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RESEARCH ARTICLE

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Detection of copy number disorders associated with congenital anomalies of the kidney and urinary tract in fetuses via single nucleotide polymorphism arrays

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Abstract

Background: While congenital anomalies of the kidney and urinary tract (CAKUT) constitute one-third of all congenital malformations, the mechanisms underlying their development are poorly understood. Some studies have reported an association between CAKUT and copy number variations (CNVs) in children and adults, but few have focused on chromosomal microarray analysis (CMA) findings in fetuses with CAKUT. Therefore, we aimed to perform a CMA on fetuses with CAKUT and normal karyotypes in the presence and absence of other structural anomalies.

Method: The study was conducted in 147 fetuses with CAKUT and normal karyotypes between January 2016 and January 2019 in the Fujian Provincial Maternal and Child Health Hospital. Single nucleotide polymorphism (SNP) analysis was performed using the Affymetrix CytoScan HD platform.

Results: The SNP array identified abnormal CNVs in 13 cases (8.8%): Six were pathogenic, and seven were variations of uncertain clinical significance (VOUS). The detection rate of abnormal CNVs in non-isolated CAKUT was higher than that in isolated CAKUT (22.7% vs 6.4%, P = .038). Within the abnormal CNV groups, the highest frequency of CNVs was identified in fetuses with polycystic kidney dysplasia (13.5%), followed by those with renal agenesis (10.5%).

Conclusion: SNP array is effective for identifying chromosomal abnormalities in CNVs in fetuses with CAKUT and normal karyotypes, and help counseling.

KEYWORDS
chromosomal abnormalities, congenital anomalies of the kidney and urinary tract, fetal, genetic counseling, single nucleotide polymorphism

The authors Meiying Cai and Na Lin are contributed equally to this article.

1 | INTRODUCTION

Congenital anomalies of the kidney and urinary tract (CAKUT) constitute one-third of all congenital malformations detected by ultrasonography.[1] CAKUT are present in three to six per 1000 live births and constitute 40%-50% of childhood chronic kidney disease cases.[2,3] Clinical manifestations of CAKUT may range from upper urinary tract conditions to phenotypes primarily affecting the lower urinary tract. CAKUT include diverse phenotypes such as hydronephrosis, renal agenesis, dysplastic kidney, duplex kidney, ectopic kidney, fused kidney, and ureteropelvic junction obstruction.[4]

Fetuses with CAKUT are the frequent causes of prenatal consultation. The etiologies causing congenital urinary abnormalities are still unknown due to the highly phenotypic heterogeneity and multifactorial genetic penetrance. Genetic predisposition plays a significant role in the pathogenesis of CAKUT.[4,5] So far, more than 40 genes have been associated with CAKUT.[6] Chromosomal microarray analyses (CMAs) have revealed the pathogenesis of neuropsychiatric disorders and craniofacial malformations.[7,8] Using CMA, some studies have also reported an association between CAKUT and copy number variations (CNVs) in children and adults,[9,10] although the etiology of fetal CAKUT is still unclear. Therefore, we performed a CMA on fetuses with CAKUT and normal karyotypes, both in the presence and absence of other structural anomalies. We also screened CNVs that may cause diseases, explored CAKUT-associated CNVs, and searched for possible pathogenic genes that could guide clinical practice.

2 | MATERIALS AND METHODS

2.1 | Patient data

A retrospective study was conducted on fetal CAKUT diagnosed prenatally by fetal ultrasound between January 2016 and January 2019 in the Fujian Provincial Maternal and Child Health Hospital. Inclusion criteria were the presence of hydronephrosis, polycystic kidney dysplasia, renal agenesis, ectopic kidney, and CAKUT with other defects. This study protocol was approved by the ethics committee of the Fujian Provincial Maternal and Child Health Hospital, and all patients provided an informed consent for invasive prenatal diagnosis with normal karyotypes. Fetal samples were collected by amniocentesis or cord blood sampling, according to gestational age. Amniotic fluid was collected by amniocentesis at 18-24 weeks of gestation, and fetal blood was collected by cordocentesis after 24 weeks of gestation. Specific post-test counseling was also provided. Clinical follow-up assessments were performed via telephone and postpartum ultrasound. Confirmed cases of CAKUT were divided into two groups: one group with isolated CAKUT and another group with non-isolated CAKUT.

2.2 | Single nucleotide polymorphism array

The single nucleotide polymorphism (SNP) array method was previously established by our laboratory.[11] Genomic DNA was directly extracted from uncultured amniotic fluid and cord blood samples using the QIAamp DNA Blood Mini Kit (Qiagen). The genome-wide high-resolution SNP array CytoScan HD (Affymetrix Genome CytoScan 750K, Affymetrix), including both SNPs and oligonucleotide probes, was used in this study. Amplification, labeling, and hybridization of 250 ng DNA were performed. The CNV reporting filter was set at >100 kb with a minimum set of 50 marker counts. The results were analyzed using the Chromosome Analysis Suite software (Affymetrix) and annotated based on GRCh37 (hg19). CNVs were classified as pathogenic, variants of uncertain significance (VOUS), or benign.[12] For fetuses with CAKUT that had abnormal SNP array results, parental testing was performed in order to determine the inheritance pattern of abnormal CNVs. Verification of copy number gains/losses was validated by fluorescence in situ hybridization.

2.3 | Statistical analysis

Statistical analysis was performed using SPSS 20 (IBM). Comparisons between isolated CAKUT and non-isolated CAKUT were performed using continuity correction. A P value of $< .05$ was considered statistically significant.

3 | RESULTS

In total, 147 fetuses with CAKUT were included. Of these, 125 (85.0%) had isolated CAKUT and 22 (15.0%) had CAKUT associated with other structural anomalies. Of the 125 isolated CAKUT fetuses, 38 had hydronephrosis, 37 had unilateral polycystic kidney dysplasia, 19 had renal agenesis, and 17 had duplex kidney (Table 1).

3.1 | Detection rates of abnormal CNVs and comparison of abnormal CNV detection rates

A total of 147 fetuses with CAKUT were included, of which 125 (85.0%) were cases of isolated CAKUT and 22 (15.0%) were cases of non-isolated CAKUT. Fetal ultrasonography showed a higher detection rate of hydronephrosis, polycystic kidney dysplasia, renal agenesis, and duplex kidney (Table 1). SNP array identified abnormal CNVs in 13 (8.8%) fetuses. Of these, six were pathogenic and seven were VOUS. Of the 13 fetuses with CAKUT harboring CNVs, parents of eight participated in the study. Five de novo mutations were found in five fetuses with CAKUT, and three cases were inherited (Table 2). The detection rate of abnormal CNVs in non-isolated CAKUT was higher than that in isolated CAKUT (5/22 (22.7%) vs 8/125 (6.4%), respectively, $P = .038$). Among the anomaly groups, CNVs were identified with the highest frequency in fetuses with polycystic kidney dysplasia (5/37; 13.5%), followed by in fetuses with renal agenesis (2/19; 10.5%; Table 1).

3.2 | Pathogenic CNVs detected in fetuses with CAKUT and normal karyotypes using SNP array

Out of the entire study population, six CAKUT fetuses had pathogenic genomic disorders (deletions of 3q28, 17q12, 17p12, and 22q11.21; duplications of 15q11.2 and 7q11.23; and losses of heterozygosity

TABLE 1 Phenotypic characteristics of 147 fetuses with congenital anomalies of the kidney and urinary tract

CAKUT classification	Number of fetuses with anomaly (%total cohort)	Number of fetuses with CNV anomaly (%total anomaly)	Number of fetuses with pathogenic CNV	Number of fetuses with VOUS CNV
Isolated CAKUT	125 (85.0)	8 (6.4)	4	4
Hydronephrosis	38 (25.9)	1 (2.6)	0	1
Polycystic kidney dysplasia	37 (25.2)	5 (13.5)	2	3
Renal agenesis	19 (12.9)	2 (10.5)	2	0
Fused kidney	9 (6.1)	0 (0)	0	0
Ectopic kidney	5 (3.4)	0 (0)	0	0
Non-isolated CAKUT with other anomalies	22 (15.0)	5 (22.7)	2	3

in 16q23.2q24.3 and 16p13.3p12.3) that had been previously described (Table 2). Of these six, two genomic regions contained genes previously associated with CAKUT: the hepatocyte nuclear factor 1 homeobox B (HNF1B) [13] and claudin 16 (CLDN16), a candidate gene related to kidney development and developmental delay[14] (Table 2).

3.3 | CNVs of uncertain significance detected in fetal CAKUT with normal karyotypes using SNP array

We detected seven CNVs of uncertain significance in the CAKUT fetuses. An atypical 1.0 Mb duplication at the 22q11.21 locus was detected in dizygotic twin fetuses. Ultrasound examination revealed that both dizygotic fetuses had unilateral polycystic kidney dysplasia. The other CNVs with uncertain significance included a 0.97 Mb deletion at 2q11.1q11.2, a 2.7 Mb deletion at q21.31q21.32, a 1.5 Mb deletion at 10q21.1, a 1.0 Mb deletion at 11p15.1p14.3, and a 0.92 Mb duplication at 16p13.11. Excluding three parents who refused genetic testing, only one CNV was inherited from unaffected parents. Furthermore, one fetal CNV with VOUS (due to fetal urorectal septum malformation sequence (URSMS)) resulted in pregnancy termination. The microarray nomenclature and inheritance status are described in Table 3.

3.4 | Benign CNVs detected in fetal CAKUT with normal karyotypes using the SNP array

In this study, benign CNVs in two CAKUT fetuses were inherited from healthy parents: a 0.49 Mb deletion at 2p15 and a 0.38 Mb deletion at 2p11.2 (Table 4). According to the DGV database, these two genes had previously been reported as polymorphisms.

4 | DISCUSSION

The development of CMA technology has greatly improved the diagnostic rate of genetic diseases that cannot be diagnosed by conventional karyotypes. Some studies have reported that in congenital structural malformations and neurocognitive developmental

TABLE 2 Six pathogenic CNVs detected in fetal CAKUT with normal karyotypes

Case	CMA results	Size (Mb)	Prenatal ultrasound	Pathogenicity classification	Candidate renal gene(s)	Inheritance
G9727	arr[hg19]17q12(34 822 465-36 31 1 009)×1	1.4	Unilateral polycystic kidney dysplasia	P	HNF1B	De novo
G9932	arr[hg19]22q11.21(18 916 842-21 8 00 471)×1	2.8	Unilateral polycystic kidney dysplasia	P	-	Not available
E2031	arr[hg19]17p12(14 083 054-15 48 2 833)×1	1.4	Left renal agenesis	P	-	Maternal
E2044	arr[hg19]3q28(188 788 120-191 33 1 505)×1, 15q11.2(23 620 191-24 978 547)×3	2.5 1.3	Right renal agenesis	P	CLDN16	Not available
P833	arr[hg19]16q23.2q24.3(79 800 878-90 146 366) hmz, 16p13.3p12.3(94 807-19 302 326) hmz	10.3	Unilateral renal agenesis; VSD; PVS; FGR	P	-	Maternal
E2401	arr[hg19]7q11.23(72 701 098-74 0 69 645)×3	1.3	Unilateral renal agenesis; VSD	P	-	De novo

Abbreviations: FGR, fetal growth restriction; P, pathogenic; PVS, pulmonary valve stenosis; VSD, ventricular septal defect.

TABLE 3 CNVs of uncertain significance detected in fetal CAKUT with normal karyotypes

Case	CMA results	Size (Mb)	Prenatal ultrasound	Pathogenicity classification	Obstetrical outcomes	Inheritance
G9728	arr[hg19]9q21.31q21.32(82 732 469-85 502 241)×1	2.7	Unilateral polycystic kidney dysplasia	VOUS	TD	Not available
P4876	Arr[hg19]22q11.21(20 730 143-21 800 471)×3	1.0	Unilateral polycystic kidney dysplasia	VOUS	TD	De novo
P4877	Arr[hg19]22q11.21(20 730 143-21 800 471)×3	1.0	Unilateral polycystic kidney dysplasia	VOUS	TD	De novo
E2657	arr[hg19]2q11.1q11.2(96 679 225-97 669 032)×1	0.97	Hydronephrosis	VOUS	TD	Not available
E2797	arr[hg19]16p13.11(15 325 072-16 272 403)×3	0.92	Unilateral polycystic kidney dysplasia, URSMS,	VOUS	TP	Not available
S19	arr[hg19]11p15.1p14.3(20 745 930-21 780 075)×3	1.0	Hydronephrosis; widening of left lateral ventricle	VOUS	TD	De novo
P1287	arr[hg19]10q21.1(59 095 330-60 684 488)×1	1.5	Hydronephrosis; VSD	VOUS	TD	Maternal

Abbrevations: TD, term delivery; TP, termination of pregnancy; URSMS, urorectal septum malformation sequence; VSD, ventricular septal defect; VOUS, variation of uncertain clinical significance.

disorders, CMA can be used to diagnose an additional 12%-15% of genetic diseases.[7,8,15] Although the association between CAKUT and CNVs has been reported in children and adults, few studies have focused on CMA findings in fetal CAKUT. Our study investigated the role of CMA findings in prenatally diagnosed CAKUT with normal karyotypes in order to better understand the relationship between CNVs and CAKUT in fetuses.

In this study, 147 pregnant women with CAKUT fetuses consented to undergo SNP array testing after fetal anatomy scans and normal karyotype findings. We obtained abnormal CNVs in 8.8% (13/147) of the fetuses. SNP array testing can significantly improve the diagnostic rate of genetic diseases. Using a similar method, Sanna-Cherchi et al[16]reported that 16.6% of individuals with CAKUT carried abnormal CNVs, and Caruanaet al.[9] reported that 10.1% of individuals with CAKUT carried abnormal CNVs. Thus, the actual clinical detection rates in our cohort were comparable with those in Caruana's study, but slightly lower than those in Sanna-Cherchi's study. These differences in the detection rates of pathogenic CNVs could attribute to differences in the proportion of individuals with non-isolated CAKUT to individuals with isolated CAKUT, sample size, and differences in the scales of array probes. In this study, the detection rates of pathogenic CNVs by SNP array differed between cases with isolated CAKUT and non-isolated CAKUT (6.4% (8/125) and 22.7% (5/22), respectively; $P = .038$). These differences may be explained by the different prenatal ultrasound equipment used or by the lower risk of genomic imbalance mutations in fetuses with isolated CAKUT than in fetuses with CAKUT and other extrarenal abnormalities.

Among the anomaly groups, the highest frequency of CNVs was recorded in fetuses with polycystic kidney dysplasia (13.5%), followed by fetuses with renal agenesis (10.5%). Patients diagnosed with multicystic dysplastic kidney had a higher incidence of CNV were comparable with those in Caruana's study.[9] Although environmental risk factors during pregnancy can influence kidney size,[17] genetic factors are also clearly involved. In this study, fetal ultrasonography showed higher detection rates of hydronephrosis, polycystic kidney, renal agenesis, and duplex kidney. This indicates that CAKUT have different ultrasonic diagnostic rates and that ultrasound is more suitable for the diagnosis of hydronephrosis, polycystic kidney, renal agenesis, and duplex kidney.

We detected six pathogenic CNVs in fetuses with CAKUT. The HNFB1 and the DiGeorge/velocardiofacial syndrome were most frequently detected.[16] We found two de novo pathogenic CNVs: a 2.5 Mb deletion at 3q28 and a 1.3 Mb duplication at 15q11.2 in fetus E2044 which involved the CLDN16 gene. According to the literature,[18,19] the CLDN16 genesis dosage-sensitive and related to kidney development and developmental delay. A 1.4 Mb deletion at 17p12 in fetus E2031 was inherited from the mother who had a

TABLE 4 Benign CNVs detected in fetal CAKUT with normal karyotypes using SNP array

Case	CMA results	Size (Mb)	Prenatal ultrasound	Pathogenicity classification	Obstetrical outcomes	Inheritance
G8182	arr[hg19]2p15(62 195 812-62 697 481)×1	0.49	Unilateral polycystic kidney dysplasia	B	TD	Paternal
G9012	arr[hg19]2p11.2(84 496 566-84 891 03)×1	0.38	Unilateral polycystic kidney dysplasia	B	TD	Maternal

Abbreviations: B, benign; TD, term delivery.

normal phenotype. According to previous studies, deletion of 17p12 results in hereditary neuropathy with liability to pressure palsy, a distinct inherited disease of the peripheral nerves.[20] We determined that the microdeletion region of chromosome 17p12 was the pathogenic CNV of fetus E2031. Fetus P833 had multiple deformations: left renal agenesis, ventricular septal defect (VSD), pulmonary valve stenosis, and fetal growth restriction accompanied by a loss of heterozygosity in 16q23.2q24.3 and 16p13.3p12.3. Parental SNP array detected that it was a result of maternal uniparental disomy. In fetus E2401, we identified a de novo 1.3-Mb duplication at 7q11.23, resulting in 7q11.23 duplication syndrome. This fetus presented with left renal agenesis and VSD. Recently, many patients with Dup7 have been reported.[21,22] These case reports described patients with dolichocephaly, long eyelashes, a high and wide nose, dental malocclusion, and severe language delay.[23-25] We classified the 1.3-Mb duplication at 7q11.23 as a pathogenic variation.

In our analysis, seven CNVs with VOUS were present with CAKUT. Ultrasonography of five fetuses showed unilateral polycystic kidney dysplasia. We detected dizygotic twin fetuses and an atypical 1.0 Mb duplication at the 22q11.2 locus accompanied by unilateral polycystic kidney dysplasia. According to the DGV database, this region includes 29 Online Mendelian Inheritance in Man (OMIM) genes, although the clinical significance is unclear. A de novo 0.92 Mb duplication at 16p13.11 was detected in fetus E2797. This fetus presented with unilateral polycystic kidney dysplasia and urorectal septum malformation sequence (URSMS). SNP array results for the parents of this fetus were normal. According to the literature, this locus refers to CNVs with VOUS. We found three CNVs with VOUS in three fetuses with hydronephrosis. Our study showed that CMA is effective in identifying abnormal CNVs in cases with CAKUT and, thus, affects the obstetrical outcomes. Six pregnant women carrying fetuses with pathogenic CNVs chose to terminate the pregnancy. Furthermore, we observed that except for one CNV case with VOUS (due to fetal URSMS) for which the pregnancy was terminated, six pregnant women carrying CNV fetuses with VOUS and two pregnant women carrying fetuses with benign CNVs chose to continue the pregnancy and had a favorable prognosis. Therefore, this emphasizes the importance of improving genetic counseling.

Our study has some limitations. Due to the small sample size, the detection rate of pathogenic CNVs in isolated fetal CAKUT by SNP array differed from those in previous reports. Additionally, SNP technology has limitations in detecting chromosome balanced translocation and monogenic diseases. Furthermore, CAKUT may be due to single-gene defects,[26] with pathogenic mutations in HNF1B, PAX2, and DSTYK among the most frequently implicated.[27-29] Therefore, increased detection of single-gene defects is necessary.

In our study, the detection rate of fetal CAKUT with normal karyotypes could be increased by an additional 8.8% using SNP array technology. Factors contributing to 91.2% (134/147) of the cases remained elusive, suggesting that environmental risk factors, different mutations, or epigenetic influences are involved in CAKUT etiology.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

ETHICAL APPROVAL

All procedures involving human participants performed in our study were in accordance with the ethics committee of the Fujian Provincial Maternal and Child Health Hospital. Informed consent was obtained from all individual participants included in the study.

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REFERENCES

1. Woolf AS, Price KL, Scambler PJ, Winyard P. Evolving concepts in human renal dysplasia. *J Am Soc Nephrol*. 2004;15(4):998.
2. Livera LN, Brookfield DS, Egginton JA, Hawnaur JM. Antenatal ultrasonography to detect fetal renal abnormalities: a prospective screening programme. *Int J Gynecol Obstet*. 1989;298(6685):1421-1423.
3. Hildebrandt F. Genetic kidney diseases. *Lancet*. 2010;375(9722):1287-1295.
4. Andreas S. Renal abnormalities and their developmental origin. *Nat Rev Genet*. 2007;8(10):791-802.
5. Asaf V, Stefan K, Daw-Yang H, Dworschak GC, Friedhelm H. Single-gene causes of congenital anomalies of the kidney and urinary tract (CAKUT) in humans. *Pediatr Nephrol*. 2014;29(4):695-704.
6. Song R, Yosypiv IV. Genetics of congenital anomalies of the kidney and urinary tract. *Pediatr Nephrol*. 2011;26(3):353-364.
7. Elia J, Glessner JT, Wang K, et al. Genome-wide copy number variation study associates metabotropic glutamate receptor gene networks with attention deficit hyperactivity disorder. *Nat Genet*. 2012;44(1):78-84.
8. Vacic V, McCarthy S, Malhotra D, et al. Duplications of the neuropeptide receptor gene VIPR2 confer significant risk for schizophrenia. *Nature*. 2011;471(7339):499.
9. Caruana G, Wong MN, Walker A, et al. Copy-number variation associated with congenital anomalies of the kidney and urinary tract. *Pediatr Nephrol*. 2015;30(3):487-495.
10. Capone VP, Morello W, Taroni F, Montini G. Genetics of congenital anomalies of the kidney and urinary tract: the current state of play. *Int J Mol Sci*. 2017;18(4):796.

11. Cai M, Huang H, Su L, et al. Chromosomal abnormalities and copy number variations in fetal ventricular septal defects. *Mol Cytogenet*. 2018;11:58.
12. Hanemaaijer NM, Sikkema-Raddatz B, van der Vries G, et al. Practical guidelines for interpreting copy number gains detected by high-resolution array in routine diagnostics. *Eur J Hum Genet*. 2012;20(2):161-165.
13. Lindner TH, Njolstad PR, Horikawa Y, Bostad L, Bell GI, Sovik O. A novel syndrome of diabetes mellitus, renal dysfunction and genital malformation associated with a partial deletion of the pseudo-POU domain of hepatocyte nuclear factor-1beta. *Hum Mol Genet*. 1999;8(11):2001.
14. Jerzy W, Carolyn NS, Cook EH, et al. Differences between the pattern of developmental abnormalities in autism associated with duplications 15q11.2-q13 and idiopathic autism. *J Neuropathol Exp Neurol*. 2012;71(5):382-397.
15. Melanie M, Louanne H. Array-based technology and recommendations for utilization in medical genetics practice for detection of chromosomal abnormalities. *Genet Med*. 2010;12(11):742-745.
16. Sanna-Cherchi S, Kiryluk K, Burgess K, et al. Copy-number disorders are a common cause of congenital kidney malformations. *Am J Hum Genet*. 2012;91(6):987-997.
17. Welham SJ, Riley PR, Wade A, Hubank M, Woolf AS. Maternal diet programs embryonic kidney gene expression. *Physiol Genomics*. 2005;22(1):48-56.
18. Konrad M, Schaller A, Seelow D, et al. Mutations in the tight-junction gene claudin 19 (CLDN19) are associated with renal magnesium wasting, renal failure, and severe ocular involvement. *Am J Hum Genet*. 2006;79(5):949-957.
19. Martin-Nunez E, Cordoba-Lanus E, Gonzalez-Acosta H, Oliet A, Izquierdo E, Claverie-Martin F. Haplotype analysis of CLDN19 single nucleotide polymorphisms in Spanish patients with familial hypomagnesemia with hypercalciuria and nephrocalcinosis. *World J Pediatr*. 2015;11(3):272-275.
20. Chance PF, Alderson MK, Leppig KA, et al. DNA deletion associated with hereditary neuropathy with liability to pressure palsies. *Cell*. 1993;72(1):143-151.
21. Kirchhoff M, Bisgaard A-M, Bryndorf T, Gerdes T. MLPA analysis for a panel of syndromes with mental retardation reveals imbalances in 5.8% of patients with mental retardation and dysmorphic features, including duplications of the Sotos syndrome and Williams-Beuren syndrome regions. *Eur J Med Genet*. 2007;50(1):33-42.
22. Prontera P, Serino D, Caldini B, et al. Brief report: functional MRI of a patient with 7q11.23 duplication syndrome and autism spectrum disorder. *J Autism Dev Disord*. 2014;44(10):2608-2613.
23. Kriek M, White SJ, Szuhai K, et al. Copy number variation in regions flanked (or unflanked) by duplicons among patients with developmental delay and/or congenital malformations; detection of reciprocal and partial Williams-Beuren duplications. *Eur J Hum Genet*. 2006;14(2):180-189.
24. Merritt JL, Lindor NM. Further clinical description of duplication of Williams-Beuren region presenting with congenital glaucoma and brachycephaly. *Am J Med Genet A*. 2010;146A(8):1055-1058.
25. Malenfant P, Liu X, Hudson ML, et al. Association of GTF2i in the Williams-Beuren syndrome critical region with autism spectrum disorders. *J Autism Dev Disord*. 2012;42(7):1459-1469.
26. Saisawat P, Kohl S, Hilger AC, et al. Whole-exome resequencing reveals recessive mutations in TRAP1 in individuals with CAKUT and VACTERL association. *Kidney Int*. 2014;85(6):1310-1317.
27. Weber S, Moriniere V, Knüppel T, et al. Prevalence of mutations in renal developmental genes in children with renal hypodysplasia: results of the ESCAPE study. *J Am Soc Nephrol*. 2006;17(10):2864-2870.
28. Thomas R, Sanna-Cherchi S, Warady BA, Furth SL, Kaskel FJ, Gharavi AG. HNF1B and PAX2 mutations are a common cause of renal hypodysplasia in the CKiD cohort. *Pediatr Nephrol*. 2011;26(6):897-903.
29. Hwang D-Y, Dworschak GC, Kohl S, et al. Mutations in 12 known dominant disease-causing genes clarify many congenital anomalies of the kidney and urinary tract. *Kidney Int*. 2014;85(6):1429-1433.

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