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Research Article

Keywords:

Posted Date: November 23rd, 2026

DOI: https://doi.org/10.21203/rs.3.rs-11678861/v1

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Clinical and Molecular Characteristics of Pediatric Congenital Anomalies of the Kidney and Urinary Tract in Northwest China: A Multicenter Prospective Cohort Study

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Abstract

Background Congenital anomalies of the kidney and urinary tract (CAKUT) are a leading cause of chronic kidney disease (CKD) in children, yet regional clinical and molecular data from Northwest China remain limited. This study characterized the clinical presentation and molecular etiology of CAKUT in a pediatric multicenter cohort, and evaluated the diagnostic utility of integrated trio whole-exome sequencing (WES) and genome-wide copy number variation sequencing (CNV-Seq).

Methods In this prospective multicenter study, 91 consecutive children with CAKUT (aged 0–14 years) were enrolled at three tertiary centers between January 2022 and December 2024. Phenotyping included kidney ultrasound graded by the Society for Fetal Urology (SFU) and Urinary Tract Dilation (UTD) systems. Molecular analysis used trio-based WES and CNV-Seq. Variants were classified per ACMG/AMP 2015 guidelines.

Results The male-to-female ratio was 3.3:1. Diagnosis was made within the first year of life in 44.0%, and 46.2% of cases were detected prenatally. Hydronephrosis was the most prevalent subtype (74.7%). Among patients with sufficient follow-up, CKD was present in 90.1%, and urinary tract infections occurred in 41.8%. Combined WES and CNV-Seq yielded a molecular diagnosis in 13.2% of patients: single-nucleotide variants or indels were identified by WES in 7.7%, and clinically significant copy number variants by CNV-Seq in 5.5%. Molecular diagnosis directly altered clinical management in several cases, including reclassification of imaging-based hydronephrosis and initiation of extra-kidney surveillance.

Conclusions In this cohort of children with CAKUT from Northwest China, integrated WES and CNV-Seq established an etiologic diagnosis in 13.2% of patients and informed clinical management. These findings support incorporation of advanced genetic testing into the diagnostic workflow for pediatric CAKUT to refine prognostication and personalized care.

Keywords CAKUT; Hydronephrosis; Whole-exome sequencing; Copy number variation; Chronic kidney disease; Children

Introduction

Congenital anomalies of the kidney and urinary tract (CAKUT) represent a spectrum of structural malformations originating from disrupted embryonic development, constituting a leading cause of chronic kidney disease (CKD) in children [1]. Phenotypic heterogeneity is vast, ranging from isolated hydronephrosis to severe bilateral renal agenesis [2]. The clinical course is often insidious, with many patients remaining asymptomatic until the development of advanced complications such as CKD, hypertension, or recurrent infections [3].

Genetic factors play a crucial role in CAKUT pathogenesis [4]. Over 50 monogenic causes and several recurrent copy number variations (CNVs), such as the 17q12 deletion, have been established [5, 6]. Despite this, a large proportion of cases remain genetically undiagnosed, highlighting etiologic complexity and potential gene-environment interactions [7].

Epidemiological data on CAKUT from Northwest China are sparse [8]. This multicenter study aims to characterize the clinical spectrum, renal outcomes, and molecular findings in a regional pediatric cohort. We employed a dual genetic testing strategy—trio-based whole-exome sequencing (WES) and CNV-Seq—to delineate genotype-phenotype correlations and assess the diagnostic yield in a real-world clinical setting.

Methods

This prospective cohort study was approved by the Institutional Review Board of the General Hospital of Ningxia Medical University (approval no. KYLL-2020-634). Consecutive pediatric patients (0-14 years) diagnosed with CAKUT at three tertiary centers between January 2022 and December 2024 were enrolled. Diagnosis was confirmed by pediatric nephrologists/urologists using standard imaging criteria. Written informed consent was obtained from guardians.

Demographics, perinatal history, family history, and clinical presentation were recorded. CAKUT was subtyped based on imaging findings (renal ultrasound, scintigraphy, CT urography). Hydronephrosis severity was graded using the Society for Fetal Urology (SFU) and Urinary Tract Dilation (UTD) classification systems. CKD was staged according to KDIGO guidelines. To screen for syndromic CAKUT, all patients underwent systematic extra-renal evaluation, including cardiac ultrasound, hearing screening by brainstem auditory evoked potentials, and ophthalmologic examination; other congenital malformations and comorbidities were recorded when present.

Genomic DNA from patient-parent trios underwent:

a) WES: Libraries prepared with Agilent SureSelect XT Human All Exon V7, sequenced on Illumina NovaSeq 6000. Variants were called against GRCh38 and annotated. Analysis focused on a curated CAKUT gene panel and exome-wide evaluation for de novo variants. Candidate variants were assessed with multiple in silico prediction tools (SIFT, PolyPhen-2, MutationTaster, and CADD) and population frequency databases as supporting evidence for classification.

b) CNV-Seq: Low-pass whole-genome sequencing was performed to detect genome-wide CNVs at ~0.1 Mb resolution. Variants were classified per ACMG/AMP 2015 guidelines [9]. A molecular diagnosis was defined by the identification of a P/LP variant in a known CAKUT-associated gene or a clinically significant CNV.

Descriptive statistics were used for demographic and clinical data. Categorical variables were compared using Chi-square or Fisher's exact tests. Correlations were assessed using Spearman's rank test. A two-tailed p-value <0.05 was considered significant. Analyses used SPSS v28.0.

Results

Cohort Characteristics: The cohort comprised 91 patients (70 male, 21 female). Median age at diagnosis was 1.2 years (IQR: 0.3–5.8), with 44.0% diagnosed in infancy. Prenatal detection occurred in 46.2% of cases. A high-risk perinatal history was common, including neonatal resuscitation (82.4%). A positive family history of renal or urinary anomalies was recorded in 2 patients (2.2%), and parental consanguinity was not documented in any case (0/91).

Gestational age at birth was full-term in 65 patients (71.4%), preterm in 23 (25.3%), including one pair of monozygotic twins and one member of a twin pair conceived by in vitro fertilization, and post-term in 2 (2.3%). Birth weight was normal in 72 patients (79.1%), whereas macrosomia, low birth weight, and very low birth weight were recorded in 3 (3.3%), 15 (16.5%), and 1 (1.1%) patients, respectively. Vaginal delivery and cesarean section accounted for 74% and 26% of births, respectively.

A positive family history of renal or urinary anomalies was recorded in 2 patients (2.2%): one girl whose father had unilateral renal agenesis with contralateral compensatory enlargement, and one boy whose cousin had undergone surgery for ureteropelvic junction obstruction with grade IV hydronephrosis and whose sister had congenital bilateral deafness with cochlear implantation. No parental consanguinity was documented. Regarding maternal history, 18 mothers reported gestational infections and 12 had a history of adverse pregnancy outcomes, including 5 with threatened miscarriage during the index pregnancy. Gestational diabetes mellitus and gestational hypertension occurred in 7 and 3 mothers, respectively. 4 mothers did not undergo regular prenatal examinations, and 1 mother smoked during pregnancy.

Clinical Spectrum and Outcomes: Fourteen CAKUT subtypes were identified. The most common were hydronephrosis (74.7%), ureteropelvic junction obstruction (UPJO; 53.8%), and ureteral dilatation (29.7%). Complex phenotypes (≥2 malformations) were present in 52.7% of patients.

In this cohort, extra-renal anomalies and comorbidities were prevalent. Cardiovascular findings included patent foramen ovale (n = 6), pericardial effusion (n = 5), and patent ductus arteriosus with pulmonary hypertension (n = 2). Other extra-renal anomalies comprised cryptorchidism (n = 6), umbilical hernia (n = 4), hearing impairment (n = 3), grade 3 retinal hemorrhage (n = 1), occult spina bifida (n = 1), and scoliosis (n = 1). Comorbid conditions included hepatitis B carrier status (n = 2) and one case each of anaphylactoid purpura, peptic ulcer disease, obesity, and epilepsy.

With a median follow-up of 18 months, CKD was observed in 90.1% of patients (n = 82), most frequently stage 3 (36.6%). Urinary tract infections occurred in 41.8% of the total cohort.

Genetic Findings and Diagnostic Yield: The overall molecular diagnostic yield was 13.2% (12/91).

WES identified P/LP single-nucleotide variants or indels in 7 patients (7.7%), involving COL4A3 (n = 1), SLC3A1 (n = 1), PAX2 (n = 1), ZMYM2 (n = 1), PKHD1 (n = 1), ATP7B (n = 1), and NPHP3/C3 (n = 1, a single patient carrying two likely pathogenic variants). PAX2 c.239C>T and ZMYM2 c.1947del were confirmed as de novo by trio analysis, with both parents being wild-type. For the remaining six variants, parental testing was either not performed or not reported, so their parental origin remains undetermined.

CNV-Seq identified clinically significant CNVs in 5 patients (5.5%): a 17q12 deletion, a 22q11.2 duplication, and an Xp22.33q28 duplication (trisomy X) classified as pathogenic, and a 16p13.3 deletion and a 17p12 duplication classified as likely pathogenic (Table 2). Abnormal CNV-Seq findings were present in 34 patients overall (37.4%); the remaining 29 patients carried copy-number variants of uncertain significance, with recurrent findings involving chromosomes 16 and 17.

WES identified VUSs in 68 patients (74.7%); recurrent VUSs involved DLG5, ROBO2, GREB1L, NPHP4, and CUBN, but none was considered diagnostic at the time of analysis.

Molecular diagnosis directly informed clinical management in several cases. The patient with a pathogenic PKHD1 variant was reclassified from an imaging-based label of hydronephrosis to autosomal recessive polycystic kidney disease-spectrum disease, prompting hepatic surveillance. The patient with a de novo PAX2 variant was referred for regular ophthalmologic and auditory evaluation. The patient with the 17q12 deletion was screened for diabetes and neurodevelopmental features of renal cysts and diabetes syndrome.

No significant association was found between phenotypic complexity and genetic diagnostic yield ($p > 0.05$).

Discussion

This study provides a detailed overview of CAKUT in a historically underrepresented region of China. The high male-to-female ratio (3.3:1) aligns with global epidemiologic trends [10], possibly reflecting sex-dependent differences in urinary tract development [11].

The predominance of hydronephrosis and its strong association with CKD progression underscore the need for vigilant, long-term monitoring of renal function in these patients, even following surgical correction [12]. The high prevalence of CKD in our cohort likely reflects tertiary-center referral bias but emphasizes the severe morbidity associated with CAKUT [1,3].

A key finding is the 13.2% molecular diagnostic yield achieved through combined WES and CNV-Seq, which is consistent with reports from diverse populations [7,13]and confirms the clinical utility of a systematic genetic approach. The detection of a 17q12 deletion, associated with a recognizable syndromic phenotype (renal cysts and diabetes syndrome), illustrates how genetic diagnosis can guide screening for extra-renal manifestations and inform family counseling [13,14]. The lack of correlation between phenotypic complexity and a positive genetic finding suggests that our current genetic tools may not capture all etiologies, pointing to oligogenic, epigenetic, or environmental contributors [7,15].

Beyond diagnostic yield, molecular findings directly informed clinical management. The patient with a pathogenic PKHD1 variant was reclassified as having autosomal recessive polycystic kidney disease-spectrum disease (multicystic/polycystic kidney dysplasia), prompting surveillance for hepatic involvement; the patient with a de novo PAX2 variant, in keeping with the renal-coloboma syndrome spectrum, was referred for regular ophthalmologic and auditory evaluation; and the patient with the 17q12 deletion was screened for features of renal cysts and diabetes syndrome, including diabetes and neurodevelopmental findings. These examples illustrate how genetic diagnosis refines phenotype-driven diagnoses and tailors follow-up strategies.

Further evidence suggests that adverse prenatal environments, including intrauterine infections [16] and teratogen exposure such as alcohol [17], contribute to CAKUT risk. The success of prenatal ultrasound screening in our region is supported by previous studies [18,19], and identified risk factors align with broader epidemiological research [20,21].

Limitations include moderate sample size and potential referral bias. The follow-up duration was insufficient to assess long-term renal outcomes in all patients. Moreover, incomplete longitudinal follow-up in a subset of patients precluded a reliable comparison of renal function trajectories between genetically diagnosed and undiagnosed patients.Future studies with extended follow-up should therefore address Kaplan–Meier analysis of time to CKD progression stratified by genetic status.

Conclusion

In this Northwest Chinese cohort, CAKUT presented with a broad clinical spectrum, a high rate of CKD, and a significant male predominance. Integrated clinical and genetic evaluation, utilizing both WES and CNV-Seq, established an etiologic diagnosis in over 13% of cases. These results advocate for the incorporation of advanced genetic testing into the standard diagnostic workflow for CAKUT, facilitating personalized management, prognostic stratification, and informed genetic counseling.

Funding

This work was supported by the Key Research and Development Program of Ningxia Hui Autonomous Region (Grant No. 2022BEG03119)

Data availability

The data are available from the authors upon reasonable request.

References

1. Kolvenbach CM, Shril S, Hildebrandt F (2023) The genetics and pathogenesis of CAKUT. Nat Rev Nephrol 19:709–720. https://doi.org/10.1038/s41581-023-00751-3
2. Vendrig LM, ten Hoor MAC, König BH, et al (2025) Translational strategies to uncover the etiology of congenital anomalies of the kidney and urinary tract. Pediatr Nephrol 40:685–699. https://doi.org/10.1007/s00467-024-06479-2
3. Hao ZH, et al (2025) Epidemiology and disease burden of pediatric congenital anomalies of the kidney and urinary tract: a national cross-sectional study of hospitalized children in China. World J Pediatr 21:306–321. https://doi.org/10.1007/s12519-025-00891-w
4. Werfel L, et al (2023) Diagnostic yield and benefits of whole exome sequencing in CAKUT patients diagnosed in the first thousand days of life. Kidney Int Rep 8:2439–2457. https://doi.org/10.1016/j.ekir.2023.08.008
5. Liu JL, Wang XW, Liu CH, et al (2023) Genetic spectrum of CAKUT and risk factors for kidney failure: a paediatric multicentre cohort study. Nephrol Dial Transplant 38:1981–1991
6. Khan K, et al (2022) Multidisciplinary approaches for elucidating genetics and molecular pathogenesis of urinary tract malformations. Kidney Int 101:473–484. https://doi.org/10.1016/j.kint.2021.09.034
7. Chevalier RL (2023) CAKUT: a pediatric and evolutionary perspective on the leading cause of CKD in childhood. Pediatr Rep 15:143–153. https://doi.org/10.3390/pediatric15010012
8. Geleta BE, Bekele BA, Afework M (2024) Spectrum of congenital anomalies of the kidney and urinary tract in a pediatric nephrology clinic in Ethiopia and factors associated with advanced chronic kidney disease: a cross-sectional study. PLOS Glob Public Health 4:e0003869. https://doi.org/10.1371/journal.pgph.0003869
9. Richards S, Aziz N, Bale S, et al (2015) Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med 17:405–424. https://doi.org/10.1038/gim.2015.30
10. Groen In 't Woud S, et al (2023) Environmental and parental risk factors for congenital solitary functioning kidney—a case–control study. Pediatr Nephrol 38:3397–3407. https://doi.org/10.1007/s00467-023-05900-6
11. Sonner S, Reilly K, Woolf AS, et al (2024) When should we offer antenatal sequencing for urinary tract malformations? A systematic review, cohort study and meta-analysis. Prenat Diagn 44:187–195. https://doi.org/10.1002/pd.6479
12. Zivotic I, et al (2024) Copy number variation analysis identifies MIR9-3 and MIR1299 as novel miRNA candidate genes for CAKUT. Pediatr Nephrol 39:2655–2665. https://doi.org/10.1007/s00467-024-06381-x
13. Lu Y, et al (2023) Integrated analysis of copy number variation-associated lncRNAs identifies candidates contributing to the etiologies of congenital kidney anomalies. Commun Biol 6:735. https://doi.org/10.1038/s42003-023-05101-9
14. Riedhammer KM, et al (2024) Implication of transcription factor FOXD2 dysfunction in syndromic congenital anomalies of the kidney and urinary tract (CAKUT). Kidney Int 105:844–864. https://doi.org/10.1016/j.kint.2023.12.012
15. Verbitsky M, Westland R, Perez A, et al (2019) The copy number variation landscape of congenital anomalies of the kidney and urinary tract. Nat Genet 51:117–127. https://doi.org/10.1038/s41588-018-0284-4
16. Celegen K, et al (2024) Risk factors of congenital anomalies of the kidney and urinary tract (CAKUT): exposure to mobile phones during pregnancy. Turk J Med Sci 54:291–300.
17. Hamada R, et al (2022) Maternal chronic disease and congenital anomalies of the kidney and urinary tract in offspring: a Japanese cohort study. Am J Kidney Dis. https://doi.org/10.1053/j.ajkd.2022.03.003
18. Alsaywid B, Mohammed A, Al Ghamdi L, et al (2022) Detection of renal anomalies using antenatal and postnatal ultrasound: the consanguinity factor. Urol Ann 14:241–246. https://doi.org/10.4103/UA.UA_147_19
19. Maternal and fetal risk factors for congenital anomalies of the kidney and urinary tract: a birth cohort study in urban China. J Nephrol 37:2521–2530 (2024). https://doi.org/10.1007/s40620-024-02066-8

20. Matsell DG, Catapang M, Becknell B (2023) Predicting outcomes in children with congenital anomalies of the kidney and urinary tract. Pediatr Nephrol 38:3407–3415. https://doi.org/10.1007/s00467-023-05949-3
21. Chen L, Yang W, Liu L, et al (2026) A cohort study of fetal urinary tract abnormalities and chromosomal copy number variations: a retrospective analysis of 9-year data. Arch Gynecol Obstet. https://doi.org/10.1007/s00404-026-08421-3

Table 1 Distribution of CAKUT subtypes by sex and age at diagnosis (n = 91)

CAKUT Subtype	Male	Female	≤1 yr	1-3 yr	3-7 yr	7-11 yr	11-14 yr	Total N (%)
Hydronephrosis	50	18	21	13	15	8	11	68 (74.7)
UPJO	40	9	16	11	11	7	4	49 (53.8)
Ureteral Dilatation	18	9	13	7	5	0	2	27 (29.7)
Polycystic Kidney	7	7	4	1	4	4	1	14 (15.4)
Renal Dysplasia	9	2	2	2	3	2	2	11 (12.1)
UVJO	7	4	4	2	2	3	0	11 (12.1)
Renal Hypoplasia	3	2	2	2	0	1	0	5 (5.5)
Renal Agenesis	4	2	0	0	0	4	2	6 (6.6)
Duplex Kidney	2	2	2	0	0	0	2	4 (4.4)
Duplicated Collecting System	2	2	2	0	0	0	2	4 (4.4)
VUR	0	4	0	2	2	0	0	4 (4.4)
Ectopic Ureteral Orifice	2	2	2	0	0	0	2	4 (4.4)
Horseshoe Kidney	2	0	0	0	0	0	2	2 (2.2)
Renal Malrotation	2	0	0	2	0	0	0	2 (2.2)

A patient with multiple subtypes is counted in each relevant row.

UPJO: ureteropelvic junction obstruction

UVJO: ureterovesical junction obstruction

VUR: vesicoureteral reflux.

Table 2 Clinical and molecular profile of patients with clinically significant copy number variants

Case	Gender	Phenotype	CNV (hg38)	Classification
1	Female	Hydronephrosis, UPJO	arr[GRCh38] 17q12(36,431,658-37,874,410)x1	P
2	Male	Polycystic kidney, Hydronephrosis, UPJO	arr[GRCh38] 22q11.21(18,900,000-21,400,000)x3	P
3	Female	Renal agenesis (unilateral)	arr[GRCh38] Xp22.33q28(2,781,919-155,612,904)x2	P
4	Female	Duplex kidney, Hydronephrosis	arr[GRCh38] 16p13.3(2,104,338-2,104,737)x1	LP
5	Male	Polycystic kidney	17p12 duplication	LP

Case 4 and case 5 coordinates require completion from the original CNV-Seq report.

Table 3 Pathogenic and Likely Pathogenic Variants Identified by Whole-Exome Sequencing

Case	**Phenotype**	**Gene**	**Variant (cDNA; protein)**	**Variant type**	**ACMG class**	**Origin**
1	Hydronephrosis	*COL4A3*	c.4793T>G; p.Leu1598Arg	Missense	LP	Not reported
2	Hydronephrosis	*SLC3A1*	c.163C>T; p.Gln55Ter	Nonsense	LP	Not reported
3	Renal hypoplasia; epilepsy; cryptorchidism	*PAX2*	c.239C>T; p.Pro80Leu	Missense	LP	De novo
4	Hydronephrosis (bilateral)	*ZMYM2*	c.1947del; p.Lys649Asnfs*29	Frameshift	P	De novo
5	Hydronephrosis	*PKHD1*	c.2507T>C; p.Val836Ala	Missense	P	Not reported
6	Polycystic kidney; renal hypoplasia	*ATP7B*	c.3316G>A; p.Val1106Ile	Missense	P	Not reported
7	Hydronephrosis; UPJO	*NPHP3*	c.2108_2109del; p.His703Leufs*30	Frameshift	LP	Not reported
8	Hydronephrosis; UPJO[a]	*C3*	c.3088G>T; p.Glu1030Ter	Nonsense	LP	Not reported

^[a] Same patient as case 7, who carried two likely pathogenic variants (NPHP3 and C3).