ORIGINAL ARTICLE

Association between the clinical presentation of congenital anomalies of the kidney and urinary tract (CAKUT) and gene mutations: an analysis of 66 patients at a single institution

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Abstract

Background The association between the clinical presentation of congenital anomalies of the kidney and urinary tract (CAKUT) and gene mutations has yet to be fully explored.

Methods In this retrospective cohort study, we examined patients with CAKUT who underwent gene analysis. The analysis was performed in patients with bilateral renal lesions, extrarenal complications, or a family history of renal disease. The data from the diagnosis, gene mutations, and other complications were analyzed.

Results In total, 66 patients with CAKUT were included. Of these, gene mutations were detected in 14 patients. Bilateral renal lesions were significantly related to the identification of gene mutations ($p = 0.02$), and no gene mutations were observed in patients with lower urinary tract obstruction (six patients). There was no significant difference in the rate of gene mutations between those with or without extrarenal complications ($p = 0.76$). The $HNF1\beta$ gene mutation was identified in most of the patients with hypodysplastic kidney with multicystic dysplastic kidney (six of seven patients). There was no significant difference in the presence or absence of gene mutations with respect to the renal survival rate (log-rank test $p = 0.53$). The renal prognosis varied, but the differences were not statistically significant for any of the gene mutations.

Conclusions CAKUT with bilateral renal lesions were significantly related to gene mutations. We recommend that CAKUT-related gene analysis be considered in cases of bilateral renal lesions. No gene mutations were observed in patients with lower urinary tract obstruction. The renal prognosis varied for each gene mutation.

Keywords CAKUT (congenital anomalies of the kidney and urinary tract) · Children · CKD (chronic kidney disease) · ESKD (end-stage kidney disease) · Gene mutation

Abbreviations

aCGH	Array-based comparative genome hybridization
BOR	Branchio-oto-renal
CAKUT	Congenital anomalies of the kidney and urinary tract
CKD	Chronic kidney disease
ESKD	End-stage kidney disease
MCDK	Multicystic dysplastic kidney
MLPA	Multiplex ligation-dependent probe amplification
NGS	Next-generation sequencing
VUR	Vesicoureteral reflux

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Introduction

Congenital anomalies of the kidney and urinary tract (CAKUT) cover a wide range of structural malformations resulting from defects in the morphogenesis of the kidney and/or urinary tract. CAKUT account for 20 to 30% of all

congenital anomalies [1] and has an incidence of three to six in 1000 births [2]. CAKUT are the leading cause of chronic kidney disease (CKD), accounting for 40–50% and 62.2% of pediatric CKD cases worldwide [3] and in Japan [4], respectively, and account for 39.8% of end-stage kidney disease (ESKD) cases in pediatric patients [5].

The mechanism of CAKUT onset has been studied [6]. However, despite the large number of studies done on the epidemiology of gene mutations in CAKUT, the association between its clinical presentations and gene mutations is still unknown. Clarifying the relationship between the clinical presentation of patients with CAKUT and the underlying gene mutations is vital to identifying patients with CAKUT for whom gene analysis should be performed.

Herein, we analyzed the clinical presentation of patients with CAKUT whose gene mutations were analyzed with the aim of clarifying the characteristics of these patients.

Materials and methods

Study design and participants

This was a retrospective cohort study of patients with CAKUT who were treated at the National Center for Child Health and Development between June 2002 and June 2018. In this study, the CAKUT cases included hypodysplastic kidney including oligomeganephromia, multicystic dysplastic kidney (MCDK), hydronephrosis, unilateral renal agenesis, cystic dysplasia, and lower urinary tract obstruction. Patients with vesicoureteral reflux (VUR) alone, and those with chromosome aberrations were not included. We analyzed gene mutations in CAKUT patients with bilateral renal lesions, extrarenal complications, or a family history of renal disease. The data pertaining to the diagnosis, gene mutations, and other complications were extracted from the medical records.

Genetic testing

All gene analyses were performed at Kobe University after written informed consent was obtained from patients' family. Gene mutations were identified using different methods, including single-gene screening, multiplex ligation-dependent probe amplification (MLPA) assay, array-based comparative genome hybridization (aCGH), gene panel, and next-generation sequencing (NGS). We performed aCGH using the SurePrint G3 Human CNV microarray 400 K kit (Agilent Technologies, Santa Clara, CA, USA) according to the manufacturer's instructions. For library preparation for NGS, we used commercially available targeted resequencing

kits, the HaloPlex Custom Kit (Agilent Technologies, Santa Clara, CA, USA), and the TruSight One Sequencing Panel (Illumina, San Diego, CA, USA) on a MiSeq platform (Illumina). For the MLPA assay, we used the P153 kit. For data analysis, we used VariantStudio ver. 2.2.1 (Illumina) and Integrative Genomics Viewer software ver. 2.3.57 (Broad Institute, Cambridge, MA, USA). Gene mutations were confirmed by standard Sanger sequencing using the 3130 genetic analyzer (Thermo Fisher Scientific, Waltham, MA, USA). Sanger sequencing data were analyzed using the CLC main workbench ver. 6.7.1 (QIAGEN, Hilden, Germany). The allele frequency in the population is available in the Single Nucleotide Polymorphism Database (dbSNP, http://www.ncbi.nlm.nih.gov/SNP/) and the Human Genome Variation Database (HGVD, http://www.genome.med.kyoto-u.ac.jp/SnpDB/index.html?) for the Japanese population. To predict splicing abnormalities, we used human splicing finder (HSF) version 3.0 (http://www.umd.be/HSF3/).

Definitions

The definitions used in the data collection were as follows.

ESKD was defined as the stage of a kidney disease at which renal replacement therapy or renal transplantation is required. Syndromic CAKUT were defined as CAKUT with extrarenal complications, including optic nerve coloboma, ear fistula, pinna deformation, hearing loss, corneal opacity, and iris adhesion. Non-syndromic CAKUT were defined as CAKUT without extrarenal complications.
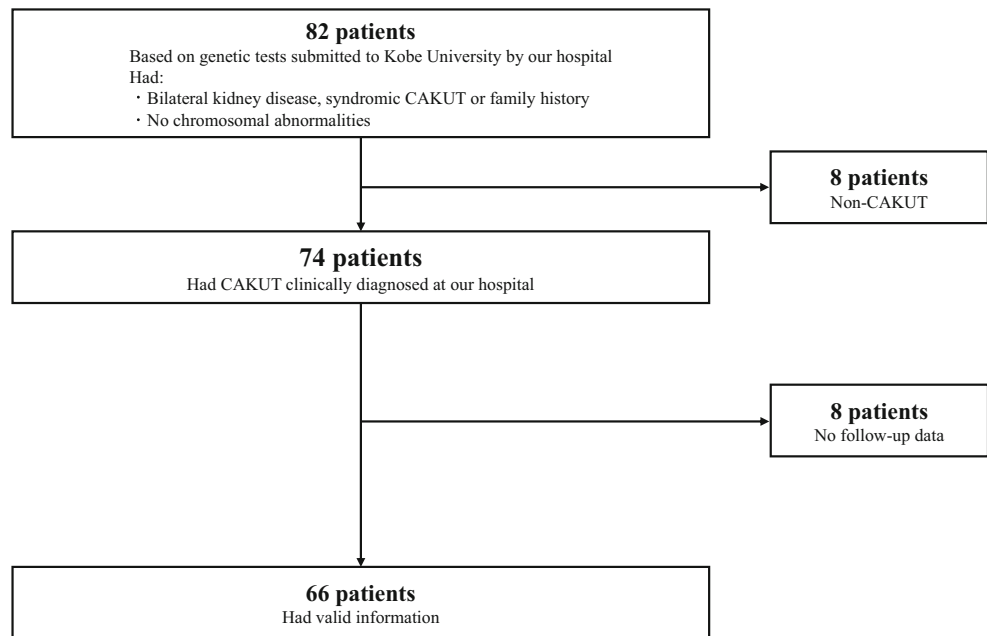
Statistical analysis

Time-to-event was calculated using Kaplan-Meier analysis to estimate renal survival, and comparisons were performed using the log-rank test. An event was defined as ESKD requiring dialysis or renal transplantation. All p values were two-sided and considered statistically significant if < 0.05. All statistical analyses were carried out using JMP version 14.0.0 (SAS Institute, Inc., Cary, NC, USA).

Results

Patients

A flow diagram of the study is shown in Fig. 1. Eighty-two patients received a gene mutation analysis. The cohort finally included 66 patients (50 males), whose background characteristics are shown in Table 1. The patients were divided into those with and those without a gene mutation. In addition, the following data were collected: sex, the presence of renal lesions, extrarenal complications, types of renal lesion, preterm, and low body weight.

Fig. 1 Study design and participants CAKUT, congenital anomalies of the kidney and urinary tract

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┌─────────────────────────────────────────────────────────────┐
│                      82 patients                             │
│  Based on genetic tests submitted to Kobe University by our  │
│  hospital                                                    │
│  Had:                                                        │
│   · Bilateral kidney disease, syndromic CAKUT or family      │
│     history                                                  │
│   · No chromosomal abnormalities                             │
└─────────────────────────────────────────────────────────────┘
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                          │──────────────────────►  ┌──────────────┐
                          │                          │  8 patients  │
                          ▼                          │  Non-CAKUT   │
┌─────────────────────────────────────────────────┐ └──────────────┘
│                   74 patients                    │
│     Had CAKUT clinically diagnosed at our        │
│     hospital                                     │
└─────────────────────────────────────────────────┘
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                          │──────────────────────►  ┌──────────────────┐
                          │                          │   8 patients     │
                          ▼                          │  No follow-up    │
┌─────────────────────────────────────────────────┐ │  data            │
│                   66 patients                    │ └──────────────────┘
│           Had valid information                  │
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Gene mutations of patients

Among the 66 patients (50 males), 14 patients (21.2%) had a gene mutation suspected of being related to disease onset. The detected gene mutations were as follows: *HNF1β* (seven patients), *PAX2* (four patients), *Eya1* (one patient), *CHD7* (one patient), and *EP300* (one patient). The patients with the *HNF1β, PAX2, Eya1, CHD7,* and *EP300* gene mutations had the diagnosis of 17q12 deletion syndrome (patient nos. 1, 2, 4, 5, 6), renal coloboma syndrome (patient nos. 8, 9, 10), branchio-oto-renal (BOR) syndrome (patient no. 12) [7], CHARGE syndrome (patient no. 13) or type 2 Rubinstein-Taybi syndrome (patient no. 14), respectively. The characteristics of the 14 patients are shown in Table 2.

Table 1 Background characteristics of the patients

Patient characteristics	Gene mutation group (n = 14)	Non-gene mutation group (n = 52)	All (n = 66)
Sex			
Male	9 (64.3)	41 (78.8)	50 (75.8)
Female	5 (35.7)	11 (21.2)	16 (24.2)
Renal lesions			
Bilateral	13 (92.9)	30 (57.7)	43 (65.2)
Unilateral	1 (7.1)	22 (42.3)	23 (34.8)
Extrarenal complications			
Syndromic	7 (50.0)	22 (42.3)	29 (43.9)
Non-syndromic	7 (50.0)	30 (57.7)	37 (56.1)
Hypodysplastic kidney	12 (85.7)	24 (46.2)	36 (54.5)
MCDK	7 (50.0)	17 (32.7)	24 (36.4)
Hydronephrosis	0 (0.0)	8 (15.4)	8 (12.1)
Unilateral renal agenesis	4 (28.6)	5 (9.6)	9 (13.6)
Cystic dysplasia	1 (7.1)	2 (3.9)	3 (4.6)
Lower urinary tract obstruction	0 (0.0)	6 (11.5)	6 (9.1)
VUR	5 (35.7)	14 (26.9)	19 (28.8)
Preterm (< 37 week)	2 (14.3)	5 (9.6)	7 (10.6)
Low body weight (< 2500 g)	5 (35.7)	9 (17.3)	14 (21.2)

All data are shown as *n* (%)

MCDK multicystic dysplastic kidney, *VUR* vesicoureteral reflux

Table 2 Characteristics of 14 patients with CAKUT-related gene mutations

ID	Gene	Age (years)	Sex	Renal lesion	Extrarenal lesion	Nucleotide change	Amino acid change	Method	Diagnosis	Renal outcome
1	HNF1β	0.5	M	Right dysplastic kidney Left MCDK	–	HNF1β heterozygous total deletion		MLPA	17q12 deletion syndrome	PD
2	HNF1β	2	M	Right MCDK Left hypodysplastic kidney	Intellectual disability	HNF1β heterozygous total deletion		MLPA	17q12 deletion syndrome	CKD stage3
3	HNF1β	2	F	Right dysplastic kidney Left MCDK	–	c.865A > C	p.Asn289His	Sanger	–	CKD stage3
4	HNF1β	11	F	Right MCDK Left hypoplastic kidney	–	HNF1β heterozygous total deletion		aCGH	17q12 deletion syndrome	Normal
5	HNF1β	13	M	Right MCDK	ADHD	HNF1β heterozygous total deletion		aCGH	17q12 deletion syndrome	Normal
6	HNF1β	14	F	Right dysplastic kidney Left MCDK	ASD, liver dysfunction, hypomagnesemia	HNF1β heterozygous total deletion		Sanger	17q12 deletion syndrome	Normal
7	HNF1β	17	M	Bilateral polycystic and hypoplastic kidney	Bladder tumor	c.130G > T	p.Glu44*	Sanger	–	CKD stage2
8	PAX2	7	M	Right hypoplastic kidney Left aplastic kidney	Optic nerve coloboma	c.344G > C	p.Arg115Pro	Sanger	Renal coloboma syndrome	CKD stage2
9	PAX2	11	M	Bilateral hypoplastic kidney	Optic nerve coloboma	c.70_72delinsA	p.Gly24Argfs*29	Sanger	Renal coloboma syndrome	Transplantation
10	PAX2	15	F	Bilateral hypoplastic kidney	Optic nerve coloboma	c.832C > T	p.Gln278*	Sanger	Renal coloboma syndrome	Transplantation
11	PAX2	30	F	Right aplastic kidney Left hypoplastic kidney	–	c.76dup	p.Val26Glyfs*28	Sanger	–	Transplantation
12	EYA1	17	M	Right aplastic kidney Left renal cyst	Ear fistula, pinna deformation, hearing loss	rsa 8q13.3 (EYA1 exon 12) ×1		MLPA	BOR syndrome	CKD stage2
13	CHD7	21	M	Right renal cyst Left aplastic kidney	Intellectual disability, hearing loss, retinal coloboma, bilateral cryptorchidism	arr[GRCh37]8q12.1q12.3 (61100205_64921214) ×1		aCGH	CHARGE syndrome	Normal
14	EP300	10	M	Bilateral hypoplastic kidney	Corneal opacity, iris adhesion	c.4296_4297delAG		TruSight Exome	type 2 Rubinstein-Taybi syndrome	CKD stage3

Reference genome; *HNF1B*, NM_000458.3; *PAX2*, NM_000458.3; *PAX2*, NM_003990.4; *EP300*, NM_001429

CAKUT congenital anomalies of the kidney and urinary tract, *M* male, *MCDK* multicystic dysplastic kidney, *MLPA* multiplex ligation-dependent probe amplification, *PD* peritoneal dialysis, *CKD* chronic kidney disease, *F* female, *aCGH* array-based comparative genome hybridization, *ADHD* attention deficit hyperactivity disorder, *ASD* Autism spectrum disorder, *BOR* branchio-oto-renal

Characteristic of patients with CAKUT-related gene mutations

Nine of 50 (18.0%) males and 5 of 16 (31.3%) females ($p = 0.30$) had a gene mutation. The detection rate of gene mutations was 30.2% for the bilateral renal lesion group and 4.4% for the unilateral renal lesion group ($p = 0.02$). Gene mutations were detected in 7 of 29 (24.1%) patients in the syndromic CAKUT group and in 7 of 37 (18.9%) patients in the non-syndromic CAKUT group ($p = 0.76$). In seven patients with hypodysplastic kidney with MCDK, six patients had the *HNF1β* gene mutation (one patient had no gene mutation). None of the six patients with lower urinary tract obstruction had a gene mutation.

Extrarenal lesions and complications of each gene mutation

Ten of 14 patients with CAKUT-related gene mutations had extrarenal lesions and complications. Of the patients with the *HNF1β* gene mutation, patient no. 6 had a liver dysfunction and hypomagnesemia, and patient nos. 2, 5, and 6 had a neurodevelopmental disorder. Patient nos. 8, 9, and 10 with a *PAX2* gene mutation had optic nerve coloboma. Details of other extrarenal lesions and complications of each gene mutation are shown in Table 2.

Renal survival

Ten-year renal survival was 75.0% and 70.3% for the gene mutation group and the non-gene mutation group, respectively ($p = 0.53$). Renal survival in the gene mutation and non-gene mutation group is shown in Fig. 2. Ten-year renal survival was 85.7% for the *HNF1β* gene mutation group, 37.5% for the *PAX2* gene mutation group, and 100% for the other gene mutation group ($p = 0.08$). Renal survival for each gene mutation group is shown in Fig. 3. No patients died during the median period of 9.9 years.

Discussion

In this retrospective cohort study of 66 patients who underwent CAKUT-related gene analysis, CAKUT with bilateral renal lesions were found to be significantly related to the identification of gene mutations. In contrast, no gene mutations were detected in patients with lower urinary tract obstruction. There was no significant difference in the rate of gene mutations between patients with or without extrarenal complications. The *HNF1β* gene mutation was detected in most of the patients with hypodysplastic kidney with MCDK (six of seven patients). To our knowledge, this is the first cohort study to describe the association between the clinical presentations of CAKUT and gene mutations.
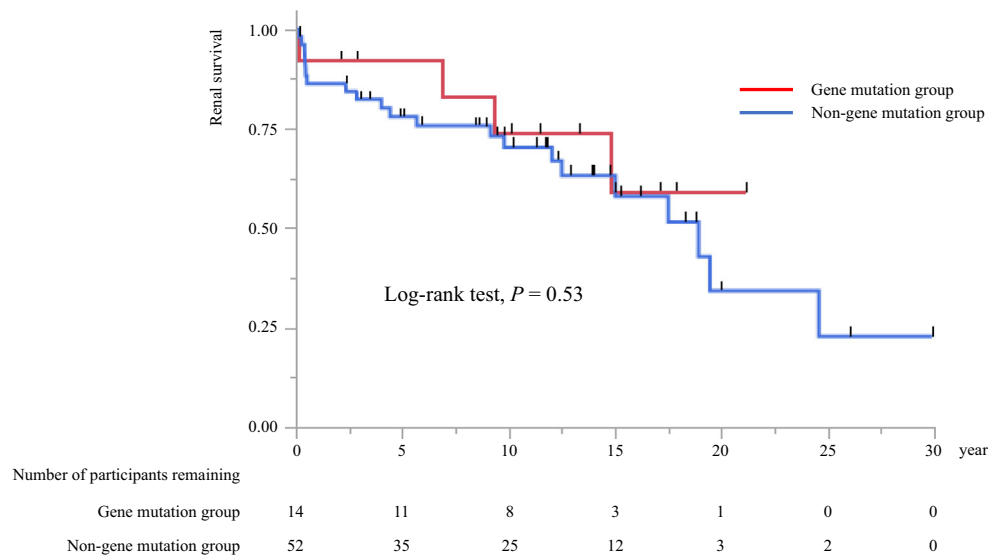
Among the patients with bilateral renal lesions, syndromic CAKUT, or a family history of renal disease, the gene mutation detection rate was significantly higher in patients with bilateral renal lesions. In total, 66 patients with CAKUT were included in the present study. Of these, a gene mutation was detected in 14 patients (21.2%). Thus far in medical research, the detection rate of gene mutations has been very low, partly due to the multifactorial pathogenesis of CAKUT, which includes environmental factors [8]. Hwang et al. in the USA exhaustively analyzed 17 causative genes in 657 CAKUT cases and identified gene mutations in 6.7% of these [9]. In a similar comprehensive analysis in Europe, Nicolaou et al. analyzed 208 gene mutations in 453 CAKUT cases but were able to identify only six cases (1.3%) in which the mutations were able to be determined as the cause of the disease [10]. In comparison with these studies, the detection rate in our study was higher, despite the smaller number of patients in our cohort. Based on these findings, gene analysis for patients with CAKUT should be restricted to those with specific clinical characteristics, including bilateral lesions.

None of the gene mutations were able to be detected in patients with lower urinary tract obstruction, suggesting that the renal lesions associated with this condition are not caused primarily by the mutations themselves but are secondary changes accompanying lower urinary tract obstruction, even in cases of bilateral renal lesions. There are no previous reports of lower urinary tract obstruction or CAKUT-related gene mutations. Among the anomalies constituting CAKUT, lower urinary tract obstruction is a major cause of CKD and ESKD and accounts for 17% of CKD cases and 20 to 40% of ESKD cases in Europe and America [11, 12]. Early diagnosis and treatment are therefore important. The absence of CAKUT-related gene mutations in cases of lower urinary tract obstruction constitutes a new finding.

There was no significant difference in the detection rate of gene mutations in relation to the presence or absence of extrarenal complications in this study. This finding suggests that gene mutations occur in a certain proportion of non-syndromic CAKUT patients. Stoll et al. reported that syndromic CAKUT comprised 34% of all CAKUT cases [13] and that the majority were non-syndromic CAKUT cases. Despite this finding, the detection rate of gene mutations in non-syndromic CAKUT patients is extremely low [9]. Our findings suggest that gene analysis for patients with non-syndromic CAKUT should be done for patients with other complications such as bilateral renal lesions.

In 14 patients with gene mutations, 7 had *HNF1β* gene mutations, the most common type of mutation. It is worth noting that most patients with hypodysplastic kidney with MCDK had this gene mutation. The *HNF1β* gene mutation has been reported in variety of individuals with renal

Fig. 2 Renal survival: the gene mutation and non-gene mutation group

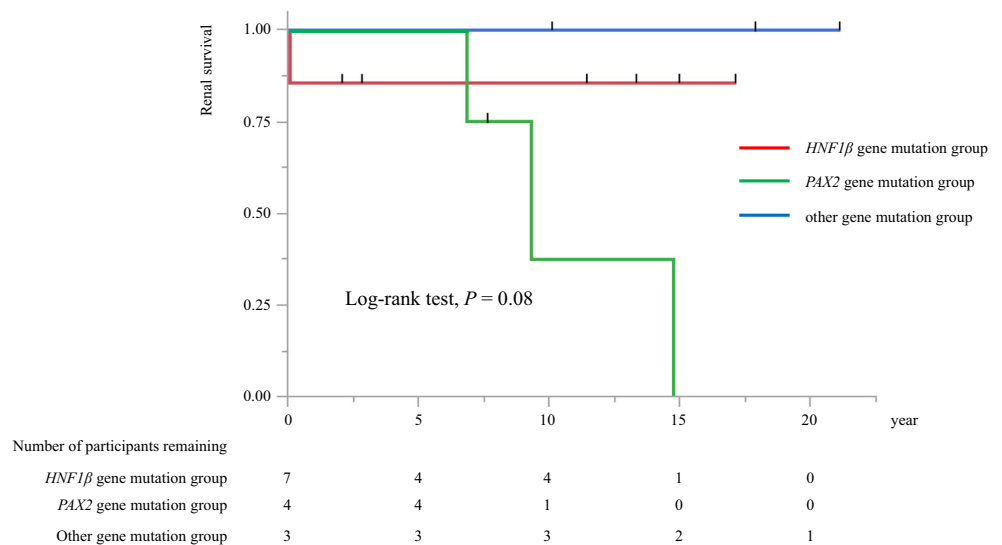| Number of participants remaining						
	0	5	10	15	20	25	30
Gene mutation group	14	11	8	3	1	0	0
Non-gene mutation group	52	35	25	12	3	2	0

malformations, such as hypodysplastic kidney, MCDK, renal cyst, aplastic kidney, and oligomeganephronia [14–17]. Furthermore, bilateral renal lesions reportedly tend to occur in association with the *HNF1β* gene mutation [18]. Ulinsli et al. analyzed 80 children who presented with multicystic dysplasia, isolated renal cysts, hypo/dysplastic kidneys, and single kidney. In this study, the use of two sonographic characteristics, the detection of bilateral renal abnormalities and the presence of cysts, enabled the detection of children with renal morphologic abnormalities with a positive predictive value of 64% (100% sensitivity and 66% specificity). The findings suggest that *HNF1β* gene mutations are an important genetic anomaly related to renal cystic dysplasia [14]. These results, including ours, suggest that the *HNF1β* gene mutation should be considered as a possibility in any type of CAKUT, particularly if hypodysplastic kidney with MCDK is present.

In seven patients with an *HNF1β* gene mutation, five had *HNF1β* heterozygous total deletion and received the diagnosis of 17q12 deletion syndrome. The presence of 17q12 deletion syndrome reportedly complicates diabetes, pancreatic exocrine deficiency, hypomagnesemia, gout, genital tract malformations, liver dysfunction, and neurodevelopmental disorder [19]. In fact, in this study, one patient had a liver dysfunction and hypomagnesemia, and three patients had a neurodevelopmental disorder. These findings indicate that the phenotype varied widely among individuals with the same mutation, and detailed evaluation of these complications is required in each patient.

Among CAKUT patients, the renal survival rate was not significantly different between the gene mutation and non-gene mutation group, suggesting that it is not the presence or absence of gene mutations, but rather the degree of hypodysplasia as seen on renal ultrasound, which impacts renal

Fig. 3 Renal survival: comparison of gene mutation groups

Number of participants remaining					
	0	5	10	15	20
HNF1β gene mutation group	7	4	4	1	0
PAX2 gene mutation group	4	4	1	0	0
Other gene mutation group	3	3	3	2	1

survival. In contrast, as shown in Table 2, the renal survival rate was favorable but renal outcome differed in those with the *HNF1β* gene mutation while it was poor in those with the *PAX2* gene mutation although the difference was not statistically significant. Because these two gene mutations generally have a high detection rate in non-syndromic CAKUT, they are primarily screened for in patients with CAKUT [20]. In non-syndromic CAKUT, mutations in the *HNF1β*, *PAX2*, *CHD1L*, *RET*, *SALL1*, *SOX17*, and *DSTYK* genes have been identified as causative [6]. In particular, *HNF1β* and *PAX2* mutations are relatively frequent, accounting for about 15% of severe CAKUT cases [21] and 10% of hypodysplastic kidney cases [22, 23]. Knowing the difference in the renal prognosis in relation to the gene mutations would therefore be useful for the treatment of some patients with CAKUT.

There are several limitations to our study. First, the gene analysis methods in our study inevitably changed widely due to the introduction of progressively newer methods during the lengthy study period. A detection rate and a proportion of each gene mutation may have been influenced by these changes. While these changes were unavoidable, the lengthy study period offered the advantage of allowing us to observe the renal prognosis over the long term. Second, because this study was done at a single institution, we were able to enroll only a small number of patients with a gene mutation. In particular, the difference in the renal prognosis for each gene mutation should be evaluated in larger cohorts. However, we were able to examine the clinical presentations of each patient in greater detail than would have been possible with a larger subject pool. Finally, the phenotype varied widely among individuals with the same mutation. Nonetheless, gene analysis enabled CAKUT to be differentiated from other congenital diseases, such as ciliopathy and renal tubular dysgenesis, which may require management different from that required for CAKUT. Furthermore, each gene mutation may be accompanied by extrarenal lesions which can be diagnosed based on the results of gene analysis.

In conclusion, CAKUT with bilateral renal lesions, especially in patients with hypodysplastic kidney with MCDK, were significantly associated with gene mutations. In contradistinction to this finding, no gene mutations were observed in patients with lower urinary tract obstruction. The *HNF1β* and *PAX2* mutations most frequently occurred in association with CAKUT, and the renal prognosis varied for each gene mutation. We recommend that gene analysis be considered for CAKUT patients with bilateral renal lesions. The findings of this study can help us identify patients with CAKUT for whom gene analysis should be performed, facilitate the prediction of renal outcomes, and contribute to the early detection of extrarenal complications.

Compliance with ethical standards The study was conducted in accordance with the ethical principles set out in the Declaration of Helsinki and the ethical guidelines for Medical and Health Research Involving Human Subject created of the Ministry of Health, Labour and Welfare in Japan. The study was approved by the ethics board of National Center for Child Health and Development (ID:1606).

Conflict of interest The authors declare that they have no conflict of interest.

Financial disclosure The authors have no financial relationships relevant to this article to disclose.

Informed consent Informed consent for participating in this study was not required in agreement with the above-mentioned guidelines. For individual gene analysis, informed consent was obtained from all individual participants or their parents.

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