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Original Article

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Importance of Parental Consanguinity and Family History of Kidney Disease in the Turkish Adult Chronic Kidney Disease Population: An Epidemiologic Study

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ABSTRACT

Background: This study aims to investigate the frequency of familial relationships and genetic predispositions to kidney disease, analyzing their correlation with chronic kidney disease (CKD).

Methods: This observational study included individuals aged 18-70 years (at the time of this study) from October 2009 to 2015. 2576 patients with diverse kidney diseases [mean age: 47 ± 16 years; 1455 men (56.5%)], were compared with 853 healthy individuals with an employed questionnaire. Variables such as siblings, familial kidney disease history, consanguineous marriage, etiology of CKD, age at the time of the study, and diagnosis were compared between groups.

Results: Parental consanguinity frequency was similar between groups [n = 174 (6.8%) in the patient group vs. n = 74 (8.7%) in the control group, $P = .06$]. Kidney disease due to family history was significantly higher in the patient group than in the control group (466 [18.1%] vs. 72 [8.4%], $P < .001$). Parental consanguinity frequency was notably higher in patients with congenital anomalies of the kidney and urinary tract (CAKUT) (n = 31/234; 13.2%) and vesicoureteral reflux (VUR) nephropathy (n = 27/131, 20.5%) compared to controls (8.7%) ($P = .036$ and $P < .001$, respectively). Multivariate analysis indicated that predictors of parental consanguinity were kidney disease due to family history (OR: 5.712; 95% CI, 4.136-7.890; $P < .001$), age at kidney disease diagnosis (OR: 0.968; 95% CI, 0.957-0.979; $P < .001$), and kidney disease replacement therapy (OR: 1.441; 95% CI, 1.020-2.038; $P = .038$).

Conclusion: The CAKUT and VUR nephropathy risks are increased in consanguineous marriages. Patients with parental consanguinity develop the disease earlier and face a higher risk of kidney failure requiring replacement therapy. Consanguineous marriage might impact the severity of kidney diseases.

Keywords: Chronic kidney diseases, consanguinity, family history, Turkish population, vesicoureteral reflux nephropathy

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INTRODUCTION

The incidence and frequency rates of kidney failure requiring replacement therapy (KFRT) continue to rise despite advancements in treatment modalities.[1] The progression of chronic kidney disease (CKD) is influenced by multiple environmental and genetic factors.[2] Limited studies have highlighted an increased frequency of familial incidences associated with KFRT, demonstrating familial clustering in various kidney conditions like polycystic kidney disease, congenital anomalies of the kidney and urinary tract (CAKUT), focal segmental glomerulosclerosis (FSGS), immunoglobulin A nephropathy (IgAN), and membranoproliferative glomerulonephritis (MPGN).[1,2] Additionally, certain ethnic groups exhibit an elevated familial tendency toward CKD, with novel genes identified as contributors to its development.[3-7]

In the Turkish population over 18 years of age, the frequency of CKD stands at 15.7%.[8] Türkiye is characterized by a high rate of consanguineous marriages (24%),

potentially heightening the risk of autosomal recessive familial kidney diseases.[8,9] Despite the growing interest in genetic kidney diseases, data exploring these conditions in countries with high rates of consanguineous marriages remains limited. Moreover, the impact of consanguineous marriage on kidney disease prognosis has been examined in a few studies.[10,11] Notably, it remains unknown whether the prognosis of patients in these countries differs from that of patients in Western nations with low consanguinity rates. This study aims to investigate the frequency of kinship relationships and family history related to kidney disease, exploring their association with the distribution and severity of CKD.

MATERIAL AND METHODS

Study Design and Participants

This observational study enrolled individuals aged 18-70 years (at the time of the study) between October 2009 and 2015 at a tertiary referral center in Istanbul and was carried out using a questionnaire. The control group comprised individuals from outpatient clinics where the investigated condition was not detected. All participants in the control group underwent assessments for kidney disease using urine analysis and serum creatinine tests. Exclusion criteria involved follow-up durations < 6 months, unconfirmed diagnoses, and refusal to participate to the study, using the available serum creatinin level at the time of the study involvement.

Data Collection

Information regarding sex, familial kidney disease history, and consanguineous marriage was obtained via a questionnaire. Data on CKD etiology, age at study, and diagnosis were extracted from medical records. The questionnaire, administered by four investigators, covered comprehensive family history details. Standardized protocol training was provided to enhance questionnaire reliability.

Measurements and Classifications

Glomerular filtration rate (GFR) was measured using the Chronic Kidney Disease Epidemiology Collaboration.[10] Chronic kidney disease staging was based on the National Kidney Foundation Kidney Disease Outcomes Quality Initiative guidelines.[10]

Chronic Kidney Disease Etiology and Family Factors

Chronic kidney disease etiology was categorized into 15 groups, including diabetic nephropathy, hypertensive nephrosclerosis, CAKUT, tubulointerstitial nephritis (TIN), AA amyloidosis due to familial Mediterranean fever, autosomal dominant polycystic kidney disease (ADPKD), thrombotic microangiopathy (TMA), IgAN, FSGS, membranous nephropathy, MPGN, Alport syndrome, systemic vasculitis affecting the kidney, and CKD of unknown etiology. Parental consanguinity was identified through participant interviews.

Family history encompassed first- (parent, sibling, or child) and second-degree relatives (niece, cousin, ancestor, aunt, uncle) with kidney disease requiring KRT or outpatient follow-up.

Statistical Analysis

Patients were stratified into CKD stages and healthy controls. Categorical variables such as age, sex, CKD etiology, consanguineous marriage, and kidney disease due to family history were presented using numbers and percentages. Continuous variables with a normal distribution, such as age at diagnosis and age at study time, were expressed as means and standard deviations. The association between categorical variables (age, sex, CKD etiology, consanguineous marriage, kidney disease due to family history) was assessed using chi-square and Fisher's exact tests where appropriate. Moreover, the *t*-test was employed to analyze data from 2 groups, while analysis of variance was utilized to ascertain the mean age at diagnosis and inclusion across more than 3 groups.

Correlation analyses were performed using the Spearman test to explore relationships among parental consanguinity, age at diagnosis, kidney replacement therapy requirement, kidney disease due to family history, age at study, and female sex. Further correlation analyses were conducted considering the presence or absence of kidney disease due to family history to investigate associations among parental consanguinity, age at diagnosis, KFRT, age at study, and female sex.

Logistic regression analysis was employed to identify characteristics associated with parental consanguinity and kidney disease due to family history. Univariate logistic regression assessed the association of parental consanguinity with variables including kidney disease due to family history, age at diagnosis, KFRT, age at study, and female sex. Similarly, the analysis for kidney disease due to family history considered age at diagnosis, parental consanguinity, KFRT, age at study, and female sex. Subsequently, a multivariate analysis incorporating the identified confounding factors from the univariate analysis was conducted. No evidence of strong collinearity was detected, and effect modifiers were not introduced into the logistic regression

MAIN POINTS

- Consanguineous marriages exhibit a heightened risk for congenital anomalies of the kidney and urinary tract and vesicoureteral nephropathy, suggesting the involvement of autosomal recessive patterns in disease development.
- Closer relationships between relatives increase the likelihood of transmitting recessive genes to offspring.
- Patients with parental consanguinity tend to manifest the disease at a younger age and have an increased risk of progressing to kidney failure requiring replacement therapy.
- Early-onset kidney disease often shows a clustering of familial cases, indicating a prevalent genetic component in its occurrence.

analysis. Odds ratios and their corresponding 95% confidence intervals were reported for a rise per individual unit in continuous variables. A *P*-value less than .05 was considered statistically significant. The study obtained approval from the Istanbul University Faculty of Medicine Medical Ethics Committee under protocol number 2016/257 in September 2016. Informed consent was obtained from the participants who agreed to take part in the study.

RESULTS

Patient Demographics and Disease Characteristics

This study comprised 2576 patients, with a mean age of 47 ± 16 years, including 1455 men. The patient cohort consisted of 1240 (48.1%) people diagnosed with stages G1-G4 CKD, 436 (16.9%) undergoing hemodialysis, 845 (32.8%) kidney transplant recipients, and 55 (2.1%) undergoing peritoneal dialysis.

The demographic characteristics of patients categorized by CKD stages and healthy controls are summarized in Tables 1 and 2. The kidney disease due to family history was significantly higher in the study group than in healthy controls [466 (18.1%) vs. 72 (8.4%), *P* < .001]. Within the study group, 743 patients (28.8%) had an unidentified cause of kidney disease. Diabetic nephropathy (n = 297, 11.5%), hypertensive nephrosclerosis (n = 261, 10.1%), CAKUT (n = 234, 9.1%), TIN (n = 194, 7.5%), IgAN (n = 168, 6.5%), FSGS (n = 167, 6.5%), AA amyloidosis due to familial Mediterranean fever (n = 121, 4.7%), and ADPKD (n = 118, 4.6%) were the most common diagnoses in the study group.

Table 1. Demographic Characteristics of Patients According to Chronic Kidney Disease Stages and Healthy Controls

	CKD 1-4 Stages (n = 1240)	Dialysis Patients (n = 491)	Transplant Recipients (n = 845)	Healthy Controls (n = 853)	*P*
Mean age at inclusion (years ± SD)	48.6 ± 16.7	51.9 ± 16	40.9 ± 11.7	44.0 ± 14.6	<.001
Mean age at diagnosis (years ± SD)	43.5 ± 17.4	42.9 ± 17.5	27.9 ± 10.1	-	<.001
Sex (%)					
Female	584 (47.1%)	212 (43.2%)	325 (38.5%)	519 (60.8%)	<.001
Male	656 (52.9%)	279 (56.8%)	520 (61.5%)	334 (39.2%)	
Etiology of CKD (n) (n,%)					
Diabetic nephropathy	175 (14.1%)	498 (20%)	24 (2.8%)	-	
Hypertensive nephrosclerosis	137 (11%)	79 (16.1%)	45 (5.3%)	-	
CAKUT	76 (6.1%)	32 (6.5%)	126 (14.9%)	-	
Tubulointerstitial nephritis	85 (6.9%)	44 (9%)	65 (7.7%)	-	
IgA nephropathy	120 (9.7%)	9 (1.8%)	39 (4.6%)	-	
Focal segmental glomerulosclerosis	133 (10.7%)	7 (1.4%)	27 (3.2%)	-	
AA amyloidosis due to FMF	61 (4.9%)	22 (4.5%)	38 (4.5%)	-	
Polycystic kidney disease	56 (4.5%)	35 (7.1%)	27 (3.2%)	-	<.001
Membranous glomerulonephritis	70 (5.6%)	2 (0.4%)	6 (0.7%)	-	
Vasculitis	41 (3.3%)	9 (1.8%)	15 (1.8%)	-	
MPGN	31 (2.5%)	6 (1.2%)	19 (2.2%)	-	
Thrombotic microangiopathy	26 (2.1%)	5 (1%)	17 (2%)	-	
Alport syndrome	-	2 (0.4%)	12 (1.4%)	-	
Etiology unknown	229 (18.4%)	141 (28.7%)	385 (45.6%)	-	
Consanguineous marriage (n, %)	59 (4.8%)	23 (4.7%)	92 (10.9%)	74 (8.7%)	<.001
The presence of kidney disease in the family (n,%)	213 (17.2%)	70 (14.3%)	177 (20.9%)	72 (8.4%)	<.001

CAKUT, congenital anomalies of the kidney and urinary tract; CKD, chronic kidney disease;FMF, familial Mediterranean fever; MPGN, membranoproliferative glomerulonephritis; SD, standard deviation.

Table 2. Demographic Characteristics of Patients According to Patient and Control Group

	Patient Group (n = 2576)	Control Group (n = 853)	*P*
Mean age at inclusion (years)	47.4 ± 15.8	44.0 ± 14.6	<.001
Sex			
Female	1121 (43.5%)	519 (60.8%)	<.001
Male	1455 (56.5%)	334 (39.2%)	
Etiology of CKD (n)			
Diabetic nephropathy	697 (27.1%)	-	
Hypertensive nephrosclerosis	261 (10.1%)	-	
CAKUT	234 (9.1%)	-	
Tubulointerstitial nephritis	194 (7.5%)	-	
IgA nephropathy	168 (6.5%)	-	
Focal segmental glomerulosclerosis	167 (6.5%)	-	
AA amyloidosis due to FMF	121 (4.7%)	-	
Polycystic kidney disease	118 (4.6%)	-	
Membranous glomerulonephritis	78 (3%)	-	
Vasculitis	65 (2.5%)	-	
MPGN	56 (2.2%)	-	
Thrombotic microangiopathy	48 (1.9%)	-	
Alport syndrome	14 (0.5%)	-	
Etiology unknown	755 (29.3%)	-	
Consanguineous marriage	174 (6.8%)	74 (8.7%)	<.06
The presence of kidney disease in the family	460 (17.9%)	72 (8.4%)	<.001

CAKUT, congenital anomalies of the kidney and urinary tract; CKD, chronic kidney disease; FMF, familial Mediterranean fever; MPGN, membranoproliferative glomerulonephritis; SD, standart deviation.

Consanguinity and Kidney Disease

The frequency of parental consanguinity was comparable between the study and control groups [6.8% (n = 174) vs. 8.7% (n = 74), *P* = .06]. Notably, consanguineous marriages were most common among first cousins (n = 121, 69.5%), followed by second cousins (n = 34, 19.5%), and remote relatives (n = 19, 11%) within the study group. The corresponding numbers in the control group were 63.5% (n = 47), 17.5% (n = 13), and 18.9% (n = 14), respectively.

Specifically, in patients with CAKUT, the frequency of consanguinity was notably higher (n = 31, 13.2%) and particularly in vesicoureteral (VUR) nephropathy patients (n = 27, 20.5%) compared to controls (8.7%) (*P* = .036 and *P* < .001, respectively). Conversely, patients with diabetic nephropathy (n = 11, 3.7%) (*P* = .005) and hypertensive nephrosclerosis (n = 11, 4.2%) (*P* = .018) exhibited significantly lower rates of consanguinity compared to controls.

Patients from consanguineous marriages were diagnosed with kidney disease at a significantly younger age (29.2 ± 13.9 years) compared to those from non-consanguineous marriages (38.9 ± 17.1 years) (*P* < .001). Additionally, patients on KRT exhibited a notably higher frequency of consanguinity (n = 115, 8.6%) compared to patients with CKD stages 1-4 (n = 59, 4.8%) (*P* < .001) (Table 3).

Simple correlation analysis showed weak associations between parental consanguinity and age at diagnosis ($r = -0.108$, $P < .001$), KRT requirement ($r = 0.064$, $P = .001$), and kidney disease due to family history ($r = 0.238$, $P < .001$). Furthermore, among patients with CKD stages 1-4, there were significant correlations with parental consanguinity regarding age at diagnosis ($r = -0.148$, $P < .001$) and the age at onset of kidney disease ($r = -0.149$, $P < .001$). In patients with CKD-5D, age ($r = -0.067$, $P = .015$), age at diagnosis of kidney disease ($r = -0.065$, $P = .017$), and kidney disease due to family history ($r = 0.258$, $P < .001$) were found to be significantly associated with parental consanguinity. In kidney transplant recipients, age ($r = -0.067$, $P = .015$), age at the diagnosis of kidney disease ($r = 0.065$, $P = .017$), and kidney disease due to family history ($r = 0.258$, $P < .001$) were associated with parental consanguinity (Table 4 and 5).

In multivariate logistic regression, kidney disease due to family history emerged as the most robust predictor of parental consanguinity (OR: 5.712; 95% CI, 4.136-7.890; *P* < .001), followed by age at diagnosis of kidney disease (OR: 0.968; 95% CI, 0.957-0.979; *P* < .001), and KFRT requirement (OR: 1.441; 95% CI, 1.020-2.038; *P* = .038). In CKD 1-4 patients, predictors of parental consanguinity were age at diagnosis of kidney disease (OR: 0.958; 95% CI, 0.940-0.975; *P* < .001) and kidney disease due to family history (OR: 5.645; 95% CI, 3.269-9.746; *P* < .001). In the CKD 1-4 group, age at diagnosis of kidney disease (OR: 0.958; 95% CI, 0.940-0.975; *P* < .001) and kidney disease due to family history (OR: 5.645; 95% CI, 3.269-9.746; *P* < .001) were the strongest predictors of parental consanguinity (Table 6). Age at diagnosis of kidney disease (OR: 0.972; 95% CI, 0.949-0.996; *P* = .02) and kidney disease due to family history (OR: 5.244; 95% CI, 3.334-8.247; *P* < .001) were found to be the only predictors of parental consanguinity in the transplant recipient groups. In the CKD-5D group, kidney disease due to family history (OR: 7.655; 95% CI, 3.209-18.260; *P* < .001) was found as the only predictor of parental consanguinity.

Family History and Kidney Disease

Of the 466 (18.1%) patients with kidney disease due to family history, affected relatives included mothers (23.1%), fathers (19.3%), sisters (21.9%), and brothers (21.2%). Among patients

Table 3. Correlation Analysis of Patient Characteristics with Parental Consanguinity

	Age at Diagnosis	KFRT	Kidney Disease due to Family History	Age at Study	Female Sex
Parental consanguinity					
Spearman *r*	−0.108	0.064	0.238	−0.053	0.021
Significance	**<.001**	**.001**	**<.001**	.081	.289
Age at diagnosis					
Spearman *r*		0.165	−0.073	0.067	−0.081
Significance		**<.001**	**<.001**	**.026**	**<.001**
KFRT					
Spearman *r*			0.017	−0.416	−0.069
Significance			.396	**<.001**	**<.001**
Kidney disease due to family history					
Spearman *r*				−0.110	0.053
Significance				**<.001**	**.008**
Age at study					
Spearman *r*					0.021
Significance					.289

Values identified as significant in the correlation analysis are presented in bold.
KFRT, kidney failure requiring replacement therapy.

diagnosed with the following conditions, the frequency of familial predisposition to kidney diseases was higher compared to the controls (n = 124, 14.5%): Alport syndrome (42.9%, *P* < .001), ADPKD (38.1%, *P* < .001), AA amyloidosis due to familial Mediterranean fever (28.9%, *P* < .001), IgAN (26.2%, *P* < .001), TMA (20.8%, *P* = .004), VUR nephropathy (20.5%, *P* < .001),

Table 4. Correlation Analysis Between Patients with Kidney Disease Due to Family History and Parental Consanguinity

	Age at Diagnosis	KFRT	Age at Study	Female Sex
Parental consanguinity				
Spearman *r*	−0.136	0.099	−0.065	0.031
Significance	**.006**	**.034**	.359	.512
Age at diagnosis				
Spearman *r*		−0.115	0.018	−0.033
Significance		**0.019**	0.804	0.504
KFRT				
Spearman *r*			−0.390	−0.082
Significance			**<0.001**	0.081
Age at study				
Spearman *r*				−0.188
Significance				**0.007**

Values identified as significant in the correlation analysis are presented in bold.
KFRT, kidney failure requiring replacement therapy.

Table 5. Correlation Analysis Between Patients Without Kidney Disease Due to Family History and Parental Consanguinity

	Age at Diagnosis	KFRT	Age at Study	Female Sex
Parental consanguinity				
Spearman *r*	−0.084	0.050	−0.024	−0.001
Significance	**<.001**	**.021**	.481	.970
Age at diagnosis				
Spearman *r*		−0.174	0.064	−0.088
Significance		**<.001**	.056	**<.001**
KFRT				
Spearman *r*			−0.422	−0.068
Significance			**<.001**	**.002**
Age at study				
Spearman *r*				−0.007
Significance				.837

Values identified as significant in the correlation analysis are presented in bold.
KFRT, kidney failure requiring replacement therapy.

Table 6. Multivariate Logistic Regression Analysis Parameters Associated with Parental Consanguinity

	Univariate Analysis			Multivariate Analysis		
	Odds Ratio	**Confidence Interval**	***P***	**Odds Ratio**	**Confidence Interval**	***P***
Age at diagnosis	0.97	0.982-0.995	**<.001**	0.968	0.957-0.979	**<.001**
Kidney disease due to family history	6.172	4.448-8.565	**<.001**	5.712	4.136-7.890	**<.001**
KFRT	1.717	1.234-2.391	**.001**	1.441	1.020-2.038	**.038**
Female sex	1.188	0.864-1.634	.29			
Age at study	1.02	0.96-1.04	.968			

Abbreviations; KFRT, kidney failure requiring replacement therapy. Values identified as significant in the logistic regression analysis are presented in bold.

membranous nephropathy (20.5%, $P < .001$), MPGN (19.6%, $P = .005$), CKD of unknown etiology (16%, $P < .001$), CAKUT (18.4%, $P < .001$), TIN (16%, $P = .001$), diabetic nephropathy (14.8%, $P = .002$). However, the occurrence rate of kidney disease due to family history was alike between patients with the following diagnosis and the controls: FSGS (13.2%, $P = .053$), vasculitis (15.45, $P = .058$), hypertensive nephrosclerosis (11.1%, $P = .19$). Patients with kidney disease due to family history were diagnosed at a younger mean age (34.4 ± 15.9 years) compared to those without a family history (39.1 ± 17.2 years) ($P < .001$). The similarity in the frequency of kidney disease due to family history was observed between patients on KFRT (n = 251, 18.8%) and those in the CKD 1-4 group (n = 215, 17.4%) ($P = .35$). Among the transplant recipient group (n = 845), the frequency of kidney disease due to family history was higher compared to the CKD 1-4 and CKD-5D groups (21.4%, 17.3%, and 14.3%, respectively; $P = .003$).

The simple correlation analysis of patient characteristics revealed that age at diagnosis ($r = −0.073$, $P < .001$) and parental consanguinity ($r = 0.238$, $P < .001$) were weakly associated with kidney disease due to family history. This association was particularly significant in patients with CKD 1-4 age ($r = −0.084$, $P = .006$), age at kidney disease diagnosis ($r = −0.090$, $P = .003$), and female sex ($r = 0.59$, $P = .039$), parental consanguinity ($r = 0.213$, $P < .001$), but not in patients with CKD-5D. In patients with CKD-5D, parental consanguinity showed a weak association with kidney disease due to family history ($r = 0.258$, $P < .001$). In kidney transplant recipients, there was an association between the age at kidney disease diagnosis (r = −0.211, $P = .020$) and kidney disease due to family history.

In multivariate logistic regression, parental consanguinity (OR: 5.642; 95% CI, 4.086-7.791; $P < .001$), age at diagnosis of kidney disease (OR: 0.988; 95% CI, 0.982-0.995; $P < .001$), and female sex (OR: 1.283; 95% CI, 1.042-1.580; $P = .019$) were associated with kidney disease due to family history (Supplementary Table 1). Among kidney transplant recipients, predictors were age at diagnosis of kidney disease (OR: 0.988; 95% CI, 0.980-0.997; $P < .001$) and parental consanguinity (OR: 5.592; 95% CI, 3.237-9.659; $P < .001$). Parental consanguinity emerged as the sole predictor of kidney disease due to family history among patients with CKD-5D (OR: 7.561; 95% CI, 83.174-18.013; $P < .001$) and transplant recipient groups (OR: 5.205; 95% CI, 3.304-8.198; $P < .001$).

DISCUSSION

Autosomal recessive hereditary diseases pose a substantial health burden in communities practicing consanguinity at higher rates.[12,13,14] Nevertheless, our understanding of the role of consanguinity in the development of kidney diseases remains limited. Moreover, these communities present an opportunity to delineate novel phenotypes, identify previously unreported genes, and elucidate pertinent pathways in autosomal recessive kidney diseases. A pivotal finding of this study is the elevated risk of CAKUT and VUR nephropathy in the offspring of consanguineous relatives. The previously reported high frequency of parental consanguinity in the Turkish population (24%) seems to be decreasing (8.7%).[9] The variations in study outcomes could be attributed to disparities in demographic characteristics among populations, differences in the timing of the studies, and variations in their respective designs. In addition, most instances of parental consanguinity involved first cousins, who are anticipated to share 12.5% of their genes. As a result, their offspring typically exhibit homozygosity at around 6.25% of the gene locus.[15]

Additionally, individuals with parental consanguinity exhibit an earlier onset of the disease and an elevated risk of KFRT. This observation implies that consanguineous marriage might influence the severity of kidney diseases.[11,16,17] The CAKUT was shown to be associated with a high frequency of parental consanguinity and signifies the predominant cause of KFRT in offspring.[18,19] The CAKUT can be inherited through autosomal dominant, autosomal recessive, or X-linked patterns, and point mutations, structural variants, and copy number variations are implicated in disease determination.[20,21,22] Based on the study findings, prioritizing whole exome sequencing for CAKUT and VUR nephropathy cases seems crucial. The higher likelihood of a recessive pathogenic mutation reduces the search scope to homozygous genomic segments, potentially expediting the discovery of novel genes.

Limited data exists regarding the impact of consanguinity on late-onset kidney disorders such as hypertension and diabetes mellitus, both of which pose significant public health challenges.[13] Nevertheless, the current study revealed a lower overall frequency of parental consanguinity among various kidney diseases. Specifically, patients diagnosed with diabetic nephropathy or hypertensive nephrosclerosis exhibited notably lower rates of parental consanguinity compared to healthy controls. Furthermore, this study demonstrated an association between parental consanguinity and the occurrence of early-onset diseases. Consequently, while not demonstrated in this study, establishing evidence-based associations between parental consanguinity and late-onset complex illnesses like diabetes and hypertension remains challenging. Further research is needed to ascertain any potential risks.[14] One plausible explanation for the lack of a discernible relationship between parental consanguinity and several kidney diseases with known genetic risk factors might be that consanguineous marriage, overall, does not escalate the risk of autosomal dominant disorders in children when a parent is affected, nor does it elevate the risk of X-linked recessive disorders when one parent remains unaffected.[23]

A significant finding in this study was the markedly higher frequency of kidney disease due to family history (18.1%) within the study group compared to the control group. This discovery underscores the clinical importance of recognizing kidney disease due to family history as a prevalent risk factor. This recognition facilitates the identification of individuals at risk for CKD and holds promise for improving the detection and management of CKD. As anticipated in this study, ADPKD, Alport syndrome, and secondary amyloidosis resulting from familial Mediterranean fever emerged as the most prevalent causes of kidney disease with a significant family history. Recent research has similarly substantiated the clustering of several kidney diseases within families affected by diabetic nephropathy, hypertensive nephrosclerosis, chronic glomerulonephritis, and lupus nephritis.[3,24,25,26] Moreover, dialysis patients exhibit a 20% frequency of having a relative with KFRT.[4] A study conducted in Norway demonstrated that individuals with first-degree relatives affected by KFRT faced a sevenfold increased risk of CKD within their relatives.[5] Interestingly, it was demonstrated that IgAN, TMA, VUR nephropathy, membranous nephropathy, MPGN, CAKUT, TIN, and diabetic nephropathy, traditionally not classified as hereditary kidney diseases, are also associated with a family history. This familial linkage implies potential genetic foundations, potentially encompassing shared genetic susceptibilities or polygenic inheritance patterns among affected families. Furthermore, environmental factors and enhanced diagnostic capabilities might contribute to revealing these familial associations, underscoring the necessity for additional research investigating genetic complexities, gene–environment interactions, and broader familial patterns in these kidney disorders. Advanced genetic investigations, larger cohort analyses, and comprehensive familial inquiries will play a pivotal role in unraveling the intricacies behind these familial connections and deepening our comprehension of their underlying mechanisms.

In the study group, it was anticipated that patients with a positive family history would predominantly be female, exhibit parental consanguinity, and receive their diagnosis at a younger age. This study revealed an augmented frequency of kidney disease due to family history in patients with KFRT, aligning with findings from previous studies.[4,5,6,24,25,26] Notably, the REGARDS study, encompassing 12,030 participants, reported that 9.5% of participants indicated a family history of KFRT in a first-degree relative.[6] Within this cohort, a correlation emerged: female sex was associated with a family history of KFRT. The higher occurrence of familial kidney disease among women might be associated with mitochondrial inheritance and X chromosome inactivation. This observation could also potentially be linked to mitochondrial mutations, akin to the identified connections between hypertension and insulin resistance in the offspring of individuals diagnosed with type 2 diabetes.[27,28]

According to our findings, the aggregation of kidney disease within families appears to be a common characteristic among individuals experiencing early-onset kidney disease.[29] This trend has been notably observed in patients diagnosed with HIV-associated nephropathy.[25] Moreover, our current study revealed that patients with a familial history of CKD tended to receive their diagnosis at a comparatively younger age than those without a familial predisposition to kidney disease. Given the high familial aggregation across various kidney diseases, proactive identification and screening of at-risk families for these conditions could be a valuable strategy in managing kidney disease.

Chronic kidney disease with an unknown etiology stands out as another kidney disease frequently associated with a substantial frequency of family history. In cases where the precise cause of CKD remains undetermined, especially in healthcare setups with limited access to advanced diagnostic tools, leveraging family history indicating genetic kidney disease or a history of parental consanguinity could signal the potential utility of recent advancements in genomic technologies.[19,27] Innovative approaches such as massively parallel sequencing offer a means to expedite disease diagnosis, potentially bypassing conventional diagnostic pathways and thereby improving health-care delivery by ensuring prompt and accurate disease identification. Consequently, considering a family history of CKD or KFRT as an additional screening tool could significantly contribute to the identification and evaluation of kidney diseases.

Our study bears certain limitations that warrant consideration. First, being a single-center study, the findings may not be universally applicable and might not generalize to other medical centers or diverse populations. Secondly, the evaluation of results should be approached cautiously, considering the inability to

definitively establish the disease-free status of the control group. Thirdly, the study's inclusion is limited to Caucasians residing in Türkiye which restricts the generalizability of the findings to other ethnic or geographical populations. Fourthly, the data collected on familial history relied on patient-administered questionnaires, potentially introducing recall bias into the study's outcomes. Additionally, differences in age and sex distributions between the study and control groups could have influenced the results. However, despite these limitations, the study results remain robust within the context of a single-center investigation.

The increased predisposition to CAKUT and VUR nephropathy among individuals in consanguineous marriages underscores the involvement of an autosomal recessive pattern in the pathogenesis of these diseases. The association of parental consanguinity with an earlier onset of disease and heightened risk of kidney failure further accentuates the potential influence of consanguineous unions on aberrant kidney function. Providing information to relatives contemplating consanguineous marriages becomes imperative in light of these findings.

The clustering of kidney diseases within families strongly implicates genetic contributions to their pathogenesis. Implementing family-based approaches for early identification and treatment of individuals with a familial predisposition to kidney disease could prove beneficial. Conducting screening studies within families will elucidate the precise role of hereditary factors in kidney diseases, paving the way for the development of genetic-based treatments.

Data Availability Statement: The data that support the findings of this study are available on request from the corresponding author.

Ethics Committee Approval: Ethics committee of Istanbul University Faculty of Medicine approved this study (approval no: 2016/257 date: 09.2016).

Informed Consent: Informed consent was obtained from the participants who agreed to take part in the study.

Peer-review: Externally peer-reviewed.

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Supplementary Table 1. Multivariate Logistic Regression Analysis Parameters Associated with Kidney Disease due to Family History

	Univariate analysis			Multivariate analysis		
	Odds ratio	**Confidence interval**	**p-value**	**Odds ratio**	**Confidence interval**	**p-value**
Age at diagnosis	**0.988**	**0.981-0.995**	**< 0.001**	**0.988**	**0.982-0.995**	**< 0.001**
Parental consanguinity	**6.172**	**4.448-8.565**	**< 0.001**	**5.642**	**4.086-7.791**	**< 0.001**
Female sex	**1.317**	**1.076-1.611**	**0.008**	**1.283**	**1.042-1.580**	**0.019**
KFRT	1.092	0.892-1.336	0.396			
Age at study	1.05	0.91-1.16	0.666			

Abbreviations; KFRT, kidney failure requiring replacement therapy. Values identified as significant in the logistic regression analysis are presented in bold.