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Diagnostic Yield and Clinical Utility of Genetic Testing in Turkish Adults with Suspected Inherited Kidney Disease: Insights from a Population with High Parental Consanguinity

Gizem Kumru,[1] Şule Altıner,[2] Ahsen Karakaya,[3] Sadiye Ekinci,[2] Timur Tuncalı,[2] Nüket Yürür Kutlay,[2] Ezgi Gökpınar İli,[2] Halil Gürhan Karabulut,[2] Sim Kutlay,[1] Şule Şengül,[1] Kenan Keven,[1] Gökhan Nergizoğlu,[1] Şehsuvar Ertürk,[1] Hatice Ilgın Ruhi,[2] Kenan Ateş[1]

[1]Department of Nephrology, Ankara University Faculty of Medicine, İbni Sina Hospital, Ankara, Türkiye
[2]Department of Medical Genetics, Ankara University Faculty of Medicine, Ankara, Türkiye
[3]Department of Internal Medicine, Ankara University Faculty of Medicine, Ankara, Türkiye

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Address for correspondence:
Gizem Kumru.
Department of Nephrology, Ankara University Faculty of Medicine, Ibni Sina Hospital, Ankara, Türkiye
Phone: +90 312 595 81 92
E-mail: gkumru@ankara.edu.tr

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ABSTRACT

Objective: Inherited kidney diseases (IKDs) significantly contribute to chronic kidney disease (CKD), particularly in regions with high consanguinity rates. Despite the increasing availability of next-generation sequencing, evidence regarding its diagnostic and clinical effectiveness in adult populations remains limited. This study evaluated the diagnostic yield and clinical implications of genetic testing in adults with suspected IKD.

Materials and Methods: A retrospective analysis of 63 adults who underwent genetic evaluation for unexplained or familial CKD was performed. Genetic testing used sequencing-based methods to identify and analyze genes relevant to the clinical phenotype. Clinical and demographic factors, diagnostic yield, genetic etiologies, and clinical utility were documented.

Results: The genetic diagnostic yield in this predominantly female cohort, with a mean age of 37.2±14.9 years, was 54.0%. Autosomal recessive disorders were the most common inheritance pattern (61.8%). Alport spectrum disorders represented the primary etiology (67.6%), followed by ciliopathies/cystic diseases (14.7%). The diagnostic yield varied across clinical diagnostic groups, with Alport spectrum disorders showing the highest yield and other glomerulopathies showing the lowest yield (75.0% vs. 4.5%, $p<0.001$). Extrarenal manifestations were significantly associated with a positive genetic diagnosis (32.4% vs. 0.0%, $p<0.001$). Genetic findings confirmed the clinical diagnosis in 70.6% of positive cases, reclassified the diagnosis in 17.6%, and identified an alternative genetic diagnosis in 11.8%.

Conclusion: Genetic testing demonstrated a high diagnostic yield and considerable clinical utility in Turkish adults with suspected IKD. These findings support the integration of genetic evaluation into routine nephrology practice, particularly for patients with syndromic features and a notable family history.

Keywords: Chronic kidney disease, extrarenal manifestations, genetic testing, inherited kidney diseases, next-generation sequencing.

INTRODUCTION

Chronic kidney disease (CKD) is a global public health concern, affecting approximately 15% of the adult population worldwide and 17% in Türkiye. [1] The causes of CKD are diverse, with diabetes, hypertension, and chronic glomerulonephritis identified as the main contributors; however, a substantial proportion of cases are still categorized as "CKD of unexplained cause" (CKDx) after conventional clinical or histological assessment.[2] The rapid progress of next-generation sequencing (NGS) technologies has significantly improved our understanding of kidney disease pathogenesis. Currently, more than 600 genes have been identified as contributors to monogenic kidney diseases.[3] Research indicates that up to 10–15% of adults with CKD may have an underlying monogenic cause; however, when genetic assessment is performed based on clinical suspicion, such as early onset, family history, and CKDx, the diagnostic yield increases to 50–65%.[4–8] Inherited kidney disease (IKD) and congenital abnormalities of the kidney and urinary tract (CAKUT) have recently been identified as the second most common cause of end-stage kidney disease (ESKD) among patients receiving kidney replacement therapy (KRT) in Europe.[9]

In Türkiye, the burden of IKD is higher than in many Western populations, largely because of the high prevalence of consanguineous marriages and familial clustering.[10] This genetic background increases the likelihood of autosomal recessive kidney disorders and underscores the importance of genetic evaluation in this population. Despite this, the diagnostic yield and clinical utility of genetic testing in the Turkish CKD population remain inadequately described. This study aimed to evaluate the diagnostic yield of NGS-based genetic testing in adults with suspected IKD and to assess its clinical utility, including its impact on diagnosis, patient management, and risk stratification.

MATERIAL AND METHODS

Study Design and Population

This study was a retrospective observational analysis of adult patients who underwent genetic evaluation for suspected hereditary CKD at our tertiary nephrology center. All individuals aged 16 years or older who underwent sequencing-based testing between January 2022 and June 2025 were included. Testing was ordered either because of clinical suspicion arising from factors such as a positive family history, early age at onset, or the presence of extrarenal symptoms, or as part of family screening. Individuals with incomplete clinical data or inadequate sequencing results were excluded. The study was approved by the Ankara University Human Research Ethics Committee in accordance with the Declaration of Helsinki (Approval Number: İ06-566-25, Date: 06.08.2025).

KEY MESSAGES

- Genetic testing provided a diagnosis in 54% of adults with suspected inherited kidney disease, and extrarenal manifestations were the strongest clinical predictor of a positive genetic result.
- Genetic findings confirmed, reclassified, or newly established diagnoses in approximately 30% of patients and directly influenced clinical management, including transplant donor selection.
- Integrating genetic evaluation into routine nephrology practice is essential for managing adult patients with early-onset disease, extrarenal manifestations, or a positive family history.

Sixty-three individuals from 44 families were included. Demographic and clinical data were obtained from electronic medical records, including age, sex, estimated glomerular filtration rate (eGFR; CKD-EPI 2021 [Chronic Kidney Disease Epidemiology Collaboration]), albuminuria levels, CKD duration, family history of kidney disease, parental consanguinity, presence of extrarenal manifestations, and previous kidney biopsy reports.

Variants of uncertain significance (VUS) were categorized as clinically highly concordant when an appropriate genotype–phenotype correlation was established and the variant was consistent with the inheritance pattern and family history. Cases were evaluated through a multidisciplinary review involving nephrologists and medical geneticists and were documented individually as potentially disease-causing variants.[11] Diagnostic yield was defined as the identification of pathogenic (P) or likely pathogenic (LP) variants explaining the phenotype, as well as VUS classified as potentially disease-causing. Cases without these variants were categorized as "negative."

Clinical diagnoses were classified as follows: (1) Alport spectrum disorders, (2) ciliopathy/cystic diseases, (3) CAKUT, (4) tubulopathies, and (5) glomerulopathies. Clinical utility was evaluated in terms of "diagnostic confirmation," indicating genetic findings consistent with the presumed clinical diagnosis; "diagnostic identification," involving the discovery of a new specific genetic diagnosis that was not previously suspected; and "diagnostic reclassification," in which genetic findings changed the original clinical diagnosis. Patients who tested negative and did not receive a diagnosis of IKD were classified as "excluded."

Genetic Testing and Variant Interpretation

Genomic deoxyribonucleic acid (DNA) was isolated from peripheral blood samples from all patients. Patients were

assigned to genetic testing arms based on a standardized clinical stratification protocol to minimize bias. Those presenting with isolated renal involvement or no more than one extrarenal feature were prioritized for targeted gene panel testing. In contrast, patients with multiple extrarenal manifestations were referred for whole-exome sequencing (WES) to evaluate potential syndromic conditions. QIAGEN QIAseq Targeted DNA technology was used in both approaches, and sequencing was performed on the Illumina NextSeq platform. Segregation analysis was systematically performed for all identified VUS variants, as well as for cases with strong family histories or recurrent familial phenotypes, provided that biological samples from relatives were available.

Sequencing data were aligned to the GRCh38 human reference genome and analyzed using QIAGEN bioinformatics software. For WES, more than 98% of the targeted exonic regions reached a minimum coverage depth of 20×. For targeted gene panel sequencing, more than 99% of the targeted regions reached a coverage depth of at least 100×.

Variant analysis focused on genes associated with inherited kidney disorders and was performed genome-wide for WES or within the preestablished kidney gene panel for targeted sequencing (Appendix 1). Variants with a minor allele frequency (MAF)≥1% in population databases were excluded. Rare variants consistent with the patients' clinical phenotypes and the expected mode of inheritance were prioritized. All candidate variants were analyzed and categorized in accordance with the American College of Medical Genetics and Genomics (ACMG) guidelines using population frequency data, computational predictions, and available clinical evidence.[12]

Statistical Analysis

All analyses were performed using IBM Statistical Package for the Social Sciences version 30.0 software (IBM SPSS Corp.; Armonk, NY, USA). The normality of continuous variables was assessed using the Shapiro–Wilk or Kolmogorov–Smirnov tests. Continuous variables are presented as mean±standard deviation (SD), whereas categorical variables are presented as counts and percentages. Comparisons between genetically positive and negative groups were performed using the chi-square test or Fisher's exact test for categorical variables and Student's t-test for normally distributed continuous variables, depending on data distribution. Statistical significance was set at $p<0.05$.

RESULTS

A molecular diagnosis was established in 54.0% of the 63 individuals assessed for suspected IKD (Fig. 1, Appendix 2). Most identified variants were classified as P/LP, whereas potentially disease-causing VUS accounted for a smaller proportion (47.1%, 44.1%, and 8.8%, respectively). Inheritance patterns reflected the underlying disease categories, with autosomal recessive disorders accounting for the largest proportion (61.8%), followed by autosomal dominant disorders (20.6%) and X-linked disease (17.6%). A genetic diagnosis was established in 21 of the 44 families assessed (47.7%). After excluding highly concordant VUS identified as potentially disease-causing (n=3), the individual-level diagnostic yield was 49.2%.

The patient population was predominantly female (58.7%), with a mean age of 37.2±14.9 years. Demographic characteristics, including sex distribution and age at the time of genetic testing, were comparable between the genetically positive and negative groups (Table 1). Similarly, kidney function, assessed by eGFR and albuminuria categories, did not differ significantly at the time of genetic evaluation. A family history of kidney disease was observed in both groups (88.2% vs. 72.4%), whereas parental consanguinity showed no association with diagnostic yield. Notably, the presence of extrarenal manifestations was significantly associated with a positive genetic diagnosis (32.4% vs. 0%, $p<0.001$). Despite comparable kidney biopsy rates between groups, it was noteworthy that 5 of the 11 patients diagnosed with an IKD who had previously undergone kidney biopsy were diagnosed with focal segmental glomerulosclerosis and subsequently received immunosuppressive therapy. Other clinical variables, including CKD duration and the indication for genetic evaluation (clinical suspicion vs. family screening), were not significantly associated with a positive diagnostic outcome. However, 54.2% (n=13) of patients with Alport spectrum disorders and 66.7% (n=3) of patients with CAKUT were identified through familial screening ($p=0.029$).

Before genetic evaluation, the most frequent clinical diagnoses were Alport spectrum disorder (38.1%) and glomerulopathy (34.9%). Genetic testing confirmed the clinical diagnosis in 70.6% of genetically positive individuals, established a new specific diagnosis in an additional 11.8%, and reclassified the presumed diagnosis in 17.6%, thereby demonstrating substantial clinical utility (Fig. 1d). Alport spectrum disorders represented the predominant diagnosis, comprising more than two-thirds of genetically confirmed cases (Fig. 2). Ciliopathies and cystic diseases accounted for 14.7%, whereas CAKUT accounted for 8.8%. Accordingly, *COL4A3*, *COL4A4*, and *COL4A5* were identified as the most prevalent disease-causing genes, including 13 affected heterozygous individuals who were diagnosed through family screening. Disease-causing variants in *PKD1*, *SALL1*, *NPHP3*, *TSC2*, *CTNS*, *CLDN16*, and *COQ6* were less frequent but clinically relevant. After the initial detection of 8 probands, familial screening led to the diagnosis of 14 additional individuals who were previously unaware of the genetic diagnosis.

Table 1. Demographic and clinical data of patients according to genetic diagnosis

Variables	Positive (n=34, 54.0%)	Negative (n=29, 46.0%)	p	Total (n=63, 100.0%)
Female sex	20 (58.8)	17 (58.6)	0.987	37 (58.7)
Age at genetic evaluation (years)	38.2±16.2	35.1±12.7	0.283	37.2±14.9
eGFR at genetic evaluation (CKD-EPI 2021, ml/min/1.73m^2)				0.332
90 or higher	14 (41.2)	8 (27.6)		22 (34.9)
60–89	0 (0.0)	3 (10.3)		3 (4.8)
30–59	6 (17.6)	4 (13.8)		10 (15.9)
15–29	2 (5.9)	3 (10.3)		5 (7.9)
<15	12 (35.3)	11 (37.9)		23 (36.5)
Albuminuria at genetic evaluation (mg/g)			0.989	
<30	12 (35.3)	10 (34.5)		22 (34.9)
30–299	5 (14.7)	4 (13.8)		9 (14.3)
300 or higher	17 (53.1)	15 (51.7)		32 (50.8)
CKD history	22 (64.7)	23 (79.3)	0.201	45 (71.4)
Family history of kidney diseases	30 (88.2)	21 (72.4)	0.111	51 (81.0)
Parental consanguinity	11 (32.4)	8 (27.6)	0.681	19 (30.2)
Extrarenal manifestations	11 (32.4)	0 (0.0)	**<0.001**	11 (17.5)
Time between CKD diagnosis and genetic evaluation (years)	8.4±5.8	7.8±6.9	0.747	8.1±6.3
Kidney biopsy before genetic evaluation	11 (32.4)	11 (37.9)	0.643	22 (34.9)
Genetic evaluation indication			0.259	
Clinical suspicion	20 (58.8)	21 (72.4)		41 (65.1)
Family screening	14 (41.2)	8 (27.6)		22 (34.9)
Clinical diagnosis before genetic evaluation			**0.039**	
Alport spectrum disorders	18 (52.9)	6 (20.7)		24 (38.1)
Ciliopathy/cystic diseases	3 (8.8)	1 (3.4)		4 (6.3)
CAKUT	2 (5.9)	5 (17.2)		7 (11.1)
Tubulopathies	3 (8.8)	3 (10.3)		6 (9.5)
Glomerulopathies	8 (23.5)	14 (48.3)		22 (34.9)

The values are described as the mean ± standard deviation or number (%). Values appears in bold if p-value was significant (below 0.05). CAKUT: Congenital anomalies of the kidney and urinary tract; CKD: Chronic kidney disease; CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration; eGFR: Estimated glomerular filtration rate.

Figure 3a shows that clinical utility differed across diagnostic categories. The categories with the highest utility were Alport spectrum disorders (66.7%) and ciliopathies/cystic diseases (50.0%) (p=0.008). Alport spectrum disorders showed the highest diagnostic rate (75.0%), whereas glomerulopathies (4.5%) and CAKUT (28.6%) had considerably lower yields (p<0.001, Fig. 3b).

DISCUSSION

In this cohort of adults assessed for suspected IKD, the genetic diagnostic yield was 54%, primarily attributed to Alport spectrum disorders. Extrarenal manifestations were identified as the main clinical predictor of positive genetic findings, highlighting the diagnostic importance of syndromic features in adult CKD. In most positive cases, genetic data supported the clinical diagnosis and directly influenced management decisions, including the assessment of potential living kidney donors. These findings indicate that genetic testing provides significant diagnostic and clinical benefits for adults with unexplained CKD, particularly in populations with a high familial disease burden and a greater prevalence of recessive disorders.

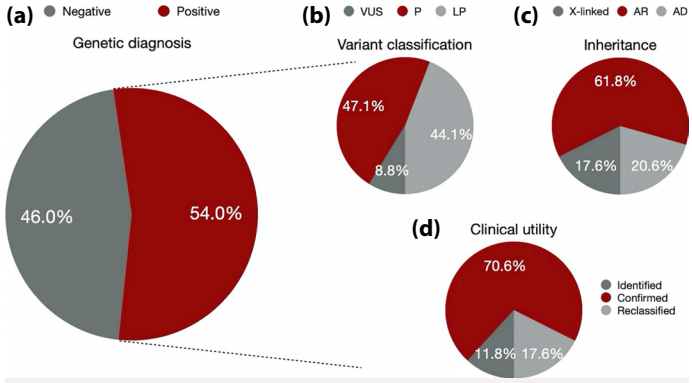

Figure 1. Results of genetic testing and patterns of inheritance. **(a)** Results classified into positive and negative categories. **(b)** Positive results classified as VUS or P/LP variants expected to cause disease. **(c)** Inheritance patterns of positive results, classified as AR, AD, or X-linked. **(d)** Clinical utility of genetic testing.

AD: Autosomal dominant; AR: Autosomal recessive; P/LP: Pathogenic/likely pathogenic; VUS: Variants of uncertain significance.

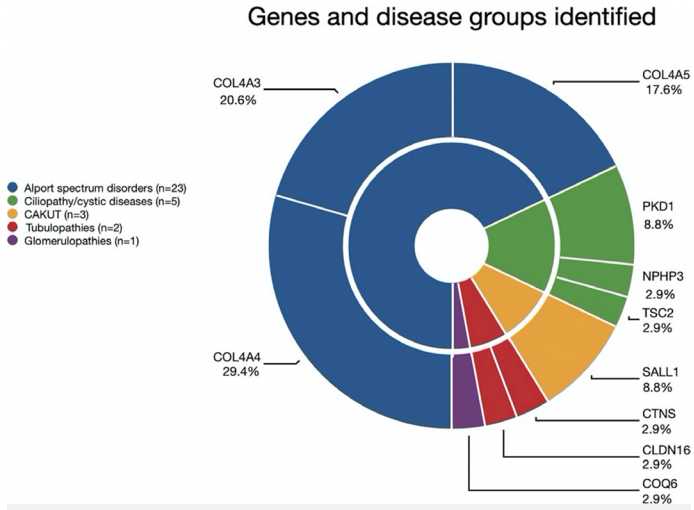

Figure 2. Overview of the study findings. The inner circle illustrates the identified disease groups, whereas the outer circle presents the genes associated with disease-causing variants identified in the study.

CAKUT: Congenital abnormalities of the kidney and urinary tract.

This study demonstrated that the *COL4A4*, *COL4A3*, and *COL4A5* genes accounted for 67.6% of genetic diagnoses, establishing Alport spectrum disorders as the most prevalent category. In large adult cohort studies of patients with early-onset CKD, 8 genes—*COL4A3*, *COL4A4*, *COL4A5*, *HNF1B*, *PKD1*, *PKD2*, *PKHD1*, and *UMOD*—were found to account for approximately two-thirds of disease-causing variants; however, Alport spectrum disorders were identified in only 15–22% of these cases.[6,7] This discrepancy may be explained by the enrichment of individuals undergoing donor screening, who may have had a higher likelihood of harboring pathogenic mutations in the *COL4A3–COL4A5* genes. Indeed, the exclusion of donor-screening cases (n=6) resulted in a reduced yet still substantial proportion of Alport spectrum disease diagnoses (n=17, 50.0%). Referral bias likely influenced this distribution, as individuals with suspected hereditary nephropathies, especially those with hematuria or a family history suggestive of Alport syndrome, may have been preferentially selected for genetic testing. Polycystic kidney diseases significantly contribute to the etiology of ESKD in Türkiye.[13] The lower prevalence of cystic kidney diseases in this study cohort, compared with national and global statistics, may be attributed to diagnoses based on family history and typical clinical presentation, which reduces the need for genetic testing.

Genetic testing provides diagnostic results in 10–20% of adult CKD patients, whereas this percentage increases to 37–65% among individuals with suspected IKD.[5–7,14–16] The young age of the cohort and the high prevalence of CKD history among patients and their families contributed to the 54.0% rate of positive genetic test results observed in our study. A family history of kidney disease is an established factor associated with genetic diagnosis.[17] However, in our cohort, more than 70% of patients and their families reported a history of CKD, and the genetic diagnostic yield remained consistent across groups. The presence of extrarenal features significantly influenced diagnostic yield, with such manifestations observed only in patients with a positive genetic diagnosis. Connaughton et al.[16] demonstrated that a monogenic etiology was identified in 36% of families with a positive family history of CKD, although the rate increased to 69% in families with extrarenal features. The broad spectrum of clinical features also contributes to substantial heterogeneity in the likelihood of obtaining a positive genetic result across different disease groups. Consistent with this, in the Alport group in our study, which had the highest genetic diagnostic yield, 95.8% of patients (n=23) had a family history of CKD, with 13 individuals (54.2%) diagnosed through family screening. These findings support the integration of genetic analysis into nephrology practice, especially for patients with extrarenal manifestations, familial disease patterns, or phenotypes suggestive of monogenic disorders, as it can markedly improve diagnostic precision.[18]

The clinical diagnosis was confirmed in 70.6% of individuals with a positive genetic result in this cohort. The predominance of diagnostic confirmation in the Alport and ciliopathy groups, compared with the lower rate in glomerulopathies,

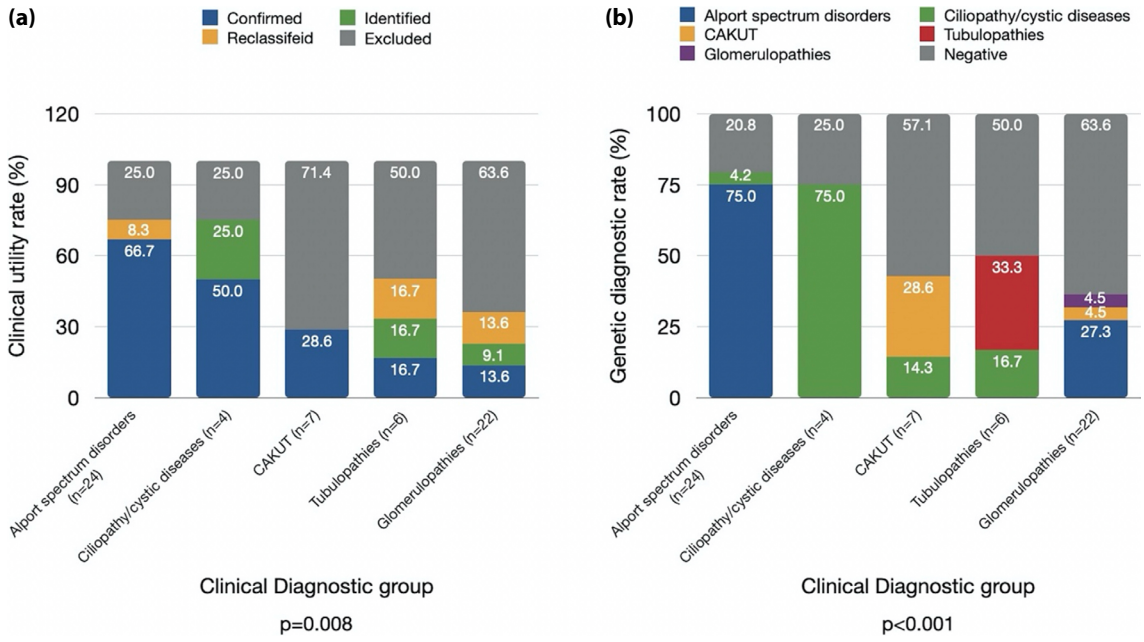

Figure 3. (a) Clinical utility yield across clinical diagnostic groups. **(b)** Genetic diagnostic yield across clinical diagnostic groups. The x-axis represents the distribution of patients across five clinical diagnostic groups before genetic testing. The y-axis illustrates the diagnostic and clinical utility yield resulting from genetic testing.

CAKUT: Congenital abnormalities of the kidney and urinary tract.

underscores the advantages of genetic testing in cases with well-defined genotype–phenotype correlations. Furthermore, a specific diagnosis was established in 11.8% of cases, and the presumptive diagnosis was reclassified in 17.6%. Consequently, a novel etiology of CKD was identified in approximately 30% of patients. The literature indicates that this patient population has high post-diagnosis management change rates, ranging from 20% to 60%.[6,15,16] Physicians have reported that genetic findings influence the medical care of 90.7% of patients with positive results, leading to changes in treatment plans, referrals for genetic counseling, guidance for genetic testing of family members, and discussions about family planning.[15] In our cohort, genetic diagnosis altered clinical interpretation in a subset of patients, particularly in 5 individuals with presumed FSGS in whom immunosuppressive therapy had been initiated but was subsequently considered unnecessary. This highlights the potential of genetic testing to prevent inappropriate treatment and related toxicity. Furthermore, all patients diagnosed with IKD received genetic counseling, and familial screening was advised according to the inheritance pattern. Given these potential advantages, essential precautions should be implemented to address barriers that prevent nephrologists from requesting genetic testing, such as insufficient genetic literacy, challenges in test selection, and time limitations.[19]

Genetic testing also provides several advantages for kidney transplant recipients and donors, including personalized interventions, risk stratification for recurrent disease, and risk assessment for potential donors.[20] Kidney donors are at increased risk of hypertension and ESKD, as well as increased cardiovascular morbidity and mortality.[21] Therefore, potential donors must undergo a thorough evaluation to reduce post-donation risks. Assessing ESKD risk in individuals with VUS and in heterozygous individuals affected by Alport syndrome is crucial for selecting living kidney transplant donors, as well as for those who receive a genetic diagnosis.[22] In this context, 9 potential kidney donors were evaluated in our cohort, leading to the acceptance of 2 candidates with negative results and 5 candidates who were heterozygous for Alport syndrome without clinical manifestations (Table S2, Patient IDs 4, 13, 15, 19, and 23). Two individuals diagnosed with Alport syndrome who presented with urinary abnormalities were disqualified based on genetic findings (Table S2, Patient IDs 1 and 2).

This study provides real-world data from a well-characterized adult cohort in a region with a high prevalence of IKD, offering valuable insights into the diagnostic utility of NGS in routine nephrology practice. The findings provide data that may help prioritize patients for genetic testing, as the inclusion criteria were designed to exclude individuals with

a low likelihood of a monogenic etiology, thereby enhancing the cost-effectiveness of genetic testing. However, certain limitations should be noted. The single-center, retrospective design may limit generalizability, and referral bias may have enriched the cohort with patients with more severe or syndromic presentations. The sample size limited the ability to conduct subgroup analyses for less prevalent disease categories. The high prevalence of familial CKD history and the younger mean age of this cohort relative to the general CKD population should be considered when extrapolating the findings. Intra-family clustering may challenge the assumption of independent observations, as multiple members of the same families were included. However, the 47.7% diagnostic yield at the family level suggests that the clustering effect was not substantial in this study. Participants aged ≥16 years were included, as this threshold is commonly used in clinical nephrology for transitioning patients to adult-oriented care settings. This should be considered when interpreting the findings, as the study population may include a small proportion of late adolescents. The use of a targeted gene panel rather than whole-exome sequencing requires regular updates to the gene list and may limit the identification of novel causal genes. The absence of functional studies for VUS is another limitation, as such analyses are necessary to determine their biological impact and support potential reclassification. A further limitation is that exon-level copy number variant (CNV) analysis was not uniformly applied across all cases, which may have limited the detection of certain structural variants; however, this reflects current real-world diagnostic practice in many clinical settings.

CONCLUSION

In this cohort of adults evaluated for suspected IKD, genetic testing provided a high diagnostic yield and demonstrated substantial clinical value. The presence of extrarenal manifestations was a significant indicator of a positive molecular diagnosis, highlighting the importance of careful clinical assessment in identifying appropriate testing strategies. Importantly, genetic findings not only confirmed or redefined clinical diagnoses but also informed essential management decisions, including the suitability of potential living kidney donors. These epidemiological characteristics underscore the importance of incorporating genetic evaluation into routine nephrology practice, particularly for patients with early-onset disease, extrarenal manifestations, or a positive family history.

Ethics Committee Approval: Ethics committee approval was obtained from Ankara University Human Research Ethics Committee in accordance with the Declaration of Helsinki (Approval Number: İ06-566-25, Date: 06.08.2025).

Informed Consent: Written informed consent was obtained for genetic testing.

Conflict of Interest: The authors have no conflicts of interest to declare.

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Appendix 1. List of genes included in the targeted nephropathy panel (97 genes)

Gene symbol	Gene symbol	Gene symbol	Gene symbol	Gene symbol	Gene symbol
ACE	*CLDN16*	*GLA*	*NEK8*	*PKHD1*	*SMARCAL1*
ACTN4	*COL4A3*	*GLIS2*	*NFIA*	*PLCE1*	*SOX17*
AGXT	*COL4A4*	*GRHPR*	*NPHP1*	*PTPRO*	*TCTN2*
APRT	*COL4A5*	*GSN*	*NPHP3*	*RET*	*TMEM216*
ATP6V0A4	*COL4A6*	*HNF1B*	*NPHP4*	*SALL1*	*TMEM231*
AVPR2	*COQ2*	*HPSE2*	*NPHS1*	*SCARB2*	*TMEM237*
B9D1	*COQ6*	*INF2*	*NPHS2*	*SCNN1A*	*TMEM67*
B9D2	*COQ8B*	*INVS*	*NR3C2*	*SCNN1B*	*TRPC6*
BICC1	*CPLANE1*	*IQCB1*	*NUP93*	*SLC12A1*	*TTC21B*
BSND	*CTNS*	*KCNJ1*	*NXF5*	*SLC12A3*	*UMOD*
CA2	*DNASE1L3*	*LAMB2*	*OCRL*	*SLC3A1*	*UPK3A*
CC2D2A	*FAN1*	*LMX1B*	*OSGEP*	*SLC4A4*	*USF2*
CCNQ	*FRAS1*	*LPIN1*	*PAX2*	*SLC5A1*	*WNK1*
CD2AP	*FREM2*	*MAP3K14*	*PDSS2*	*SLC5A2*	*WNK4*
CDC5L	*FXYD2*	*MKS1*	*PKD1*	*SLC7A9*	*WT1*
CEP290	*GATA3*	*MYO1E*	*PKD2*	*SLC9A3R1*	*XDH*
CLCN5					

Appendix 2. Disease-causing variants identified in the cohort (n=34)

Patient ID	Age at Dx	Sex	Kidney manifestation	Extrarenal manifestations	Indication	Family history	Gene and transcript (inheritance)	Variant	Zygosity	Variant classification
Alport spectrum disorders										
1	42	M	Nephrotic range proteinuria	SNHL	Clinical suspicion	Yes	*COL4A4* NM_000092 (AR)	c.1321_1369+3del*	Hom	P
2	51	F	Mild proteinuria	No	Family screening	Yes	*COL4A4* NM_000092 (AR)	c.1321_1369+3del*	Aff. Het	P
3	24	F	Nephrotic range proteinuria, reduced GFR	SNHL	Clinical suspicion	Yes	*COL4A4* NM_000092 (AR)	c.372+1G>A	Hom	LP
4	57	F	Hematuria	No	Family screening	Yes	*COL4A4* NM_000092 (AR)	c.372+1G>A	Aff. Het	LP
5	50	M	No	No	Family screening	Yes	*COL4A4* NM_000092 (AR)	c.372+1G>A	Aff. Het	LP
6	16	F	No	No	Family screening	Yes	*COL4A4* NM_000092 (AR)	c.372+1G>A	Aff. Het	LP
7	25	F	Hematuria	No	Family screening	Yes	*COL4A4* NM_000092 (AR)	c.372+1G>A	Hom	LP
8	38	F	Moderate proteinuria, reduced GFR	No	Clinical suspicion	Yes	*COL4A4* NM_000092 (AR)	c.1321_1369+3del	Aff. Het	P
9	51	F	Moderate proteinuria, reduced GFR	No	Clinical suspicion	Yes	*COL4A4* NM_000092 (AR)	c.5032C>T p.Q1678*	Hom	LP
10	48	M	Nephrotic range proteinuria, reduced GFR	No	Clinical suspicion	Yes	*COL4A4* NM_000092 (AR)	c.3807T>G p.Asp1269Glu	Aff.Het	VUS
11	16	F	Nephrotic range proteinuria,	SNHL	Clinical suspicion	Yes	*COL4A3* NM_000091.5 (AR)	c.2371C>T p.Arg791*	Hom	P
12	64	F	Mild proteinuria	No	Family screening	Yes	*COL4A3* NM_000091.5 (AR)	c.2371C>T p.Arg791*	Aff. Het	P
13	45	M	Mild proteinuria	No	Family screening	Yes	*COL4A3* NM_000091.5 (AR)	c.2371C>T p.Arg791*	Aff. Het	P
14	18	M	Moderate proteinuria, hematuria	SNHL	Clinical suspicion	Yes	*COL4A3* NM_000091.5 (AR)	c.2371C>T p.Arg791*	Hom	P
15	48	M	No	No	Family screening	Yes	*COL4A3* NM_000091.5 (AR)	c.2371C>T p.Arg791*	Aff. Het	P
16	46	F	Moderate proteinuria, hematuria	No	Clinical suspicion	Yes	*COL4A3* NM_000091.5 (AR)	c.898G>A p.Gly300Arg	Aff. Het	LP
17	48	F	Moderate proteinuria	No	Family screening	Yes	*COL4A3* NM_000091.5 (AR)	c.898G>A p.Gly300Arg	Hom	LP
18	43	M	Nephrotic range proteinuria, reduced GFR	No	Clinical suspicion	Yes	*COL4A5* NM_000495.5 (XL)	c.3052G>T p.Gly1018Cys	Hemi	LP
19	63	F	Hematuria	No	Family screening	Yes	*COL4A5* NM_000495.5 (XL)	c.3052G>T p.Gly1018Cys	Aff. Het	LP
20	40	F	Hematuria	No	Family screening	No	*COL4A5* NM_000495.5 (XL)	c.3052G>T p.Gly1018Cys	Aff. Het	LP
21	16	M	Moderate proteinuria, hematuria	SNHL	Clinical suspicion	Yes	*COL4A5* NM_000495.5 (XL)	c.3170G>T p.Gly1057Val	Hemi	P
22	16	M	Nephrotic range proteinuria, reduced GFR	SNHL	Clinical suspicion	Yes	*COL4A5* NM_000495.5 (XL)	c.3170G>T p.Gly1057Val	Hemi	P
23	46	F	No	No	Family screening	Yes	*COL4A5* NM_000495.5 (XL)	c.3170G>T p.Gly1057Val	Aff.Het	P
Ciliopathy/cystic disorders										
24	42	F	Nephrotic range proteinuria, reduced GFR	*Bronchiectasis*	Clinical suspicion	No	*PKD1* NM_001009944.3 (AD)	c.1522T>C p.Cys508Arg	Het	LP
25	16	M	Medullary nephrocalcinosis	No	Clinical suspicion	Yes	*PKD1* NM_001009944.3 (AD)	c.12607C>T p.Arg4203Trp	Het	VUS
26	63	M	Polycystic kidney	No	Clinical suspicion	Yes	*TSC2* NM_000548.5 (AD)	c.5238_5255del p.His1746_Arg1751del	Het	P
27	54	F	Angiomyolipomas	Epilepsy, LAM, angiofibromas	Clinical Suspicion	Yes	*NPHP3* NM_153240.5 (AR)	c.3287T>C p.Leu1096Pro	Hom	LP
28	58	M	Polycystic kidney	No	Clinical Suspicion	Yes				
CAKUT										
29	20	F	Reduced GFR	Hallux anomaly, mild intellectual disability	Clinical suspicion	Yes	*SALL1* NM_002968.3 (AD)	c.2287dupA p.Arg763Lysfs*42	Het	P
30	21	M	Reduced GFR	No	Family screening	Yes	*SALL1* NM_002968.3 (AD)	c.2287dupA p.Arg763Lysfs*42	Het	P
31	45	F	Reduced GFR	No	Family screening	Yes	*SALL1* NM_002968.3 (AD)	c.2287dupA p.Arg763Lysfs*42	Het	P
Tubulopathies										
32	26	F	Fanconi syndrome	Neurologic dysfunction, ocular involvement, diabetes	Clinical suspicion	No	*CTNS* NM_004937.3 (AR)	c.681G>A p.Glu227Glu	Hom	P
33	24	M	Bilateral atrophic kidneys	*Pure* red cell *aplasia*	Clinical suspicion	Yes	*CLDN16* NM_006580.4 (AR)	c.130C>T p.R44*	Hom	LP
Glomerulopathies										
34	16	F	Nephrotic range proteinuria	No	Clinical suspicion	No	*COQ6* NM_182476.3 (AR)	c.1383del p.Ilr462LeufsTer18	Hom	VUS

A: adenine; AD: autosomal dominant; Aff: Affected; AR: Autosomal recessive; CAKUT: Congenital anomalies of the kidney and urinary tract; Dx: Diagnosis; F: Female; GFR: Glomerular filtration rate; Hemi: Hemizygous; Het: Heterozygous; Hom: Homozygous; LAM: Lymphangioleiomyomatosis; LP: Likely pathogenic; M: Male; P: Pathogenic; SNHL: Sensorineural hearing loss; VUS: Variant of uncertain significance; XL: X-linked.