DOI: 10.5152/turkjnephrol.2026.25860

Original Article

Turkish Journal of Nephrology

Whole Exome Sequencing Reveals New Genetic Variants in Pediatric Congenital Anomalies of the Kidney and Urinary Tract: A Regional Study Highlighting *CEP290* and *KMT2A*

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ABSTRACT

Background: Congenital anomalies of the kidney and urinary tract (CAKUT) are the leading cause of chronic kidney disease in childhood and are frequently associated with monogenic disorders. Whole exome sequencing (WES) has become an important diagnostic tool, particularly in patients with syndromic features or severe kidney phenotypes. This study aimed to investigate the genetic etiology of pediatric CAKUT using WES and to evaluate genotype–phenotype correlations in a carefully phenotyped cohort.

Methods: Thirty-one pediatric patients diagnosed with CAKUT were enrolled. Detailed clinical phenotyping was performed, including evaluation of extrarenal manifestations and family history. Whole exome sequencing was conducted, and variants were interpreted according to American College of Medical Genetics and Genomics criteria. Segregation analyses were performed when possible.

Results: The overall diagnostic yield of WES was 16.1% (5/31). Pathogenic or likely pathogenic variants were identified in *PAX2*, *MYCN*, *KMT2A*, *CEP290*, and a variant of uncertain significance in *CHD7*. All genetically solved patients presented with bilateral kidney anomalies and/or prominent extrarenal findings suggestive of syndromic disease. The findings were consistent with papillorenal syndrome, Feingold syndrome, Joubert syndrome, and Wiedemann–Steiner syndrome phenotypes. The identification of *KMT2A* and *CEP290* variants in patients with classical CAKUT features suggests that epigenetic regulatory and ciliary genes may contribute to the CAKUT spectrum.

Conclusion: Whole exome sequencing provides meaningful diagnostic information in selected CAKUT patients, particularly those with syndromic features. Careful clinical phenotyping is essential to guide genetic testing. The findings expand the understanding of genotype–phenotype relationships in CAKUT and highlight the potential role of emerging genes such as *KMT2A* and *CEP290* in kidney developmental disorders.

Keywords: CAKUT, CEP290, genotype, KMT2A, phenotype, whole exome sequencing

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Received: August 20, 2025 **Revision Requested:** September 30, 2025
Last Revision Received: March 13, 2026 **Accepted:** May 12, 2026 **Publication Date:** October 9, 2026

Cite this article as: Gençler A, Öz Ö, Mutlu MB. Whole exome sequencing reveals new genetic variants in pediatric congenital anomalies of the kidney and urinary tract: a regional study highlighting *CEP290* and *KMT2A*. *Turk J Nephrol.* 2026;35(4):312-318.

INTRODUCTION

Congenital anomalies of the kidney and urinary tract (CAKUT) constitute the leading cause of chronic kidney disease (CKD) and kidney failure in childhood and early adulthood, accounting for approximately 40%-50% of pediatric CKD cases worldwide.[1] Congenital anomalies of the kidney and urinary tract comprises a heterogeneous group of structural malformations arising from disrupted nephrogenesis and urinary tract development, with clinical presentations ranging from mild unilateral anomalies to severe bilateral defects progressing to end-stage kidney disease. Clinically, CAKUT may occur as an isolated kidney phenotype or as part of a multisystem disorder.[2,3]

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Genetic factors play a central role in the etiology of CAKUT.[4] Monogenic causes have been identified in approximately 12%-20% of affected individuals, with pathogenic variants reported in more than 50 genes involved in nephrogenesis and urinary tract morphogenesis. Among the most frequently implicated genes are *PAX2*, *HNF1B*, and *EYA1*.[5] However, CAKUT exhibits marked genetic heterogeneity, incomplete penetrance, and variable expressivity, indicating that additional disease-associated genes and modifying factors remain to be elucidated.

Whole exome sequencing (WES) has emerged as a powerful diagnostic tool for identifying monogenic causes of CAKUT. Importantly, the diagnostic yield of WES is not uniform across all CAKUT presentations.[6] Previous studies have demonstrated that WES is particularly informative in patients with bilateral kidney anomalies, extrarenal developmental features (including neurological, ocular, skeletal, or cardiac involvement), positive family history, or parental consanguinity, where the likelihood of a monogenic etiology is significantly increa sed.[2,5,7-9] In contrast, the yield of WES in isolated or mild CAKUT is lower, and genetic testing in such cases is most effective when guided by careful clinical phenotyping and a stepwise diagnostic approach.

Recent large-scale WES studies have substantially expanded the understanding of the genetic architecture of CAKUT and have identified novel gene–phenotype associations beyond the classical kidney developmental genes. These studies demonstrated that genes involved in ciliary function, chromatin remodeling, and epigenetic regulation may contribute to urinary tract malformations, particularly in patients presenting with syndromic or multisystem involvement.[10-13] Such findings have reshaped current concepts of kidney developmental biology and highlighted that CAKUT is frequently part of broader developmental disorders rather than an isolated urinary tract condition. Consequently, WES has emerged as a particularly valuable diagnostic approach in carefully phenotyped CAKUT patients with extrarenal manifestations, family history, or parental consanguinity. This evolving perspective provides the rationale for selecting WES as the primary diagnostic tool in the present study.

The present study was conducted at a tertiary pediatric nephrology center in southeastern Türkiye, a region characterized by a relatively high rate of consanguinity, which may influence the spectrum of genetic variation. In this context, the study aimed to investigate the genetic etiology of CAKUT in a pediatric cohort using WES, with particular emphasis on patients exhibiting complex phenotypes suggestive of an underlying monogenic disorder. By integrating detailed clinical phenotyping with comprehensive exome analysis, this study sought to identify pathogenic or potentially clinically relevant variants and to contribute regional data and novel gene–phenotype associations to the expanding literature on CAKUT genetics.

MAIN POINTS

- Whole exome sequencing (WES) achieved a diagnostic yield of 16.1% in children with congenital anomalies of the kidney and urinary tract (CAKUT).
- All genetically solved cases showed syndromic features or extrarenal manifestations, supporting phenotype-driven patient selection for WES.
- Variants in *CEP290* and *KMT2A* were identified in association with CAKUT within syndromic contexts, expanding the genetic spectrum of kidney developmental anomalies.
- Interpretation of heterozygous variants requires cautious genotype–phenotype correlation, particularly in the absence of functional validation.
- Integration of detailed clinical phenotyping with genomic testing facilitates early diagnosis, prognostic assessment, and genetic counseling in pediatric CAKUT.

MATERIAL AND METHODS

Study Design and Patient Selection

This prospective single-center study included pediatric patients diagnosed with CAKUT and followed at the Harran University Faculty of Medicine, Department of Pediatric Nephrology, between January 2018 and December 2022.

Patients aged between 1 month and 18 years with a confirmed diagnosis of CAKUT based on imaging studies were eligible for inclusion. Patients were referred for genetic evaluation based on the presence of 1 or more of the following features: bilateral kidney anomalies, extrarenal manifestations suggestive of syndromic disease, positive family history of kidney or multisystem disorders, parental consanguinity, or early-onset or severe kidney dysfunction. Patients with isolated mild CAKUT without additional clinical features and those with insufficient clinical or genetic data were excluded.

A total of 31 patients met the inclusion criteria and were enrolled in the study. Written informed consent was obtained from all participants or their legal guardians.

The study was conducted in accordance with the Declaration of Helsinki and approved by the Harran University Clinical Research Ethics Committee (Approval No: HRÜ/22.20.21; Date: October 17, 2022).

Clinical and Phenotypic Evaluation

Detailed demographic data, medical history, family history (including consanguinity), and clinical findings were systematically recorded. Phenotypic classification was performed by consensus between 2 pediatric nephrologists based on clinical examination, imaging findings, and available subspeciality evaluations.

Extrarenal manifestations were categorized by organ system (neurological, ocular, auditory, cardiac, skeletal, and developmental). Anthropometric measurements (height, weight, and body mass index) and blood pressure were evaluated using age- and sex-adjusted percentile or SD score references. Kidney function was assessed using estimated glomerular filtration rate, calculated with the bedside Schwartz formula.

DNA Extraction and Whole Exome Sequencing

Genomic DNA was extracted from peripheral blood samples using a commercial DNA extraction kit (manufacturer and catalog number provided in Supplementary Table 1), according to the manufacturer's instructions. DNA concentration and purity were assessed using spectrophotometric methods.

Exome libraries were prepared using the IDT xGen (IDT xGen Exome Research Panel (Integrated DNA Technologies, USA) DNA Library Prep and Exome Capture Kits and sequenced on an Illumina platform. Sequencing achieved a mean coverage depth of 70×-100×, with over 95% of targeted coding regions covered at ≥20×.

Bioinformatics Analysis

Sequence alignment was performed against the GRCh37/hg19 human reference genome using standard alignment software. Variant calling, annotation, and quality control were conducted using validated bioinformatics pipelines (software names and versions listed in Supplementary Table 2). Variants were filtered based on a minor allele frequency < 1% in population databases including gnomAD, ExAC, dbSNP, and ClinVar (database versions and access dates provided).

Analysis focused on protein-coding exons and ±10 bp flanking intronic regions. In silico pathogenicity, predictions were performed using Sorting Intolerant From Tolerant (SIFT), PolyPhen-2, MutationTaster, Deleterious Annotation of Genetic Variants using Neural Networks (DANN), and Genomic Evolutionary Rate Profiling (GERP).

Variant Interpretation and Validation

Variants were classified according to the American College of Medical Genetics and Genomics (ACMG) guidelines. Computational evidence (PP3) was applied in accordance with current recommendations. All pathogenic and likely pathogenic (LP) variants were confirmed by Sanger sequencing. Segregation analysis was performed in available family members to assess inheritance patterns and de novo status.

RESULTS

Study Cohort and Diagnostic Yield

Whole exome sequencing was performed in a total of 31 pediatric patients diagnosed with CAKUT. Of these, 21 patients (67.7%) were male and 10 (32.3%) were female. The median age at genetic testing was 5.6 years (range: 1 month-18 years). Parental consanguinity was present in 16 patients (51%), and a positive family history of kidney or multisystem disease was documented in 10 patients (32.2%).

Pathogenic or LP variants were identified in 5 of 31 patients, yielding an overall diagnostic rate of 16.1%. The remaining 26 patients (83.9%) did not harbor variants meeting ACMG criteria for pathogenicity. A summary of the study cohort, including solved and unsolved cases, is presented in Figure 1.

Kidney Phenotypes

The kidney phenotypes observed in the cohort included horseshoe kidney (n = 5), unilateral kidney agenesis (n = 5), ureteropelvic junction obstruction (n = 5), duplicated collecting system (n = 4), vesicoureteral reflux (n = 2), posterior urethral valves (PUV) (n = 2), ectopic kidney (n = 3), kidney hypoplasia (n = 3), polycystic kidney disease (n = 1), and multicystic dysplastic kidney (n = 1).

Among genetically solved cases, bilateral kidney involvement was observed in 4 patients, and severe or early-onset kidney dysfunction was present in 3 patients. Extrarenal manifestations were identified in all genetically positive patients.

Of 31 pediatric patients with CAKUT who underwent whole exome sequencing (WES), pathogenic or likely pathogenic variants were identified in 5 patients (16.1%), while 26 patients (83.9%) remained genetically unsolved.

Patients undergoing WES	n = 31
Solved cases (P/LP variants)	n = 5 (16.1%)
Unsolved cases	n = 26 (83.9%)

Figure 1. Flow diagram of the study cohort and diagnostic yield. CAKUT, congenital anomalies of the kidney and urinary tract; WES, whole exome sequencing.

Identified Genetic Variants

Whole exome sequencing identified 6 pathogenic or LP variants across 6 genes: *CHD7*, *PAX2*, *RRM2B*, *KMT2A*, *MYCN*, and *CEP290*. Variant details, including Human Genome Variation Society (HGVS) nomenclature, ACMG classification, inheritance pattern, and segregation results, are summarized in Table 1.

Patient 1—CHD7

A heterozygous missense variant (NM_017780.4:c.4075A>T; p.Arg1359Trp) classified as a variant of uncertain significance (VUS) was identified in *CHD7*. The patient exhibited multiple phenotypic features consistent with CHARGE syndrome, including cleft palate, characteristic facial and ear anomalies, horseshoe kidney, sensorineural hearing loss, ocular coloboma, developmental delay, and cardiac anomalies. Segregation analysis demonstrated maternal inheritance. Due to the absence of functional validation, this variant was interpreted cautiously as a possible contributor to the phenotype.

Patient 2—PAX2

A heterozygous pathogenic variant (NM_000278.5:c.212G>A; p.Arg71Lys) was detected in the *PAX2* gene in a patient presenting with bilateral kidney hypodysplasia, retinal abnormalities, hearing loss, and family history of kidney disease. The clinical findings were consistent with papillorenal syndrome. Segregation analysis revealed paternal inheritance. The same variant was detected in the affected father, supporting autosomal dominant inheritance.

Patient 3—RRM2B and KMT2A

Two heterozygous variants were identified in this patient: a LP variant in *RRM2B* (NM_001172477.1:c.211_212insA; p.Arg71GlnfsTer28) inherited from both parents, and a de novo LP variant in *KMT2A*. The patient presented with PUV, bilateral VUR, neurodevelopmental delay, and facial dysmorphism. Considering the known association of *KMT2A* (NM_001197104.2:c.4884dup; p.Glu1629Ter) with Wiedemann–Steiner syndrome and genitourinary anomalies, this gene was considered the primary contributor to the kidney phenotype, while *RRM2B* may explain additional neurological findings.

Patient 4—MYCN

A heterozygous nonsense variant (NM_005378.6:c.940C>T; p.Gln314Ter) was identified in *MYCN*. The patient presented with bilateral hypoplastic kidneys, PUV, microcephaly, syndactyly, and early-onset kidney failure, consistent with Feingold syndrome type 1. The variant was not detected in either parent, indicating a de novo event.

Patient 5—CEP290

A heterozygous nonsense variant (NM_025114.4:c.5668G>T; p.Gly1890Ter) was detected in *CEP290*. The patient had an ectopic kidney with cortical cysts and neurological findings consistent with Joubert syndrome, including the molar tooth sign on brain magnetic resonance imaging. Segregation analysis showed parental heterozygosity.

Summary of Genotype–Phenotype Correlations

All genetically solved cases exhibited extrarenal manifestations and fulfilled clinical criteria suggestive of syndromic disease. The overall diagnostic yield of 16.1% is consistent with previously reported WES-based CAKUT cohorts. Variants in *CEP290* and *KMT2A* expand the spectrum of genes associated with CAKUT within syndromic contexts.

DISCUSSION

Whole exome sequencing has significantly advanced the understanding of the genetic basis of CAKUT, particularly in patients with syndromic features or multisystem involvement. In this study, WES identified pathogenic or LP variants in 5 of 31 pediatric patients with CAKUT, yielding an overall diagnostic rate of 16.1%. This detection rate is consistent with previously reported WES-based CAKUT cohorts, where diagnostic yields typically range between 12% and 20%.[4,6,8] Importantly, all genetically solved cases in the cohort exhibited extrarenal manifestations and clinical features suggestive of syndromic disease, underscoring the value of WES in selected CAKUT patients rather than as a uniform diagnostic tool for all presentations.

The high frequency of syndromic features among genetically positive patients supports current evidence that WES is most informative in children with bilateral kidney anomalies, multisystem involvement, positive family history, or parental consanguinity.[9] The findings reinforce the concept that careful clinical phenotyping is essential for appropriate patient selection and for maximizing the diagnostic utility of exome sequencing in CAKUT.

Among the identified genes, *CHD7* and *PAX2* are well-established causes of syndromic CAKUT, and the phenotypes observed in the patients were consistent with previously described clinical spectra.[14-23] However, given the classification of the detected *CHD7* variant as a VUS and the lack of functional validation, this finding was interpreted cautiously as a potential contributor to the phenotype rather than definitive evidence of causality. Although the patient's clinical features fulfilled the diagnostic criteria for CHARGE syndrome, a definitive molecular diagnosis could not be established. This case highlights the challenges of interpreting WES findings in syndromic presentations and underscores the importance of careful genotype–phenotype correlation and cautious clinical interpretation in the context of VUS results. A pathogenic heterozygous variant in *PAX2* was identified in a patient presenting with bilateral kidney hypodysplasia, ocular abnormalities, hearing loss, and a positive family history of kidney disease, findings consistent with papillorenal syndrome. *PAX2* is a well-established gene in CAKUT and plays a critical role in nephrogenesis and urinary tract development. The clinical presentation and segregation findings in this case are in accordance with previously reported gene–phenotype associations, further supporting the role of *PAX2* as one of the principal monogenic contributors to CAKUT.

Table 1. Clinical and Genetic Characteristics of CAKUT Patients with Pathogenic or LP Variants

Patient ID	Gene	Variant (HGVS cDNA/Protein)	ACMG Classification	Inheritance/ De novo	Sex/Age	Kidney Phenotype	Extrarenal Finding	Final Clinical Diagnosis	Validation/ Segregation
P1	*CHD7*	NM_017780.4:c.4075A>T/p. Arg1359Trp	VUS	Maternal inheritance	M/6 years	Horseshoe kidney	Cleft lip and palate, characteristic ear anomaly, sensorineural hearing loss, chorioretinal coloboma, developmental delay, ADHD	Suspected CHARGE syndrome	Sanger sequencing; parental testing
P2	*PAX2*	NM_000278.5:c.212G>A/p.Arg71Lys	P	Autosomal dominant (father affected)	F/15 years	Bilateral kidney hypodysplasia	High-frequency sensorineural hearing loss, retinal vascular and RPE changes	Papillorenal syndrome (PAPRS)	Sanger sequencing; familial segregation
P3	*RRM2B*	NM_001172477.1:c.211_212insA/p. Arg71GlnfsTer28	LP	Autosomal recessive	M/1 year	Posterior urethral valves, bilateral vesicoureteral reflux	Growth and developmental delay, hypotonia	Suspected mitochondrial disorder	Sanger sequencing; parental testing
P3	*KMT2A*	NM_001197104.2:c.4884dup/p. Glu1629Ter	LP	De novo	M/1 year	Posterior urethral valves, bilateral hydronephrosis	Facial dysmorphism, hypotonia, neurodevelopmental delay	Wiedemann–Steiner syndrome	Sanger sequencing; parental testing
P4	*MYCN*	NM_005378.6:c.940C>T/p. Gln314Ter	P	De novo	M/4 months	Bilateral kidney hypoplasia	Microcephaly, syndactyly of toes	Feingold syndrome type 1	Sanger sequencing; parental testing
P5	*CEP290*	NM_025114.4:c.5668G>T/p. Gly1890Ter	P	Autosomal recessive	M/5 years	Ectopic kidney, cortical kidney cysts	Hypotonia, nystagmus, molar tooth sign on brain MRI	Joubert syndrome	Sanger sequencing; parental testing

Gene names are written in italics in accordance with HGVS recommendations. All pathogenic and LP variants were confirmed by Sanger sequencing.
ACMG, American College of Medical Genetics and Genomics; ADHD, attention deficit hyperactivity disorder; LP, likely pathogenic; MRI, magnetic resonance imaging; RPE, retinal pigment epithelium; VUS, variant of uncertain significance.

A key finding of this study is the identification of variants in *CEP290* and *KMT2A* in patients with CAKUT phenotypes within syndromic contexts. *CEP290* encodes a ciliary protein critical for primary cilium function, and pathogenic variants are well known to cause Joubert syndrome and related ciliopathies, many of which include kidney involvement such as nephronophthisis, cystic kidney disease, or structural anomalies overlapping with CAKUT.[24] The findings support the role of ciliary dysfunction as a mechanistic link between neurodevelopmental abnormalities and kidney malformations.[25]

KMT2A encodes a histone methyltransferase involved in chromatin remodeling and transcriptional regulation during embryonic development. Pathogenic variants in *KMT2A* cause Wiedemann–Steiner syndrome, in which genitourinary anomalies have been reported in a substantial proportion of affected individuals.[26] Although the precise mechanisms by which *KMT2A* dysfunction influences kidney and urinary tract development remain unclear, disrupted epigenetic regulation of developmental gene networks may contribute to abnormal nephrogenesis and urinary tract morphogenesis. The identification of a truncating *KMT2A* variant in a patient with CAKUT and syndromic features expands the phenotypic spectrum associated with this gene.[27, 28]

A de novo pathogenic *MYCN* variant was identified in a patient with bilateral kidney hypodysplasia, microcephaly, and digital anomalies consistent with Feingold syndrome type 1.[29,30] Although kidney findings are not the primary feature of this syndrome, reported cases indicate that kidney malformations may occur. This finding suggests that *MYCN*-related developmental pathways may contribute to kidney anomalies; however, it should be interpreted within a syndromic context rather than as evidence of a primary CAKUT gene.[28-32]

In the patient carrying variants in both *RRM2B* and *KMT2A*, *KMT2A* was prioritized as the primary contributor to the phenotype. This decision was based on the presence of syndromic features, including developmental delay and extrarenal manifestations, which are more consistent with the known clinical spectrum associated with *KMT2A*-related disorders. In contrast, the identified *RRM2B* variant has a less well-established association with kidney malformations and did not fully explain the observed phenotype. Furthermore, the current literature supports the role of epigenetic regulators such as *KMT2A* in organogenesis and kidney development. Therefore, the variant in *KMT2A* was considered more likely to account for the clinical presentation. Nevertheless, the potential contribution of *RRM2B* cannot be completely excluded, and this case highlights the complexity of variant interpretation in the context of multilocus findings.

Overall, the results emphasize that WES should be considered within a stepwise diagnostic framework. Chromosomal microarray analysis and targeted gene panels may be appropriate first-line tests in certain clinical contexts, whereas WES may be prioritized in patients with syndromic, familial, bilateral, or severe CAKUT presentations. Integration of genetic findings with detailed clinical evaluation is essential for accurate diagnosis and optimal patient management.

In conclusion, this study demonstrates the clinical utility of WES in selected pediatric patients with CAKUT, particularly those with syndromic features and multisystem involvement. A diagnostic yield of 16.1% was achieved, consistent with previous WES-based CAKUT studies. The findings expand the genetic spectrum associated with CAKUT by identifying variants in *CEP290* and *KMT2A* within syndromic contexts. Early genetic diagnosis facilitates accurate clinical classification, informs prognosis, and supports effective genetic counseling and family planning. Careful patient selection and cautious interpretation of genetic findings remain essential to maximize the clinical benefit of WES in CAKUT.

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

Artificial Intelligence Usage Statement: The authors declared that no artificial intelligence tool was used in the preparation of the manuscript.

Ethics Committee Approval: Ethical committee approval was received from the Ethics Committee of Harran University (Approval no: HRÜ/22.20.21, Date: October 17, 2022).

Informed Consent: Written informed consent for genetic testing and participation in the study was obtained from the parents or legal guardians of all participants

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – A.G.; Design – A.G.; Supervision – A.G.; Resources – A.G.; Materials – M.B.M.; Data Collection and/or Processing – A.G., M.B.M., Ö.Ö.; Analysis and/or Interpretation – A.G., M.B.M., Ö.Ö.; Literature Search – A.G., M.B.M.; Writing Manuscript – A.G., M.B.M., Ö.Ö.; Critical Review – A.G

Declaration of Interests: The authors have no conflict of interest to declare.

Funding: The authors declared that this study has received no financial support.

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Supplementary Table 1. Whole exome sequencing quality metrics

Parameter	Description
Sequencing platform	Illumina
Mean coverage depth	70–100×
Coverage ≥20×	>95% of coding regions
Reference genome	GRCh37 / hg19
Variant classification	ACMG guidelines
Validation method	Sanger sequencing

Supplementary Table 2. Bioinformatics software and versions

Analysis step	Software / Tool	Version
Quality control	FastQC	v0.11.9
Read alignment	BWA-MEM	v0.7.17
BAM processing	SAMtools	v1.10
Variant calling	GATK HaplotypeCaller	v4.1.9.0
Variant annotation	ANNOVAR	2020-06-08
Variant interpretation	VarSeq (Golden Helix)	v2.2.5
Population database	gnomAD	v2.1.1
Population database	ClinVar	2023-01
In silico prediction	SIFT / PolyPhen-2 / MutationTaster	Various
Validation	Sanger sequencing	—