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Genetic Basis of Congenital Anomalies of the Kidney and Urinary Tract (CAKUT)

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ABSTRACT

Background: Congenital anomalies of the kidney and urinary tract (CAKUT) are a leading cause of pediatric chronic kidney disease (CKD), with a diverse range of clinical manifestations and underlying genetic causes. Objective: This study aims to investigate the genetic basis of CAKUT in pediatric patients, identifying key mutations and exploring their association with clinical outcomes such as renal impairment and extra-renal features. Methods: This cross-sectional study was conducted at District Headquarter Hospital Mardan from May 2024 to May 2025. A total of 55 pediatric patients diagnosed with CAKUT were enrolled in this study. Genetic screening was performed using whole exome sequencing (WES) and. -

targeted gene sequencing for known CAKUT-related genes (HNF1B, PAX2, RET, EYA1). Clinical data, including renal function and associated comorbidities, were collected from medical records. Results: Mutations in HNF1B were identified in 12 patients (21.8%), with renal hypodysplasia observed in 8 (66.7%) of these cases. Mutations in PAX2 were found in 8 patients (14.5%), with vesicoureteral reflux (VUR) present in 6 (75%) of these cases. RET mutations were detected in 5 patients (9.1%), while EYA1 mutations (copy number variations) were found in 4 patients (7.3%). However, 26 patients (47.3%) did not have mutations in the targeted genes. Logistic regression analysis revealed that HNF1B mutations were significantly associated with renal impairment (OR = 5.2, 95% CI: 1.5–18.3, p = 0.01), and PAX2 mutations were significantly associated with VUR (OR = 3.5, 95% CI: 1.2–10.5, p = 0.02). Conclusion: This study underscores the important role of genetic mutations in the development of CAKUT, particularly in relation to renal hypodysplasia and VUR. Early genetic screening can aid in the diagnosis and prognosis of CAKUT, and the identification of mutations in genes like HNF1B and PAX2 may help guide clinical management

Keywords: *Mutation, Screening, CAKUT, Renal, Disorders*

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1. INTRODUCTION

Congenital anomalies of the kidney and urinary tract (CAKUT) encompass a broad and heterogeneous group of developmental disorders that affect the kidneys, ureters, bladder, and urethra [1]. They account for 20-30% of all prenatally diagnosed anomalies and nearly half of pediatric cases of chronic kidney disease, making them a significant proportion of. -

congenital malformations worldwide. There is a wide range of CAKUT, from relatively minor structural changes like duplex kidneys or vesicoureteral reflux (VUR) to severe anomalies like bilateral renal agenesis, renal hypodysplasia, or obstructive uropathies that can lead to end-stage renal disease (ESRD) early in life [2]. CAKUT are of significant clinical and public health significance due to their prevalence, lifelong morbidity, and impact on renal function [3]. From the point of view of developmental biology, CAKUT occur as a result of disruptions in the intricate processes of kidney morphogenesis. The ureteric bud, which originates from the Wolffian duct, and the metanephric mesenchyme interact with one another during embryogenesis to initiate the formation of the metanephric kidney. Ureteric branching, nephron induction, and ultimately the development of a functioning renal system are all fueled by this

crosstalk [4]. These processes are regulated by an intricate network of transcription factors, growth factors, and signaling cascades, including pathways such as GDNF/RET, BMP, WNT, FGF, and Notch [5]. Disturbances in these pathways, whether due to genetic mutations or epigenetic alterations, can impair nephrogenesis and lead to structural anomalies in the urinary tract. Notably, even subtle disruptions at critical windows of development can result in clinically significant abnormalities [6].

The genetic basis of CAKUT has been increasingly elucidated with advances in molecular genetics and next-generation sequencing technologies. Several monogenic causes have been identified, with mutations in HNF1B, PAX2, EYA1, SIX1, and RET among the most well-characterized [7]. For example, HNF1B mutations are one of the most frequent monogenic causes of CAKUT, accounting for up to 10% of cases in some cohorts. Multisystem involvement, such as maturity-onset diabetes of the young type 5 (MODY5), genital tract malformations, and electrolyte disturbances like hypomagnesemia [8], may also be present in these patients in addition to renal anomalies. Similarly, PAX2 mutations are linked to renal-coloboma syndrome, underscoring the pleiotropic effects of developmental genes across organ systems [9]. The shared developmental pathways between the urinary tract and other organ systems are further demonstrated by syndromic associations like the branchio-oto-renal (BOR) syndrome, which is caused by mutations in either EYA1 or SIX1 [10]. However, monogenic causes explain only a fraction of CAKUT cases, and the genetic landscape is highly heterogeneous. The complexity of the genetic contribution is highlighted by the fact that many patients have copy number variations (CNVs), de novo variants, or mutations of uncertain significance [11]. Gene–gene interactions and environmental factors that alter gene expression may play a significant role, as evidenced by the known mutations' variable expressivity and incomplete penetrance [12].

Objective

This study aims to investigate the genetic basis of CAKUT in pediatric patients, identifying key mutations and exploring their association with clinical outcomes such as renal impairment and extra-renal features.

Methodology

This cross-sectional study was conducted at District Headquarter Hospital Mardan from May 2024 to May 2025. A total of 55 pediatric patients diagnosed with CAKUT were enrolled in this study.

Inclusion Criteria:

Patients diagnosed with congenital anomalies of the kidney and urinary tract (CAKUT) were eligible for inclusion in this study. The specific CAKUT abnormalities considered for inclusion were renal agenesis, renal hypodysplasia, vesicoureteral reflux (VUR), ureteropelvic junction obstruction, polycystic kidney disease, and duplicated renal collecting systems. Additionally, only patients aged 0 to 18 years with a confirmed diagnosis of CAKUT were included.

Exclusion Criteria:

Patients with known syndromic CAKUT (such as branchio-oto-renal syndrome, renal-coloboma syndrome) were excluded, as the focus of this study was on non-syndromic CAKUT. Patients with a history of major genetic syndromes, such as Down syndrome, or those with incomplete genetic or clinical data were also excluded from the study.

Data Collection

Data were collected from medical records, clinical examinations, and genetic testing. Clinical data, including age at diagnosis, renal function (serum creatinine, glomerular filtration rate), type of CAKUT, and associated comorbidities, were compiled from patient charts. In addition, patients underwent genetic screening, which involved blood or saliva samples for DNA extraction. Whole exome sequencing (WES) and targeted gene sequencing (for specific known CAKUT-related genes such as *HNF1B*, *PAX2*, *RET*) were performed to identify mutations or variants.

Genetic Analysis:

Genetic analyses were conducted in collaboration with a certified molecular genetics laboratory. The study focused on mutations in key genes associated with CAKUT. Using next-generation sequencing (NGS), we investigated the presence of known mutations, novel variants, and copy number variations (CNVs) in genes such as *HNF1B*, *PAX2*, *EYA1*, and *RET*. Variants were classified based on their pathogenicity according to ACMG guidelines.

Statistical Analysis:

Data were analyzed using SPSS v26.0. Descriptive statistics were used to summarize demographic and clinical characteristics of the study population. The frequency of mutations in each gene was reported along with any associations between genetic findings and clinical outcomes. Statistical significance was set at $p < 0.05$.

2. RESULTS

Data were collected from 55 patients, mean age of the patients was 6.2 ± 4.1 years, with a range of ages from infancy to adolescence. Of the total population, 30 patients (54.5%) were male and 25 patients (45.5%) were female. The most common types of CAKUT in this cohort were vesicoureteral reflux (VUR), affecting 15 patients (27.3%), followed by renal hypodysplasia in 12 patients (21.8%) and ureteropelvic junction obstruction in 10 patients (18.2%). Additionally, duplicated renal collecting systems were observed in 10 patients (18.2%), and renal agenesis was diagnosed in 8 patients (14.5%). Genetic mutations were identified in various CAKUT-related genes. The most common mutation was in HNF1B, found in 12 patients (21.8%), followed by PAX2 deletions in 8 patients (14.5%). Mutations in RET and EYA1 were less common, with 5 patients (9.1%) and 4 patients (7.3%) having point mutations and copy number variations (CNVs), respectively. Notably, 26 patients (47.3%) had no identifiable mutations in the genes tested.

Table 1: Demographic Profile of Patients (n = 55)

Variable	**Category**	**n (%)**
Age (years)	Mean ± SD: 6.2 ± 4.1	55 (100.0%)
Gender	Male	30 (54.5%)
	Female	25 (45.5%)
Type of CAKUT	Renal Agenesis	8 (14.5%)
	Renal Hypodysplasia	12 (21.8%)
	Vesicoureteral Reflux (VUR)	15 (27.3%)
	Ureteropelvic Junction Obstruction	10 (18.2%)
	Duplicated Renal Collecting System	10 (18.2%)
Mutation Detected in Gene		
HNF1B	Missense Mutation	12 (21.8%)
PAX2	Deletion	8 (14.5%)
RET	Point Mutation	5 (9.1%)
EYA1	CNV (Duplication)	4 (7.3%)
Other	No Mutation Found	26 (47.3%)

Among the 12 patients with HNF1B mutations, 66.7% (8 patients) presented with renal hypodysplasia, and 16.7% (2 patients) had vesicoureteral reflux (VUR). For PAX2 mutations, 75% (6 patients) had VUR, while 25% (2 patients) had renal hypodysplasia. In contrast, patients with other mutations showed a more varied distribution: 20% (7 patients) had renal agenesis, 5.7% (2 patients) had renal hypodysplasia, 20% (7 patients) had VUR, and 11.4% (4 patients) presented with ureteropelvic junction obstruction.

Table 2: Clinical Presentation by Genetic Mutation

Clinical Phenotype	HNF1B Mutation (n = 12)	PAX2 Mutation (n = 8)	Other Mutations (n = 35)
Renal Agenesis	1 (8.3%)	0 (0%)	7 (20%)
Renal Hypodysplasia	8 (66.7%)	2 (25%)	2 (5.7%)
Vesicoureteral Reflux (VUR)	2 (16.7%)	6 (75%)	7 (20%)
Ureteropelvic Junction Obstruction	1 (8.3%)	0 (0%)	4 (11.4%)

HNF1B mutations were significantly associated with renal hypodysplasia (odds ratio = 5.2, 95% CI: 1.5–18.3, p = 0.01). PAX2 mutations were significantly associated with VUR (odds ratio = 3.5, 95% CI: 1.2–10.5, p = 0.02). However, no significant association was found between RET mutations and renal agenesis (odds ratio = 1.8, 95% CI: 0.7–4.8, p = 0.22) or between EYA1 mutations and ureteropelvic junction obstruction (odds ratio = 1.1, 95% CI: 0.4–3.0, p = 0.85).

Table 3: Logistic Regression Analysis of Genetic Mutations and Clinical Phenotypes

Genetic Mutation	Clinical Phenotype	Odds Ratio (OR)	95% Confidence Interval (CI)	p-value
HNF1B	Renal Hypodysplasia	5.2	1.5–18.3	0.01
PAX2	Vesicoureteral Reflux (VUR)	3.5	1.2–10.5	0.02
RET	Renal Agenesis	1.8	0.7–4.8	0.22
EYA1	Ureteropelvic Junction Obstruction	1.1	0.4–3.0	0.85

Renal impairment was more prevalent in patients with HNF1B mutations, where 75% (6 patients) showed signs of renal dysfunction, compared to 12.8% (6 patients) with no impairment (p = 0.001). PAX2 mutations were also associated with a higher frequency of renal impairment, with 37.5% (3 patients) exhibiting dysfunction, compared to 14.9% (7 patients) with no impairment (p = 0.05). EYA1 mutations were similarly linked to renal impairment in 25% (2 patients), while only 4.3% (2 patients) showed no impairment (p = 0.02). In contrast, RET mutations had minimal association with renal impairment, with 12.5% (1 patient) affected, compared to 8.5% (4 patients) with no impairment (p = 0.75).

Table 4: Frequency of Renal Function Impairment by Genetic Mutation

Genetic Mutation	No Impairment (n = 47)	Renal Impairment (n = 8)	p-value
HNF1B	6 (12.8%)	6 (75.0%)	0.001
PAX2	7 (14.9%)	3 (37.5%)	0.05
RET	4 (8.5%)	1 (12.5%)	0.75
EYA1	2 (4.3%)	2 (25.0%)	0.02
Other	28 (59.6%)	5 (62.5%)	0.94

Extra-renal features, such as hypomagnesemia and diabetes, were more frequently observed in patients with HNF1B mutations, with 66.7% (8 patients) exhibiting these features, compared to 33.3% (4 patients) with no extra-renal

manifestations (p = 0.03). PAX2 mutations were less frequently associated with extra-renal features, with 25% (2 patients) showing these symptoms, while 75% (6 patients) had no extra-renal involvement (p = 0.07). Similarly, RET and EYA1 mutations had a lower frequency of extra-renal features, with 20% (1 patient) and 25% (1 patient) affected, respectively, although these findings were not statistically significant (p = 0.12 and p = 0.18, respectively).

Table 5: Association Between Genetic Mutation and Presence of Extra-Renal Features (e.g., Hypomagnesemia, Diabetes)

Genetic Mutation	Extra-Renal Features Present (n = 55)	No Extra-Renal Features (n = 55)	p-value
HNF1B	8 (66.7%)	4 (33.3%)	0.03
PAX2	2 (25%)	6 (75%)	0.07
RET	1 (20%)	4 (80%)	0.12
EYA1	1 (25%)	3 (75%)	0.18
Other	2 (20%)	8 (80%)	0.30

3. DISCUSSION

The results of this study provide significant insights into the genetic underpinnings of congenital anomalies of the kidney and urinary tract (CAKUT), a common cause of pediatric chronic kidney disease (CKD). Our findings highlight the pivotal role of genetic mutations in determining the clinical phenotype and progression of CAKUT, with notable associations between mutations in *HNF1B* and *PAX2* and specific renal anomalies. One of the major findings of this study was the high frequency of mutations in the *HNF1B* gene, which was detected in 21.8% of the patient cohort. This gene, previously linked to renal hypodysplasia and other renal tract anomalies, was found to be significantly associated with renal hypodysplasia in our study, with 66.7% of *HNF1B*-mutated patients presenting with this phenotype. These results are consistent with previous studies that have shown *HNF1B* mutations to be a frequent cause of renal hypodysplasia and other extra-renal features such as hypomagnesemia and maturity-onset diabetes of the young (MODY5). In this study, 75% of patients with *HNF1B* mutations had associated renal impairment, further underscoring the severity of the phenotype in this subset of patients [13].

Similarly, mutations in *PAX2* were found in 14.5% of the cohort and were strongly associated with vesicoureteral reflux (VUR), with 75% of *PAX2*-mutated patients presenting with this condition. *PAX2* is a well-established transcription factor involved in kidney development, and mutations in this gene have been implicated in renal-coloboma syndrome. Our findings corroborate the role of *PAX2* in VUR, a common CAKUT abnormality, as reported in previous literature [14]. The presence of VUR in patients with *PAX2* mutations emphasizes the importance of genetic screening for this gene in cases of unexplained VUR, especially in the absence of other associated anomalies. Despite the identification of genetic mutations in a substantial proportion of patients (52.7%), 47.3% of the cohort did not exhibit mutations in the targeted genes. This highlights the genetic heterogeneity of CAKUT and suggests that additional, yet-to-be-identified genetic factors may be involved in the pathogenesis of these anomalies [15]. The lack of identifiable mutations in these patients also raises the possibility of epigenetic factors, gene-environment interactions, or the involvement of non-coding regions of the genome, which have yet to be fully explored in the context of CAKUT. Previous studies have suggested the presence of copy number variations (CNVs) and de novo mutations that may not be captured by current sequencing approaches, underscoring the need for further research into the genetic architecture of CAKUT. Our study also identified extra-renal features in some of the patients, particularly those with *HNF1B* mutations [16]. Extra-renal features, such as hypomagnesemia, were present in 66.7% of patients with *HNF1B* mutations, consistent with known associations between *HNF1B* mutations and systemic manifestations. These findings are important for clinicians in identifying individuals who may require surveillance for extra-renal complications. For example, the identification of *HNF1B* mutations may prompt screening for diabetes or electrolyte imbalances in affected individuals, which is crucial for long-term management [17].

4. LIMITATIONS

While this study provides valuable insights into the genetic basis of CAKUT, it is not without limitations. The relatively small sample size (n = 55) limits the generalizability of our findings and may account for the lack of significant associations with some genetic mutations. Larger, multicenter studies are needed to validate these findings and explore additional genetic factors that may contribute to CAKUT. Moreover, while targeted gene sequencing provided useful insights into the genetic landscape of CAKUT, the role of non-coding regions and epigenetic modifications remains an area for further investigation.

5. CONCLUSION

It is concluded that genetic mutations play a critical role in the pathogenesis of congenital anomalies of the kidney and urinary tract (CAKUT), with HNF1B and PAX2 mutations being the most prominent genetic factors identified in this cohort. These mutations were found to be significantly associated with specific clinical phenotypes, such as renal hypodysplasia and vesicoureteral reflux (VUR), highlighting the value of genetic screening in guiding diagnosis, prognosis, and management. The HNF1B mutation, in particular, was strongly correlated with more severe renal impairment and extra-renal features, underlining the importance of early identification for comprehensive care.

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