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CLINICAL RESEARCH

Genetic Spectrum of Congenital Anomalies of the Kidney and Urinary Tract in Chinese Newborn Genome Project

Zhelan Huang[1], Qian Shen[2], Bingbing Wu[1], Huijun Wang[1], Xinran Dong[1], Yulan Lu[1], Guoqiang Cheng[3], Laishuan Wang[3,4], Wei Lu[5], Liping Chen[6], Wenqing Kang[7], Long Li[8], Xinnian Pan[9], Qiufen Wei[9], Deyi Zhuang[10], Dongmei Chen[11], Zhaoqing Yin[12], Ling Yang[13], Qi Ni[1], Renchao Liu[1], Gang Li[1], Ping Zhang[1], Yanyan Qian[1], Xiaomin Peng[1], Yao Wang[1], Yun Cao[3,4], Hong Xu[2], Liyuan Hu[3,4], Lin Yang[5] and Wenhao Zhou[1,3,4,10]

[1]Center for Molecular Medicine, Children's Hospital of Fudan University, Shanghai, China; [2]Department of Nephrology, Children's Hospital of Fudan University, Shanghai, China; [3]Division of Neonatology, Children's Hospital of Fudan University, Shanghai, China; [4]Key Laboratory of Birth Defects, Children's Hospital of Fudan University, Shanghai, China; [5]Department of Endocrinology and Inherited Metabolic Diseases, Children's Hospital of Fudan University, Shanghai, China; [6]Jiangxi Provincial Children's Hospital, Nanchang, China; [7]Children's Hospital Affiliated to Zhengzhou University, Zhengzhou, China; [8]Department of Neonatology, People's Hospital of Xinjiang Uygur Autonomous Region, Urumqi, China; [9]Maternal and Child Health Care Hospital of Guangxi Zhuang Autonomous Region, Nanning, China; [10]Xiamen Children's Hospital, Xiamen, China; [11]Quanzhou Women and Children's Hospital, Quanzhou, China; [12]The People's Hospital of Dehong, Dehong, China; and [13]Hainan Women and Children's Medical Center, Haikou, China

Introduction: Congenital anomalies of the kidney and urinary tract (CAKUT) corresponds to a spectrum of defects. Several large-cohort studies have used high-throughput sequencing to investigate the genetic risk of CAKUT during antenatal, childhood, and adulthood period. However, our knowledge of newborns with CAKUT is limited.

Methods: This multicenter retrospective cohort study explored the genetic spectrum of CAKUT in a Chinese neonatal cohort. Clinical data and whole exome sequencing (WES) data of 330 newborns clinically diagnosed with CAKUT were collected. WES data were analyzed for putative deleterious single nucleotide variants (SNVs) and potential disease-associated copy number variants (CNVs).

Results: In this study, pathogenic variants were identified in 61 newborns (18.5%, 61/330), including 35 patients (57.4%) with SNVs, 25 patients (41%) with CNVs, and 1 patient with both an SNV and a CNV. Genetic diagnosis rates were significantly higher in patients with extrarenal manifestations ($P < 0.001$), especially in those with cardiovascular malformations ($P < 0.05$). SNVs in genes related to syndromic disorders (CAKUT with extrarenal manifestations) were common, affecting 20 patients (57.1%, 20/35). *KMT2D* was the most common gene (5 patients) and 17q12 deletion was the most common CNV (4 patients). Patient 110 was detected with both a CNV (17q12 deletion) and an SNV (a homozygous variant of *SLC25A13*). Among the newborns with positive genetic results, 22 (36.1%, 22/61) patients may benefit from a molecular diagnosis and change in clinical management (including early multidisciplinary treatment, disease-specific follow-up, and familial genetic counseling).

Conclusion: This study shows the heterogeneous genetic etiologies in a Chinese CAKUT neonatal cohort by using WES. Patients with CAKUT who have extrarenal manifestations are more likely to harbor genetic diagnoses. Kabuki syndrome and 17q12 deletion syndrome were the most common genetic findings. Approximately 36.1% of the patients may benefit from molecular diagnoses and a change in clinical management.

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Correspondence: Hong Xu, Department of Nephrology, Children's Hospital of Fudan University, 399 Wanyuan Road, Shanghai, 201102, China. E-mail: hxu@shmu.edu.cn; or Liyuan Hu, Division of Neonatology, Children's Hospital of Fudan University; Key Laboratory of Birth Defects, Children's Hospital of Fudan University, 399 Wanyuan Road, Shanghai 201102, China. E-mail: nowadays921@126.com; or Lin Yang, Department of Endocrinology and Inherited Metabolic Diseases, Children's Hospital of Fudan University, 399 Wanyuan Road, Shanghai 201102, China. E-mail: linyang09@fudan.edu.cn

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CAKUT corresponds to a spectrum of defects that may lead to chronic kidney disease and present an economic burden on families and the society.[1] It is estimated that 4 to 60 per 10,000 newborns are diagnosed with CAKUT.[2-5] As a clinically heterogeneous phenotype, CAKUT can present as an isolated renal condition, including defects in the kidney, ureters, bladder and urethra, or as part of a clinical syndrome.[6,7] It has been suggested that CAKUT is related to embryonic defects with genetic, epigenetic, and environmental causes,[8-10] and genetic variants account for approximately 20% of cases.[11] Multiple lines of evidence, such as familial segregation of CAKUT cases and identification of causative genes, support the contribution of genetic factors.[12]

Due to the advantages of massive parallel sequencing technologies, clinical and molecular laboratories have largely adopted next-generation sequencing for genetic testing.[13] Apart from SNVs, a significant number of patients with CAKUT carry CNVs, indicating susceptibility to a syndrome diagnosis.[14-16] Compared to previous analyses of individual candidate genes, WES provides an opportunity to accurately diagnose both SNVs and CNVs using a single test. WES has extensively defined the genetic landscape of CAKUT. Several studies have used high-throughput sequencing in large cohorts to investigate the genetic risk of CAKUT during the antenatal, childhood, and adulthood periods.[14,17-23] However, studies on newborn with CAKUT are limited.

In the present study, we investigated the utility of WES for molecular diagnosis of CAKUT in newborn patients. In particular, we identified circumstances that increase the possibility for patients with CAKUT to harbor genetic variants. We also analyzed the genetic findings for both SNVs and CNVs, which helps to obtain a more comprehensive understanding of the genetic etiologies associated with CAKUT.

METHODS

Study Design and Participant Recruitment

The patients in this study were recruited through the China Neonatal Genomes Project.[24] CAKUT encompasses diverse anatomical anomalies of the kidney and urinary tract, including congenital hydronephrosis, multicystic dysplastic kidney (MCDK), renal agenesis, renal duplication, renal dysplasia, crossed fused renal ectopia, ectopic kidney and lower urinary tract anomalies.[7,11] The clinical manifestations are not obvious in the neonatal period and some patients cannot be diagnosed with a specific CAKUT phenotype. Excluding hydronephrosis, many patients with neonatal CAKUT may be missed. Therefore, in this study, we used a description of ultrasonic findings, including congenital hydronephrosis. MCDK was diagnosed via ultrasound evidence of a kidney with parenchyma completely substituted by large cysts of varying sizes, with the absence of kidney function determined via kidney scintigraphy.[25] Furthermore, polycystic kidney disease and MCDK are difficult to distinguish between each other based on clinical manifestations in the neonatal period. Renal dysplasia is characterized by varying degrees of defective kidney formation. Only a kidney biopsy can help distinguish between the 2. Therefore, renal hypoplasia and dysplasia were placed under the same category. Anomalies of the lower urinary tract include obstruction of ureteropelvic junction, ureterovesical junction obstruction, vesicoureteral reflux, posterior urethral valves, cystoschisis, megaloureter, ureterocele, and hypospadias. A prenatal diagnosis was made through a fetal ultrasound examination (oligohydramnios or variations in the gross morphology of the kidney, ureter, or bladder).[25] However, due to the retrospective nature of this study, the information regarding maternal obstetric examinations relying on neonatal clinical records in the neonatal intensive care unit may be incomplete. Asymptomatic patients may be detected incidentally when imaging methods are used for a different issue. The manifestation rate includes extrarenal structural manifestations, such as special facial features, congenital heart disease, cerebral abnormalities, digestive tract malformations, musculoskeletal malformation, and reproductive malformations.

Newborns diagnosed with CAKUT between January 2016 and June 2021 were recruited. The inclusion criteria were infants (≤28 days old, age at admission) with CAKUT who had at least 1 of the above-mentioned diagnoses. The exclusive criterion was incomplete clinical information. For each enrolled patient, clinical information was obtained by reviewing medical records. Clinical information was reviewed from the hospital clinical notes by an experienced neonatologist. The samples used in this study were collected with appropriate informed consent and approval from the Ethics Committee of the Children's Hospital of Fudan University (2015-169).

WES

Genomic DNA samples were extracted from peripheral blood and WES was performed using the Agilent (Santa Clara, CA) SureSelectXT Human All Exon 50Mb kit. Sequencing was performed on the HiSeq2000/2500 (Illumina, San Diego, CA) sequencer according to the manufacturer's instructions. For full information on WES, please see the previously published studies.[26,27]

SNVs Calling and Validation via Sanger Sequencing

Variant calling was performed using the Genome Analysis Toolkit Best Practices and an in-house pipeline.[28] Variants were obtained using Genome Analysis Toolkit, and subsequently annotated by ANNOVAR,[29] VEP[30] software, and the Human Gene Mutation Database (professional version) and the ClinVar database (https://www.ncbi.nlm.nih.gov/clinvar/). The variant filtering process was combined with a phenotype-scoring algorithm named PhenoPro.[31] The diagnosed variants were confirmed in the probands by Sanger sequencing. A segregation analysis was performed when familial DNA (from parents or siblings) was available. Polymerase chain reaction products were sequenced using the BigDye Terminator v3.1 Cycle Sequencing Kit (Applied Biosystems, Carlsbad, CA).

Criteria for Classifying SNVs/CNVs

The pathogenicity of the variants was defined based on the American College of Medical Genetics and Genomics criteria.[32] Specifically, a case was molecularly diagnosed when the identified pathogenic or likely pathogenic variants were truncating variants or reported missense variants detected in a disease gene that sufficiently explained the phenotypes of the studied individual.[33] CNVs were analyzed with the use of a home-modified CANOES17 using a read depth calculated by BEDtools (V.2.17) (https://bedtools.readthedocs.io/en/latest/index.html).[34] Annotation at the gene level was based on in-house databases and the following 4 public databases: OMIM, Human Gene Mutation Database, Swiss-Prot, and RefSeq. Region-level annotation was performed by the Database of Genomic Variants, and the Database of Genomic Variation and Phenotype in Humans using Ensembl Resources. CNVs that passed computational phenotype filtration, overlapped with a pathogenic CNV previously reported in published studies or internal databases (the overlapped region was >70% of the reported pathogenic CNV). The overlapping region included a gene with loss-of-function because the known pathogenesis or established/predicted haploinsufficiency, or both breakpoints of the CNV were within the same established haploinsufficiency gene.

Statistical Analysis

Differences in clinical characteristics between the study groups were analyzed using a t-test for continuous variables and the chi-square test or Fisher exact test for categorical variables. $P < 0.05$ was considered statistically significant. Statistical analyses were conducted using SPSS software version 20 (IBM, Armonk, NY).

RESULTS

Demographic and Clinical Characteristics

A total of 330 newborns were enrolled in this study. Among them, 69.1% (228/330) were male. The average birth weight was 2984 ± 781.1 g, and the average gestational age was 37.37 (± 3.03) weeks (±days). Eight patients had a family history of renal anomalies. Nine types of CAKUT were detected in this cohort. Congenital hydronephrosis was the most common CAKUT type (73.6%, 243/330), followed by anomalies of lower urinary tract (8.5%, 28/330), renal agenesis (6.4%, 21/330), polycystic kidney disease (6.1%, 20/330), renal duplication (4.8%, 16/330), renal dysplasia (4.8%, 16/330), crossed fused renal ectopia (4.5%, 15/330), MCDK (3.9%, 13/330) and ectopic kidney (3.3%, 11/330). Approximately 30.5% (118/330) of patients had extrarenal manifestations, with the cardiovascular system ranking first (45.8%, 54/118). The clinical characteristics of the included cases are summarized in Table 1 and detailed information is provided in Supplementary Table S1.

Genetic Diagnostic Yield

In our cohort, all patients underwent WES. Overall, diagnostic findings were identified in 61 of 330 patients (18.5%); 35 patients had pathogenic or likely pathogenic SNVs, 25 had CNVs, and 1 patient had both an SNV and a CNV (Figure 1). The manifestation rate (CAKUT with extrarenal manifestations, see details in the "Methods" section above) was higher in the diagnosed group (34/61, 55.7%; $P < 0.001$) than in the undiagnosed group (84/269, 31.2%). However, there were no other significant differences in the major clinical features between the diagnosed and undiagnosed groups (Table 1). Notably, patients with CAKUT with extrarenal manifestations (especially congenital heart diseases) strongly suggested a genetic etiology. Furthermore, patients with CAKUT and cardiovascular deformities had the highest diagnostic rate (42.6%, 23/54), followed by those with facial deformities (38.7%, 12/31).

Monogenic Disease Spectrum

In total, 45 pathogenic or likely pathogenic SNVs in 30 genes were identified in 35 patients (10.6%) (Supplementary Table S2). The inheritance modes of the 30 detected genes were autosomal dominant (13/30, 43.3%), autosomal recessive (10/30, 33.3%), autosomal dominant or recessive (4/30, 13.3%), X-linked dominant (1/30, 3.3%), and X-linked dominant or recessive (2/30, 6.7%). Half of the detected genes were associated with syndromic disorders (15/30, 50.0%) (Supplementary Table S4).

Table 1. Demographic and clinical characteristics of study CAKUT population

Characteristics	All (n = 330)	Diagnosed (n = 61)	Undiagnosed (n = 269)	P-value
Sex				0.203
Male, n (%)	228 (69.1%)	38 (62.3%)	190 (70.6%)	
Female, n (%)	102 (30.9%)	23 (37.7%)	79 (29.4%)	
Birth Weight, mean ± SD (n)	2984 ± 781.1 (293)	2954 ± 743.8 (50)	2990 ± 788.5 (243)	0.767
Gestational age, mean ± SD (n)	37.37 ± 3.03 (272)	37.52 ± 2.65 (46)	37.34 ± 3.09 (226)	0.713
CAKUT family history[a]				0.041
Yes, n (%)	8 (2.4%)	4 (6.6%)	4 (1.5%)	
No, n (%)	322 (97.6%)	57 (93.4%)	265 (98.5%)	
CAKUT phenotypes,[b] n (%)				
Congenital hydronephrosis	243 (73.6%)	43 (70.5%)	200 (74.3%)	0.537
Polycystic kidney disease	20 (6.1%)	3 (4.9%)	17 (6.3%)	> 0.999
Renal agenesis	21 (6.4%)	1 (1.6%)	20 (7.4%)	0.143
Renal duplication	16 (4.8%)	3 (4.9%)	13 (4.8%)	> 0.999
Renal dysplasia	16 (4.8%)	3 (4.9%)	13 (4.8%)	> 0.999
Crossed fused renal ectopia	15 (4.5%)	2 (3.3%)	13 (4.8%)	> 0.999
Multicystic dysplastic kidney	13 (3.9%)	5 (8.2%)	8 (3.0%)	0.071
Ectopic kidney	11 (3.3%)	1 (1.6%)	10 (3.7%)	0.696
Anomalies of lower urinary tract[c]	28 (8.5%)	5 (8.2%)	23 (8.6%)	> 0.999
Extrarenal manifestations, n (%)[d]	118/330 (35.8%)	34/61 (55.7%)	84/269 (31.2%)	< 0.001
Special face feature	31/118 (26.3%)	12/34 (35.3%)	19/84 (22.6%)	0.157
Cardiovascular system	54/118 (45.8%)	23/34 (67.6%)	31/84 (36.9%)	0.002
Neurologic system	12/118 (10.2%)	3/34 (8.8%)	9/84 (10.7%)	> 0.999
Digestive system	32/118 (27.1%)	8/34 (23.5%)	24/84 (28.6%)	0.577
Respiratory system	7/118 (5.9%)	1/34 (2.9%)	6/84 (7.1%)	0.672
Musculoskeletal system	33/118 (28.0%)	7/34 (20.6%)	26/84 (31.0%)	0.256
Reproductive system	15/118 (12.7%)	3/34 (8.8%)	12/84 (14.3%)	0.549

CAKUT, congenital anomalies of the kidney and urinary tract.
[a]Postive family history was defined as any family member with urinary structural abnormalities.
[b]One patient may have more than 1 clinical features.
[c]Anomalies of lower urinary tract include obstruction of ureteropelvic junction, ureterovesical junction obstruction, vesicoureteral reflux, posterior urethral valves, cystoschisis, megaloureter, ureterocele and hypospadias.
[d]Patent foramen ovale was excluded in manifestations of cardiovascular system as it is very common in neonatal period.

In this cohort, the variants detected in 2 or more patients were *KMT2D* and *PTPN11*, accounting for 20.0% (7/35) of the 35 patients with SNVs. *KMT2D*, the pathogenic gene of Kabuki syndrome was detected in 5 patients along with polycystic kidney disease, MCDK, ectopic kidney, and horseshoe kidney disease. All *KMT2D* variants were deleterious (frameshift, nonsense, and microdeletion). Facial deformity was observed in 40% (2/5) of patients, and congenital heart disease was observed in 60% (3/5) (Table 2).

CNV Spectrum

We detected 29 CNVs in 25 patients (25/330, 7.6%), including 16 deletions and 13 duplicates (Supplementary Table S3, Figure 2). Four patients exhibited deletions in

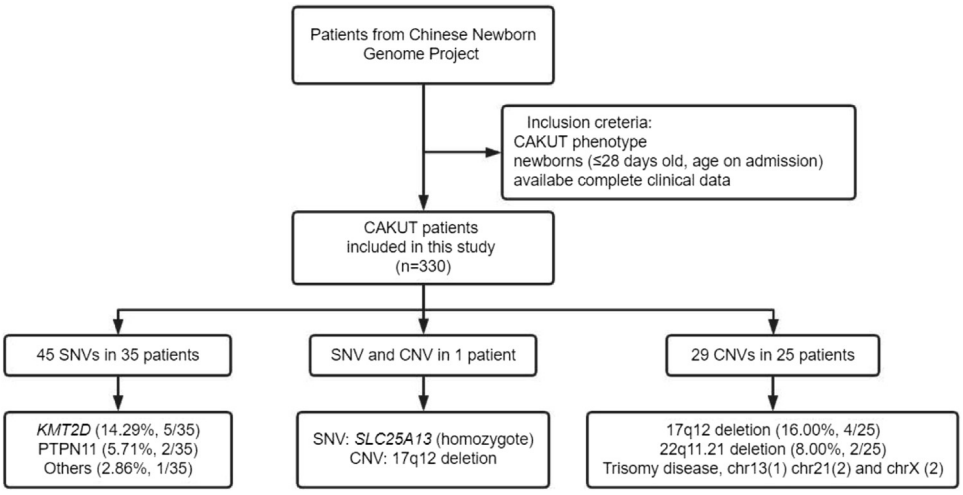

Figure 1. Flow diagram of recruitment and analysis of patients with CAKUT. CAKUT, congenital anomalies of the kidney and urinary tract.

Table 2. The clinical information and genetic diagnosis among 5 patients with a *KMT2D* variant

ID	Sex	Diagnosed age	Variant	HGMD	Zygosity	Inheritance	CAKUT phenotype	Head	Cardiovascular system	Others
72	M	16 d	c.13895delC (p.P4632HfsTer8)	DM	Het	*De novo*	Polycystic kidney (right)	Micrognathia, frontal bossing	Secundum atrial septal defect (0.45 cm), patent ductus arteriosus	Neonatal hypoglycemia, intracranial hemorrhage
104	M	11 d	c.16489_16470delAA (p.K5490RfsTer21)	DM	Het	*De novo*	Multicystic dysplastic kidney (right)	N	N	Respiratory failure
167	F	4 d	c.12809dupA (p.T4271Dfs*63)	Novel	Het	*De novo*	Ectopic kidney (right)	N	Coarctation of aorta	Congenital hypothyroidism, neonatal hypoglycemia
250	M	26 d	c.1961_1962delinsA (p.S654YfsTer276)	Novel	Het	NA	Horseshoe kidney	Congenital external ear malformation, cleft palate	Congenital heart disease	Neonatal hypoglycemia, neonatal seizure
283	M	Prenatal	c.15148_15156delCTGAACCTG (p.L5050_L5052del)	Novel	Het	NA	Horseshoe kidney	N	Atrial septal defect (0.38 cm), patent ductus arteriosus, persistent superior vena cava, tricuspid regurgitation	Congenital hypothyroidism, anorectal malformation, brachydactyly

CAKUT, congenital anomalies of the kidney and urinary tract; d, day; DM, disease-causing mutation; F, female; Het, heterozygous; HGMD, Human Gene Mutation Database; M, male; N, No; NA, not available.

17q12, which contains the *HNF1B* gene. Congenital hydronephrosis and polycystic kidney were observed in patients with CAKUT with deletions in 17q12. Deletion of 22q11.21, duplication of chromosome 21, and duplication of chromosome X were detected in more than 1 patient. Both CNVs and SNVs were detected in patient 110, and ultrasonography of their uropoietic system indicated congenital hydronephrosis (caused by ureteropelvic junction obstruction). The patient carried a deletion in 17q12. Furthermore, neonatal intrahepatic cholestasis was discovered in patient 110 and a homozygous variant of *SLC25A13* may account for his phenotype.

Proportion of Genetic Disorders With Specific Treatment

The molecular diagnoses made using the medical exome directly affected medical management in 22 of the 61 patients (36.1%) after the results were reported (Supplementary Table S5). Seventeen patients underwent multidisciplinary treatment and disease-specific follow-up, which created opportunities to detect

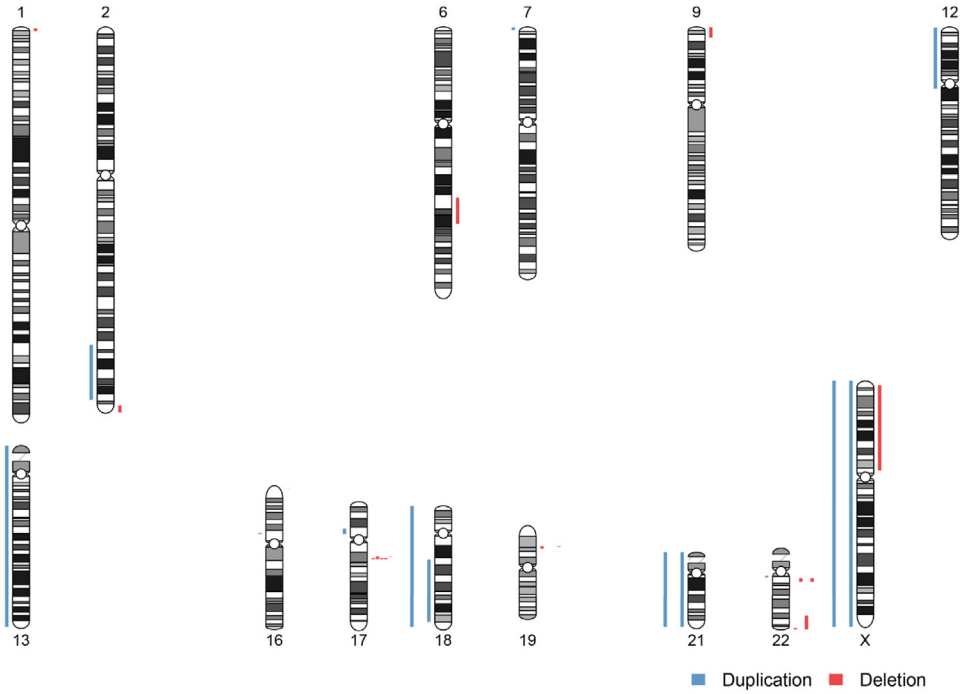

Figure 2. Distribution of copy number variants in this study. Duplications are presented in blue and on the left of the chromosome. Deletions are presented in red and on the right of the chromosome. The length of the bar represents the size of each duplication or deletion in proportion to the size of the chromosome.

complications that could not be foreseen. For example, 2 probands with 17q12 deletion (chromosome 17q12 deletion syndrome, OMIM: 614527) had a chief complaint of CAKUT; however, the genetic diagnosis also suggested extrarenal complications: patient 127 exhibited delayed myelination and intellectual disability, and patient 173 exhibited congenital heart disease. In addition to targeting multisystem assessment at an early stage, molecular diagnoses were also instructive and meaningful for treatments. For example, Patient 235, detected with a variant in *NPHP3* (Meckel syndrome, OMIM: 267010) was recommended to undergo kidney transplantation surgery at an early stage, because Meckel syndrome is regarded as a lethal disease that may result in severe extrarenal complications. In addition to the potential effect on proband clinical management, 3 families with a definitive molecular diagnosis underwent prenatal diagnosis based on the proband genetic findings (ID 88, 89 and 210). Furthermore, patient 194, who exhibited a variant in *PKD2* (OMIM: 613095), underwent long-term follow-up. A follow-up visit to the adult nephrology department was also recommended for his mother because polycystic kidney disease is an autosomal dominant genetic disorder.

DISCUSSION

Genetic variants account for 5% to 20% of CAKUT cases.[35] The inconsistency in genetic diagnosis rates among different studies might be due to the lack of consensus on the inclusion/exclusion criteria.[7,11] Studies have used WES in large cohorts to identify the genetic background associated with CAKUT, most of which have focused on the antenatal and childhood period.[23,36–39] The present study used WES to investigate the genetic etiology of CAKUT in 330 newborns. Genetic diagnoses were confirmed in 61 newborns with CAKUT (18.5%, 61/330).

No consensus has been reached regarding which patients with CAKUT are more likely to harbor genetic variants. Here, we found that patients with CAKUT and extrarenal manifestations, especially those with cardiovascular complications, were more likely to exhibit genetic findings. Jiang *et al.*[40] found that the incidence of CAKUT in patients with congenital heart disease was significantly higher than that in the general population. Furthermore, a recent study in mice indicated a significant overlap in the genetic etiology of congenital heart disease and congenital kidney abnormalities, suggesting that many variants that cause heart defects also cause renal anomalies.[41] Although there was a statistically significant difference ($P < 0.05$) between the groups with positive and negative family histories, more cases are needed to confirm this result. CAKUT is reported to segregate within families (approximately 10%–25%).[42]

Currently, more than 50 single-gene disorders underlying isolated and syndromic CAKUT have been identified.[43,44] The complex phenotypes of CAKUT may result from disruptions in transcription factors or signaling molecules[45,46] and spatiotemporal interactions between the outgrowing ureteric bud and the metanephric mesenchyme. Detrimental SNVs were detected in 31 genes in our study. Consistent with previous studies,[43] most detected variants were autosomal dominant and occurred *de novo*. Interestingly, we found that *KMT2D*, the pathogenic gene of Kabuki syndrome was the most commonly detected gene in 5 patients. Although CAKUT is a known manifestations of Kabuki syndrome, studies focusing solely on kidney involvement are scarce, and its prevalence is most likely underestimated.[47] Therefore, pediatric nephrotic assessment is warranted as part of the routine multidisciplinary evaluation of patients diagnosed with Kabuki syndrome. However, many of the identified variants were unique to a single patient, and whether the results can be replicated in other cohorts remains to be confirmed. Therefore, it is of prime importance to combine the above-mentioned results with functional validation to understand the genomic landscape of CAKUT.

Despite the identification of hundreds of candidate genes, CAKUT cannot be attributed to a monogenic cause in >80% of cases,[11,48] suggesting that CNVs are also important contributors to CAKUT, because they are always combined with complex extrarenal phenotypes. In this study, we identified CNVs in 8.2% (27/330) of patients. The detected CNV sizes varied widely, ranging from a small deletion that included only a renal-related gene (such as *HNF1B*, *TBX6*, *CRKL*, or *PKD1*) to a large duplication related to trisomy. Most CNVs were associated with various syndromes, whereas renal symptom was part of their phenotypic spectrum. Previous studies suggested that the most frequently identified genomic disorder was 17q12 deletion, indicating renal cyst and diabetes syndrome, 22q11.2 deletion, indicating the DiGeorge syndrome, and 1q21 deletion.[14] Consistent with previous reports, the most common CNV in our cohort was 17q12 deletion. These findings expand the CNV spectrum of patients with CAKUT.

Patients with CAKUT are at risk of ignoring severe chronic kidney disease, as well as overtreatment of relatively mild kidney disease, which places a great burden on their families and society.[49] Genetic diagnoses in the early stages of the diagnostic trajectory are beneficial to patients and their caregivers, resulting

in a considerably shorter and less complicated diagnostic process through proper clinical management.[43,50] However, translation to care for patients with CAKUT has been slow because of the paucity of knowledge related to the clinical actionability of identified variants.[49,51] Therefore, it is necessary to devise and implement standardized, evidence-based approaches to accurately characterize the clinical actionability of genomic findings, which is particularly important for CAKUT. In this study, 22 (36.1%, 22/61) patients with diagnostic genetic results may benefit from molecular diagnosis and altered clinical management (including early multidisciplinary treatment, disease-specific follow-up, and familial genetic counseling). In our previous study,[25] we analyzed the genes that progressed to kidney failure in a childhood cohort and found that patients carrying *PAX2*, *TNXB*, *EYA1*, *HNF1B*, or *GATA3* variants or with the 48, XXYY karyotype had a shorter predicted kidney survival. In the future, we will continue to follow-up with the neonatal CAKUT cohort to verify the above findings and provide more robust conclusions.

Our study has several limitations in providing an accurate understanding of the genetic landscape of CAKUT. First, we did not present secondary findings. Our research group previously published an article demonstrating the detection of secondary findings in neonates from the China Neonatal Genomes Project.[52] In the future, we plan to continue exploring secondary findings in all neonates enrolled in the China Neonatal Genomes Project cohort. Second, our study cohort which consisted of newborns who were hospitalized in the neonatal intensive care unit and lacked complete maternal obstetric examination information, and genetic findings, based on hospitalized CAKUT newborns, may not extend to the general CAKUT population without larger sample sizes and more systematic design.

To the best of our knowledge, this is the first large-scale multicenter Chinese cohort of newborn CAKUT tested using WES, which is more representative of the Chinese population. This study provides an in-depth understanding of clinical utility. However, this study had several limitations. More follow-up data should be collected to confirm the long-term efficacy of genetic tests. Moreover, these results need to be combined with functional validation of sequence variants to understand the genomic landscape of CAKUT.

DISCLOSURE

The authors declared no competing interests.

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SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Table S1. Detailed clinical profile of the Chinese CAKUT cohort.

Table S2. List of SNVs identified in the Chinese CAKUT cohort.

Table S3. List of CNVs identified in the Chinese CAKUT cohort.

Table S4. The OMIM diseases and multiple organs or systems involved for syndromic genes.

Table S5. Specific Treatments for molecular diagnosed patients in the Chinese CAKUT cohort.

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