenic, likely pathogenic variant, or variant with unknown significance was not detected in the PKD1 and PKD2 genes. The variants detected in the PKD1 gene are shown in Table 3. All the mutations defined in the patients were heterozygous. Of the mutations detected in the PKD1 gene, 10 were not previously reported in the literature and databases. These mutations were c.1256G>A (p.C419Y), c.823G>C (p.A275P), c.3216C>G (p.N1072L), c.11243T>A (p.L3748Q), c.11376delG (p.Thr3793ArgfsX32), c.5877_5882delCC (p.Ala1961_Gln1962del), c.12057C>G (p.C4019W), c.12007C>T (p.Q4003X), c.6574_6580delACCGCCA p.Thr2192AlafsX18, c.3284A>C (p.T1095S), and c.624G>C (p.E208D).

The mutations detected in the PKD2 gene are listed in Table 4. All the mutations detected were heterozygous, and 3 of them were not previously reported in the literature. These novel variants are c.2019+1G>T, c.205delG/p.Ala69ProfsX48, and c.1077_1078insA/p.Pro360ThrfsX12. There was no difference between the patients with PKD1 and PKD2 mutations in terms of the presence of the liver cysts and hypertension. Selected clinical data of the patients are presented in the Table 2. The 4 patients who were on dialysis (ages 57, 63, 73, and 57 years) were given renal replacement therapy. A new mutation was detected in 1 of these 4 patients (c.2019+1G>T). None of the remaining patients progressed to the end-stage renal failure in the 3-year follow-up period. Because the vast majority of the patients did not adhere to the clinical visits, the rate of decrease in the GFR could not be assessed prospectively during the study; therefore, this study lacks data on the relationship between genotype and phenotype in terms of decrease in GFR. Median proteinuria level was low as expected; there were 4 patients with proteinuria levels higher than 1 mg/dL creatinine, and all had GFR lower than 50 mL/min/1.73 m^2. The patients

Table 3. Polycystic kidney disease 1 variants detected in patients and their pathogenicity classification

Case no.	Exon/intron	cDNA	Protein	Class
5	6	c.1256G>A	p.C419Y	Likely pathogenic
	5	c.823G>C	p.A275P	Variant of uncertain significance
	14	c.3216C>G	p.N1072L	Variant of uncertain significance
	44	c.12086C>T	p.T4029I	Variant of uncertain significance
8	39	c.11243T>A	p.L3748Q	Likely pathogenic
	44	c.12094C>G	p.L4032V	Variant of uncertain significance
14	40	c.11376delG	p.Thr3793ArgfsX32	Pathogenic
17	15	c.5877_5882del CC	p.Ala1961_Gln1962del	Likely pathogenic
	44	c.12057C>G	p.C4019W	Variant of uncertain significance
20	17	c.7204C>T	p.R2402X	Pathogenic
23	44	c.12007C>T	p.Q4003X	Pathogenic
24	15	c.6574_6580del ACCGCCA	p.Thr2192AlafsX18	Pathogenic
28	18	c.7288C>T	p.R2430X	Pathogenic
29	15	c.4531C>T	p.P1511S	Variant of uncertain significance
31	14	c.3284A>C	p.T1095S	Likely pathogenic
33	5	c.624G>C	E208D	Variant of uncertain significance
35	5	c.971G>T	p.R324L	Pathogenic
37	5	c.971G>T	p.R324L	Pathogenic

Table 4. Polycystic kidney disease 2 variants detected in patients and their pathogenicity classification

Case no.	Exon/intron	cDNA	Protein	Class
1	8	c.1837C>T	p.Q613X	Pathogenic
4	9	c.2019+1G>T		Pathogenic
22	1	c.205delG	p.Ala69ProfsX48	Pathogenic
25	4	c.1077_1078insA	p.Pro360ThrfsX12	Pathogenic
33	9	c.2019+1G>T		Pathogenic

had been screened for cerebral aneurysms, and none of them had vascular aneurysm. We also gathered the data for association between the new mutation and hepatic cysts. The data for 27 patients were available; 9 of them had hepatic cysts, and 5 patients with liver cysts were detected to have a new mutation. We had no data on colonic diverticula. Coronary angiography of 20 patients was available; 4 of them were diagnosed with an occlusive coronary disease. Severely decreased GFR (eGFR <50 mL/min), the most frequent complication of the disease, was observed in 4 patients with new mutations (Case 4 [c.2019+1G>T], Case 5 [c.1256G>A, c.823G>C, c.3216C>G, and c.12086C>T], Case 23 [c.12007C>T], and Case 33 [c.624G>C]).

DISCUSSION

ADPKD is the most frequent inherited kidney disease owing to mutations in the PKD1 and PKD2 genes. Although there are many studies in the medical literature investigating mutations in PKD1 and PKD2 with NGS, to our knowledge, this is the first study to be reported from Turkey. We aimed to investigate the mutations and frequencies of mutations in the PKD1 and PKD2 genes in patients from Sivas, which might help in genetic counseling of the families. On the basis of this genetic counseling, *in vitro* fertilization (IVF) and PGD may provide a decrease in the frequency of the disease-causing gene. This is the first study from Turkey using NGS technique to investigate the mutations in ADPKD.

In a study related to PKD1 and PKD2 by Xu et al. (10), the mutations were detected in 98 (81.7%) of 120 Chinese families. Similarly, in this study, we detected genetic mutations in 63% of the patients, either in 1 or both of the genes. Unlike the study of Xu et al. (10), we detected the mutations in either PKD1 or PKD2 at a frequency of 48.1% and 18.5%, respectively. Kinoshita et al. (11) detected the mutations in 89.1% of the patients. Mutation frequencies of PKD1 and PKD2 genes were 87.2% and 12.8%, respectively.

Tan et al. (12) reevaluated the ADPKD cases with NGS after the research conducted by Sanger sequencing method. Their results showed that there is no difference between the 2 methods in terms of sensitivity and specificity. Therefore, we used only the NGS method to detect the mutations. We detected 10 new variants in PKD1 and 3 new variants in PKD2, which were not reported previously. However, the frequency of PKD1 mutations was lower and that of PKD2 mutations was higher in our study than those of the previous reports in the medical literature (85%-90% for PKD1 and 10-15% for PKD2). Although the mutations can be determined in most individuals with ADPKD, approximately 10% of the affected families have no detectable mutations. Some PKD1 or PKD2 mutations may not be detected by the NGS method (13). In our study, we could not detect any mutation in 10 patients. In this group with no mutation detected using NGS, PKD1 mutations may be detected by MLPA and Sanger sequencing methods. Another cause of this discordance may be the small sample size of our study. However, the data obtained in this study still suggest that the PKD1 gene may be the major gene responsible for ADPKD in the Turkish population, as in Asian and European populations.

A high heterogeneity of alleles and presence of 6 pseudogenes on PKD1 complicates the molecular analysis of this gene. Although a large number of studies have been reported on families with Asian ADPKD population, only a few of them address this issue (14). Ranjzad et al. (15) investigated the frequency of PKD1 and PKD2 mutations in 9 nonrelated Iranian ADPKD families by the NGS method and detected 3 new mutations. They suggested that the defects of the Ig-like repeat domain in the PKD1 protein may cause male reproductive tract cysts; thus, male patients with pathogenic mutations in the Ig-like repeat domain of PKD1 may have a high risk of infertility. In a Chinese study, 76 mutations were detected in 77 families, and 38 of them were found with new mutations (16).

CONCLUSION

The value of early identification of candidates of the disease in relatives of the patients with ADPKD by genetic analysis of PKD1 and PKD2 genes should not be ignored. Early identification, at the beginning of the renal pathological process or when the disease is still asymptomatic, may help in providing close follow-up, necessary changes in diet, and early education of the potential patient. Furthermore, IVF combined with PGD could contribute to the birth of healthy infants for generations and may have economic benefits to the society. The retrospective nature of the clinical data and small sample size prevented

us from arriving at exact conclusions regarding the phenotype-genotype relationship, and further studies with larger sample sizes are necessary to clarify this issue.

Ethics Committee Approval: Ethics committee approval was received for this study from the Ethics Committee of Sivas Cumhuriyet University School of Medicine (Approval Date: June 28, 2016; Approval Number: 2016-06/03).

Informed Consent: Written and verbal informed consent was obtained from the patients who participated in this study.

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REFERENCES

1. Tan YC, Blumenfeld J, Rennert H. Autosomal dominant polycystic kidney disease: Genetics, mutations and microRNAs. Biochim Biophys Acta 2011; 1812: 1202-12. [Crossref]
2. Luciano RL, Dahl, NK. Extra-renal manifestations of autosomal dominant polycystic kidney disease (ADPKD): Considerations for routine screening and management. Nephrol Dial Transplant 2013; 29: 247-54. [Crossref]
3. Grantham JJ. Clinical practice. Autosomal dominant polycystic kidney disease. N Engl J Med 2008; 359: 1477-85. [Crossref]
4. Torres VE, Harris PC. Autosomal dominant polycystic kidney disease: The last 3 years. Kidney Int 2009; 76: 149-68. [Crossref]
5. Cordido A, Besada-Cerecedo L, García-González MA. The genetic and cellular basis of autosomal dominant polycystic kidney disease-a primer for clinicians. Front Pediatr 2017; 5: 279. [Crossref]
6. Porath B, Gainullin VG, Cornec-Le Gall E, Dillinger EK, Heyer CM, Hopp K, et al. Mutations in GANAB, encoding the glucosidase IIα subunit, cause autosomal-dominant polycystic kidney and liver disease. Am J Hum Genet 2016; 98: 1193-207. [Crossref]
7. Liu B, Chen SC, Yang YM, Yan K, Qian YQ, Zhang JY, et al. Identification of novel PKD1 and PKD2 mutations in a Chinese population with autosomal dominant polycystic kidney disease. Sci Rep 2015; 5: 17468. [Crossref]
8. Harris PC, Rossetti S. Molecular diagnostics for autosomal dominant polycystic kidney disease. Nat Rev Nephrol 2010; 6: 197-206. [Crossref]
9. Choi R, Park HC, Lee K, Lee MG, Kim JW, Ki CS, et al. Identification of novel PKD1 and PKD2 mutations in Korean patients with autosomal dominant polycystic kidney disease. BMC Med Genet 2014; 15: 129. [Crossref]
10. Xu D, Ma Y, Gu X, Bian R, Lu Y, Xing X, et al. Novel Mutations in the PKD1 and PKD2 genes of Chinese patients with autosomal dominant polycystic kidney disease. Kidney Blood Press Res 2018; 43: 297-309. [Crossref]
11. Kinoshita M, Higashihara E, Kawano H, Higashiyama R, Koga D, Fukui T, et al. Technical evaluation: Identification of pathogenic mutations in PKD1 and PKD2 in patients with autosomal dominant polycystic kidney disease by next-generation sequencing and use of a comprehensive new classification system. PLoS One 2016; 11: e0166288. [Crossref]
12. Tan AY, Michaeel A, Liu G, Elemento O, Blumenfeld J, Donahue S, et al. Moleculardiagnosis of autosomal dominant polycystic kidney disease usingnext-generation sequencing. J Mol Diagn 2014; 16: 216-28. [Crossref]
13. Murphy EL, Droher ML, DiMaio MS, Dahl NK. Preimplantation genetic diagnosis counseling in autosomal dominant polycystic kidney disease. Am J Kidney Dis 2018; 72: 866-72. [Crossref]
14. Phakdeekitcharoen B, Watnick TJ, Ahn C, Whang DY, Burkhart B, Germino GG. Thirteen novel mutations of the replicated region of PKD1 in an Asian population. Kidney Int 2000; 58: 1400-12. [Crossref]
15. Ranjzad F, Aghdami N, Tara A, Mohseni M, Moghadasali R, Basiri A. Identification of three novel frameshift mutations in the PKD1 gene in Iranian families with autosomal dominant polycystic kidney disease using efficient targeted next-generation sequencing. Kidney Blood Press Res 2018; 43: 471-8. [Crossref]
16. He WB, Xiao WJ, Tan YQ, Zhao XM, Li W, Zhang QJ, et al. Novel mutations of PKD genes in Chinese patients suffering from autosomal dominant polycystic kidney disease and seeking assisted reproduction. BMC Med Genet 2018; 19: 186. [Crossref]