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PKD1 gene rs7185040 polymorphism and progression of chronic kidney disease in patients with ADPKD

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ABSTRACT

Introduction: Autosomal dominant polycystic kidney disease (ADPKD) is a commonly encountered genetic condition contributing to chronic renal failure in both pediatric and adult populations. Roughly 89% of individuals with ADPKD exhibit mutation in either the PKD1 or PKD2 genes. If there is a family history of the disease, PKD1 is the predominant gene associated.

Objectives: The objective of this research was to investigate tag-single nucleotide polymorphisms (tag-SNPs) rs7185040 within the PKD1 gene in the advancement of chronic kidney disease (CKD) among individuals affected by ADPKD.

Patients and Methods: In this current case-control study, we examined the prevalence of PKD1 tag SNP rs7185040 within a cohort comprising 102 ADPKD-affected individuals and 106 control subjects. We utilized the fluorescent resonance energy transfer (FRET)-based KASPar method for genotyping the PKD 1 tag SNP. We employed the χ^2 association test to unravel the CKD progression among the ADPKD and to find an association between those with ADPKD and controls.

Results: The AA, AC and CC genotypes of PKD1 tag SNP (rs7185040) as well as the A and C alleles showed no notable significance in distribution between patients with ADPKD and controls. In addition, there was no significant difference in distribution of PKD1 (rs7185040) genotypes between early and advanced stages of CKD among the ADPKD cohort.

Conclusion: Our results indicated no significant association between the PKD1 polymorphism rs7185040 and CKD progression in ADPKD patients.

Original Article

Implication for health policy/practice/research/medical education:
The genetic variation rs7185040 within the PKD1 gene is recognized for its association with autosomal dominant polycystic kidney disease (ADPKD). PKD1 (rs7185040) might act as a biomarker for predicting the progression of chronic kidney disease (CKD) to advanced stages. Our study findings indicate no notable association between ADPKD and controls regarding rs7185040 polymorphism. Further, in this study SNP was not contributing to the development of CKD among those with ADPKD.

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Introduction

Autosomal dominant polycystic kidney disease (ADPKD) stands out as a prevalent hereditary renal condition characterized by the progressive formation of cysts, resulting in the enlargement and deformation of the kidneys, causing the deterioration of kidney function, and frequently culminating in end-stage renal disease (ESRD) (1). Genetic research has revealed that the prevalence of ADPKD is approximately 1 per 1000 individuals, while studies based on population data have estimated its prevalence to be in the range of 25–68 cases per 100 000 people (2,3). Individuals with chronic kidney disease (CKD) and ESRD have reduced glomerular filtration rate (GFR), which may eventually necessitate advanced interventions like kidney dialysis or transplantation to manage the condition (4). Hypertension is an early sign of ADPKD and is seen in 60% of ADPKD cases and can be an early predictor of disease progression (5). PKD1 and PKD2 are the most common genes involved with ADPKD, and their polymorphism contributes

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to genetic changes in the development of ADPKD (6). The PKD1 gene, found on chromosome 16, encodes the polycystin-1 protein (PC1), a significant glycoprotein that resides within the cell membrane. This gene encompasses 46 exons, featuring an extensive duplicated segment spanning exons 1–33. Interestingly, this duplicated region exhibits a significant similarity in sequence with six other pseudogenes located near PKD1 on the same chromosome (16p) (7). Dysfunction of PKD1 is responsible for approximately 77–78% of cases of ADPKD (8). Despite being attributed to mutations in PKD1 and PKD2, fully penetrant PKD mutations are rare, occurring in roughly 0.1% or fewer of all chromosomes (9). ADPKD exhibits genetic heterogeneity. The variation in phenotypes within and between families contributes to this disparity. Notably, individuals from families linked to PKD1 tend to experience renal disease progression approximately 15 years earlier than those from PKD2-linked families (10). Previous studies did not establish an association between PKD1 (rs7185040), the primary SNP, and ADPKD. This particular SNP is recognized as a quantitative trait locus associated with the decreased expression of PKD1 (11). In mouse models, it has been demonstrated that the PKD1 gene plays a role in the formation of bone cells, and knock-out mutations of pkd1 resulted in bone abnormalities (12); however, no such data are recorded for ADPKD. However, it is worth noting that PKD1 (rs7185040) is associated with CKD (11).

Objectives

Our objective is to investigate the potential association between PKD1 (rs7185040) and the progression of CKD with ADPKD patients. Further, we investigated the role that tag-SNPs in the PKD1 gene play in the progression of CKD from early stage to advanced stage in individuals with ADPKD.

Patients and Methods

Study participants

This study was conducted as a case-control study and enlisted 208 individuals of South Indian descent who sought care at the department of nephrology, Sri Ramachandra University, Chennai. Among them, 102 were diagnosed with ADPKD, while 106 served as healthy controls devoid of a family history of CKD, hypertension, or diabetes. ADPKD diagnosis adhered to the Ravine ultrasound criteria (13). Ultrasound scans were employed to ascertain the total cyst count, and the Modification of Diet in Renal Disease (MDRD) formula determined the estimated glomerular filtration rate (eGFR) (14). CKD staging for ADPKD patients followed Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines. Patients were stratified into early (CKD stages 1–3) and advanced (CKD stages 4 and 5) based on eGFR data (15).

PKD1 (rs7185040) and genotyping

The incidence of the tag SNP rs7185040 in the two groups was studied. DNA was extracted from peripheral blood leukocytes using the phenol–chloroform extraction method followed by ethanol precipitation (16). The selection of the tag SNP for rs7185040 within the PKD1 gene was based on data from the phase II HapMap project. The criteria used for choosing this tag SNP included an $r^2 \geq 0.8$ and a minor allele frequency of at least 5% in the Gujarati Indians in Houston (GIH) population (17, 18). The KASPar SNP Genotyping Method (KBioscience, Herts., UK) was utilized, which employs fluorescent resonance energy transfer (FRET) technology for genotype analysis. This method involves the utilization of fluorescent probe primers (K Bioscience, UK using Kraken™ software system) (19,20).

Statistical analysis

Allele frequencies were computed using the gene counting method (21). An association $\chi 2$ test was conducted to determine the correlation between ADPKD patients and controls. Additionally, univariate logistic regression analysis was employed to evaluate the influence of genotypes on CKD progression. All statistical computations were carried out utilizing SPSS software (version 27.0 for Windows, SPSS Inc., Chicago, IL). Significance was set at a p-value of < 0.05.

Results

The mean age of individuals with ADPKD was 46.8 ± 11.5 years, whereas for controls, it was 54.0 ± 12.8 years. Males represented 55.88% of the ADPKD cohort and 59.43% of controls, with females comprising 44.12% of ADPKD patients and 40.57% of controls. The clinical characteristics of controls and ADPKD patients are compared in Table 1. The number of cysts; levels of blood urea nitrogen, creatinine, hemoglobin, bicarbonate, and calcium; and eGFR showed a significant association ($P < 0.001$) between ADPKD and controls. However, sodium, potassium, and chlorine levels were not found to be significant.

PKD1 (rs7185040) polymorphism and ADPKD

The results of genetic analysis assessing the frequency of genotypes and alleles for the PKD1 (rs7185040) polymorphism in the patients with ADPKD and controls are provided in Table 2. Genotype frequencies in both the ADPKD and control cohorts were consistent with the Hardy-Weinberg equilibrium (HWE). Moreover, no statistically significant ($P < 0.05$) disparities were noted in the distribution of PKD1 (rs7185040) genotype and allele frequencies between the control and ADPKD samples.

Table 1. Baseline characteristics of ADPKD and control groups

Characteristics	Control (n=106)	ADPKD (n=102)	*P* value*
Age (y)	54.00±12.80	46.80±11.50	0.001
Gender, male	63 (59.43)	57 (55.88)	
Hemoglobin (g/dL)	11.70±2.50	10.70±2.00	0.001
Cyst number	0	4.40±1.60	0.001
BUN (mg/dL)	13.40±6.96	28.00±24.60	0.001
Creatinine (mg/dL)	0.90±0.21	3.0±2.6	0.001
Sodium (mmol/L)	136.50±5.80	137.10±8.70	0.550
K (mmol/L)	3.90±0.85	4.40±2.10	0.030
Cl (mmol/L)	101.10±6.09	101.30±11.80	0.930
HCO_3 (mmol/L)	24.60±3.80	22.90±4.20	0.001
Calcium (mg/dL)	10.20±1.43	7.70±1.10	0.001
eGFR (mL/min/1.73 m^2)	82.70±20.82	43.80±34.7	0.001

BUN: Blood urea nitrogen; K: Potassium; Cl: Chloride; HCO_3: Bicarbonate; eGFR: estimated glomerular filtration rate.
* Indepedent samples t-test was done to compare the quantifiable variables among the baseline characteristics of both groups.

Table 2. Genotype association test

rs7185040	Control (n=106)	Case (n=102)	OR (95% CI)	*P* value*
AA	93 (87.7)	89 (87.2)	Reference	Reference
AC	11 (10.3)	9 (8.8)	0.85 (0.33–2.16)	0.740
CC	2 (1.8)	4 (3.9)	2.08 (0.37–11.69)	0.391
AC+CC	13 (12.2)	13 (12.7)	1.04 (0.45–2.37)	0.916
CC	2 (1.8)	4 (3.9)	Reference	Reference
AA+AC	104 (98.1)	98 (96.1)	0.47 (0.08–2.63)	0.380
A	197 (92.9)	187 (91.7)	Reference	Reference
C	15 (7.1)	17 (8.3)	1.19 (0.57–2.45)	0.630
HWE–X^2	4.71	18.20	–	–
MAF	7.08	8.33	–	–

OR: Odds ratio; CI: Confidence interval; HWE: Hardy-Weinberg equation; MAF: Minor allele frequency.
*χ^2 test.

The distribution of PKD1 (rs7185040) genotypes among ADPKD patients and their association with CKD stages

Among the patients with ADPKD, 49 individuals (52%) were found to have advanced-stage disease, while 53 (48%) had early-stage CKD. The PKD1 (rs7185040) genotype distribution data are provided in Table 3, along with the information on its correlation with early- and advanced-stage CKD. Univariate analysis revealed no correlation between the PKD1 (rs7185040) genetic variation and progression to advanced-stage CKD.

Discussion

Analysis of the PKD1 (rs7185040) SNP in patients with ADPKD and controls revealed no substantial and statistically significant association of SNP with ADPKD. Further, there was no significant association

Table 3. The distribution of PKD1 (rs7185040) genotype and its association with CKD stages

rs7185040	Early stage (n=53)	Advanced stage (n=49)	OR (95% CI)	*P* value*
AA	48 (90.50)	41 (83.60)	Reference	Reference
AC	2 (3.70)	7 (14.20)	4.09 (0.80–20.82)	0.069
CC	3 (5.60)	1 (2.00)	0.39 (0.03–3.89)	0.407
AC+CC	5 (9.43)	8 (16.30)	1.87 (0.56–6.17)	0.296
CC	3 (5.60)	1 (2.00)	Reference	Reference
AA+AC	50 (94.30)	48 (98.00)	2.8 (0.28–28.65)	0.346
A	98 (92.50)	89 (90.80)	Reference	Reference
C	8 (7.50)	9 (9.20)	1.23 (0.45–3.34)	0.672

OR: Odds ratio; CI: Confidence interval.
*χ^2 test.

between rs7185040 and progression to advanced-stage CKD among patients with ADPKD. A genome-wide association study revealed that the rs7185040 SNP of PKD1 was an important cause of inherited muscle weakness (22); however, no studies exist on its role in ADPKD. Computational tools have been conducted to identify SNPs in PKD1 gene that may be pathogenic for ADPKD progression and thereby aid in the genetic screening of at-risk patients with ADPKD. For example, a cysteine-to-arginine mutation at 508 positions, noted as rs58598099, was the most damaging SNP in one analysis. Hence the relationship between genotypic variation through polymorphisms and the phenotype of ADPKD was established (23). The study by Parfrey et al demonstrated that dysregulation of the PKD1 gene was associated with renal cyst formation, leading to the onset of ESRD at an early age in these individuals compared with the risk in those without a family history of renal cysts (24). Several studies on KO and CKO mice showed that targeting the pkd1 gene followed by treatment with drugs/inhibitors like MitoQuinone, Mdivi-1, and 666-15 resulted in inhibition of epithelial cysts, suppression of PKD progression, and improvement of renal function (25-27). In one study on $Pkd1^{RC/+}$ and $Pkd1^{RC/-}$ cell lines generated from the kidneys of Pkd1RC/flox male mice, the elimination of $Pkd1^{\Delta 17}$ and $Pkd2^{\Delta 17}$ motif improved the stability of mRNA, leading to reduced cyst growth in murine PKD models. Further, it has been shown in a murine model that when Pkd1/2 cis-inhibition is prevented, it reduces the severity of PKD (28). In the study by Gregory et al, tissues (UT1270 and JHU496) from ADPKD2 patients were assessed, leading to the identification of somatic mutations in 71% of the examined cysts. These mutations were unique to each cyst. Notably, in addition to PKD2 mutations, PKD1 mutations were also observed, and UT1270 showed a loss of heterogeneity for multiple SNPs. Their study further suggested that somatic PKD1 mutations might influence the severity of ADPKD2. The combined loss of function of these genes at the somatic level could potentially disrupt the associated signaling pathway (29). Thus, the findings of these studies suggest that PKD1 can be a target molecule in the regulation of ADPKD.

Our study demonstrated PKD1 (rs7185040) polymorphisms in adult patients with ADPKD. Bergmann et al stated that PKD1 alleles could modify the phenotypic presentation of ADPKD such as age of onset and severity (30). Our study highlights that the polymorphism shows dominance with age, and the disease is, thus, detected at a later stage. Moreover, the study by Buchholz et al (31) demonstrated that cyst enlargement is induced by increased chloride secretion by calcium-activated chloride channels regulated by polycystin-2 in the endoplasmic reticulum, stimulated by PKD genes. In the present study, although there was a slight increase (0.2 mmol/L) in chloride levels in ADPKD patients compared with those in control, it was not significant. Meanwhile, studies from Saudi Arabia (32), China (33), Korea (34), Taiwan (35), America (36), Italy (37), and Greece (38) found a significant association between PKD1 gene polymorphism and ADPKD, in contrast to findings from Europe (39) and Pakistan (40) that found no association. In the case of India, there is uncertainty about whether PKD1 or PKD2 dominates, thus making it unclear which polymorphism leads to the progression of CKD in ADPKD patients (41).

This is the very first study that aimed to find the correlation of rs7185040 tag SNP of the PKD1 gene with the progression of CKD in ADPKD. We also found no association of PKD1 (rs7185040) with ADPKD, similar to the findings of studies from Pakistan and Europe. This can be mainly due to heterogeneity and diverse communities among the Indian population. However, we assessed only PKD1 polymorphism in this study; thus, there could be a potential PKD2 polymorphism in the majority of the study cohort. Further, there might have been a selection bias during participant recruitment, which might be a limitation of this study. Family history and consanguinity are also important factors to consider in autosomal dominant disease. The inclusion of these two factors could lead to variations in the findings. The study's limited sample size could also serve as a constraint in its findings. Nonetheless, this investigation has shown that despite the presence of the PKD1 (rs7185040) polymorphism in the population, the risk of developing CKD remains relatively low in individuals with ADPKD and there was no correlation between the polymorphism and progression of CKD. Therefore, it is essential to establish a well-validated functional SNP for PKD1 (rs7185040) to gain a more definitive involvement of the PKD1 (rs7185040) variant in CKD progression among individuals with ADPKD.

Conclusion

This case-control study revealed no significant correlation between the rs7185040 polymorphism in the PKD1 gene and the progression of CKD in ADPKD. However, as the study only analysed the PKD1 gene, there might be a possibility of the presence of PKD2 polymorphism in the study cohort. In conclusion, genetic screening and early detection of disease biomarkers may prevent the progression of early-stage CKD to advanced-stage CKD and improve diagnostic outcomes. Further, investigating the other important polymorphisms of PKD1 might help us understand their influence on ADPKD. Additionally, a large-scale population study is required to validate these findings.

Limitations of the study

- The study may be constrained by a limited sample size.
- There might be a possibility of the presence of PKD2 polymorphism in the majority of the study cohort than PKD1.
- During the selection of patients, there might have been a bias.

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Authors' contribution

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Data curation: Aiswarya Kosaraju, Sandhya Suresh, Ramprasad Elumalai, Gnanasambandan Ramanathan.
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Writing–review & editing: Ramprasad Elumalai.

Conflicts of interest

The authors declare that they have no competing interests.

Ethical issues

The research adhered to the principles outlined in the Declaration of Helsinki. The study's procedural plan received approval from the Institutional Ethics Committee (IEC-NI/09/MAR/08/09) at Sri Ramachandra University in Chennai, India. Additionally, informed consent was obtained from all the participants involved in the study. Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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