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Mutations in 12 known dominant disease-causing genes clarify many congenital anomalies of the kidney and urinary tract

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Abstract

Congenital anomalies of the kidney and urinary tract (CAKUT) account for approximately half of children with chronic kidney disease. CAKUT can be caused by monogenic mutations, however, data are lacking on their frequency. Genetic diagnosis has been hampered by genetic heterogeneity and lack of genotype-phenotype correlation. To determine the percentage of cases with CAKUT that can be explained by mutations in known CAKUT genes, we analyzed the coding exons of the 17 known dominant CAKUT-causing genes in a cohort of 749 individuals from 650 families with CAKUT. The most common phenotypes in this CAKUT cohort were 288 with vesicoureteral reflux, 120 with renal hypodysplasia and 90 with unilateral renal agenesis. We identified 37 different heterozygous mutations (33 novel) in 12 of the 17 known genes in 47 patients from 41 of the 650 families (6.3%). These mutations include (number of families): *BMP7* (1), *CDC5L* (1),

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CHD1L (5), *EYAI* (3), *GATA3* (2), *HNFB* (6), *PAX2* (5), *RET* (3), *ROBO2* (4), *SALL1* (9), *SIX2* (1), and *SIX5* (1). Furthermore, several mutations previously reported to be disease-causing are most likely benign variants. Thus, in a large cohort over 6% of families with isolated CAKUT are caused by a mutation in 12 of 17 dominant CAKUT genes. Our report represents one of the most in-depth diagnostic studies of monogenic causes of isolated CAKUT in children.

Keywords

renal agenesis; renal development; genetic renal disease

INTRODUCTION

Congenital anomalies of kidney and urinary tract (CAKUT) are observed in 3–6 per 1,000 live births and account for 40–50% of the etiology of chronic kidney disease (CKD) in children worldwide^{1, 2}. CAKUT cover a wide range of structural malformations that result from a defect in the morphogenesis of the kidney and/or the urinary tract^{3–5}. The condition may appear as an isolated feature or as part of a syndrome in association with extra-renal manifestations^{6, 7}. In addition, CAKUT may either be diagnosed sporadically or was described with familial aggregation in up to 15% of cases^{8, 9}. In familial cases, the mode of inheritance in most pedigrees is autosomal dominant with variable expressivity and reduced penetrance¹⁰. The pathogenesis of CAKUT is based on the disturbance of normal nephrogenesis, and can be due to genetic abnormalities in renal developmental genes that direct the process^{1, 3–5, 11–13}. To date, about 20 monogenic CAKUT causing genes have been identified to result in isolated CAKUT or syndromic CAKUT with mild extra-renal manifestations^{14–34}. Only a few studies have screened large cohorts of CAKUT patients for disease-causing mutations^{35–40}. These studies screened for 1–5 disease-causing genes and some were pre-selected for chronic renal insufficiency or severe disease phenotypes^{35–37}. Hence, data are lacking on the frequency of monogenic forms of CAKUT in large cohorts.

To address these issues we investigated the frequency of mutations in 17 known dominant CAKUT-causing genes in a phenotypically non-selective international cohort of 749 CAKUT individuals out of 650 different families. We show that mutations in known CAKUT-causing genes are present in more than 6% of these families, and we outline possible pitfalls in analyzing autosomal dominant single-gene disorders.

RESULTS

Our cohort of 749 individuals from 650 different families with CAKUT originated from Eastern Europe (63.6%), Western Europe (12.7%), Arab countries (10%), India (7.9%), Roma populations (1.5%), and Asia (0.7%) (Supplementary Table S1). There were 414 male (55%) and 331 female (44.2%) individuals. The most common CAKUT phenotype was vesicoureteral reflux (n=288), followed by renal hypodysplasia (n=120) and unilateral renal agenesis (n=90). One hundred and sixty-one individuals from 100 families are considered as familial CAKUT according to clinical questionnaires in our cohort. These families have 2 to 6 affected individuals. The most common familial CAKUT phenotypes include

vesicoureteral reflux (n=68), duplex system (n=29), followed by renal hypodysplasia (n=19), and others. For detailed cohort characteristics see Supplementary Table S1.

By targeted re-sequencing of 170 coding exons of 17 genes known to cause autosomal dominant CAKUT we identified 144,382 single-nucleotide variants (SNVs) and 39,081 insertion-deletion variants in the 650 families. Following our variant filtering as described in the Methods, we retained 341 variants as potentially deleterious alleles. One hundred fifty-two of these were confirmed by Sanger sequencing whereas the others represented low-representation artifacts of multiplex PCR. In order to distinguish benign variants from disease-causing mutations we carefully evaluated each variant individually based on criteria as described in the Methods section. Overall 105 variants did not meet our criteria for being probably disease causing. Among these, 43 variants were previously reported as mutations in individuals with CAKUT (Supplementary Table S2), and 62 variants were not previously reported (Supplementary Table S3) in the Human Gene Mutation Database (<http://www.hgmd.cf.ac.uk/ac/index.php>).

In 749 patients with CAKUT from 650 families, disease-causing heterogeneous dominant mutations were identified in 41 unrelated families (6.3%) (Table 1). Mutations were detected in the following genes: *BMP7* (1 family), *CDC5L* (1 family), *CHD1L* (5 families), *EYA1* (3 families), *GATA3* (2 families), *HNF1B* (5 families), *PAX2* (5 families), *RET* (3 families), *ROBO2* (4 families), *SALL1* (9 families), *SIX2* (1 family), and *SIX5* (1 family) (Table 1). No causative mutations were identified in the genes *SOX17*, *UMOD*, *BMP4*, *SIX1* and *UPK3A*. In total, 33 of the 37 mutations were novel pathogenic mutations.

DISCUSSION

We here examined a large international cohort of 650 unrelated families with CAKUT for the presence of mutations in 17 autosomal dominant known CAKUT-causing genes. We identified 37 different heterozygous mutations in 12 different genes in 41 of the 650 families (6.3%). Thirty-three of the 37 mutations detected were novel.

Our findings also revealed that some variants previously reported as disease-causing cannot be accepted as such based on the finding of lack of segregation of these genetic variants in families with multiple affected individuals. For example, the *BMP4* variant p.S91C and the *SIX2* variant p.P241L, have been reported to lead to CAKUT among 5 unrelated patient¹⁵. We detected these two variants among 13 unrelated families in our cohort and five of them did not segregate with the disease, i.e. not all affected family members have the variant. These findings reveal that these two variants cannot be considered as disease-causing. These findings encourage us to adhere to our strict definition of disease-causing variants as outlined in 'Methods' and are consistent with the findings that many alleles published as disease-causing may not reliably have such a role^{41, 42}. We found that 9 variants (43 individuals) in previously CAKUT-related publications and 50 HGMD-unreported variants (62 individuals) did not fulfill our criteria (Supplementary Tables S2 and S3, respectively).

This work, to the best of our knowledge, is the most extensive genetic screening of known CAKUT-causing genes. *SALL1*, *HNF1B* and *PAX2* were the most prevalent disease causing

genes in our cohort. This is in line with the predominance of *HNF1B* and *PAX2* mutations that has been described in patients with renal hypodysplasia^{35, 36, 38}. *HNF1B* and *PAX2* were previously reported to be disease-causing in 5–20% of CAKUT cases^{35–40}. The finding that *PAX2* and *HNF1B* mutations were seen at higher frequency in previous studies on CAKUT is most likely explained by the fact that these studies use CAKUT cohorts preselected for CKD and in prenatal findings with severe renal anomalies^{35–37}. Our data are consistent with previous publications describing that oligosyndromic CAKUT-causing genes can lead to an isolated CAKUT phenotype³⁵.

The fact that we did not identify mutations in *SOX17*, *UMOD*, *BMP4*, *SIX1*, and *UPK3A* suggests that mutations in those genes are rarer. The identification of *SALL1* mutations > 1% of our cohort, suggests that this gene may be more common cause of CAKUT than previously believed³⁵. It should be emphasized that in the current study we did not screen our cohort for copy number variations. It was previously shown that some of the known CAKUT-causing genes may be disrupted by deletions or duplications, such as heterozygous *HNF1B* deletion³⁵. Moreover, in a recent study involving 522 patients with CAKUT, 72 distinct known or novel copy-number variations in 87 (16.6%) patients were identified, suggesting that kidney malformations can, in part, result from pathogenic genomic imbalances⁴³.

Our study supports the observation that CAKUT is a genetically very heterogeneous disease with diverse clinical phenotypes. We provide further evidences that the role of specific oligosyndromic CAKUT genes (i.e. *SALL1*) have a higher contribution in CAKUT than previous thought. The numbers of known CAKUT genes are expanding with the recent discovery of several novel genes, including *FGF20*, *TNXB*, *WNT4*, and *DSTYK*^{31–34}, which were not included in our study because they were described after completion of our study. We expect the list of CAKUT-causing genes to keep growing with the increasing application of next generation sequencing techniques. Identification of the monogenetic causes of CAKUT will have important implications in assessing the risk towards progression into end-stage renal disease (ESRD), for this group of diseases that causes ~50% of all ESRD in the first two decades of life.

MATERIALS AND METHODS

Human subjects

We obtained blood samples and pedigrees following informed consent from individuals with CAKUT. The study was approved by the institutional review board of the University of Michigan Medical School and Boston Children's Hospital. Patients were included in the study if a diagnosis compatible with CAKUT was established by a pediatric nephrologist investigator. The study comprised 749 individuals from 650 families with CAKUT from 25 different pediatric nephrology units worldwide (see Supplementary Table 1). Excluded from the study were patients with CAKUT associated with prominent involvement of other organs (syndromic CAKUT).

Mutation analysis

DNA was extracted according to standard method from peripheral blood obtained from all study participants. As previously described by our group^{35, 39}, multiplexed PCR-based amplified products using Fluidigm Access-Array™ technology followed by barcoding and next-generation re-sequencing on an Illumina MiSeq platform. Sanger DNA sequencing was further conducted for single mutation conformation. All coding exons and adjacent splice sites of the following 17 autosomal dominant genes that are known to cause non-syndromic or oligo-syndromic CAKUT were screened: *BMP4*, *BMP7*, *CDC5L*, *CHD1L*, *EYA1*, *GATA3*, *HNF1B*, *PAX2*, *RET*, *ROBO2*, *SALL1*, *SIX1*, *SIX2*, *SIX5*, *SOX17*, *UMOD*, and *UPK3A*.

Primer design

We designed 252 target-specific primer pairs to cover all 170 coding exons and intron/exon boundaries of the 17 known dominant CAKUT-causing genes (PCR primers are available upon request). The maximum amplicon size was chosen as 150–300 bp. Universal primer sequences 5-ACACTGACGACATGGTTCTACA-[target-specific forward]-3' and 5'-TACGGTAGCAGAGACTTGGTCT-[target-specific reverse]-3' were added at the 5' end to all target-specific forward and reverse primers, respectively.

Target DNA enrichment and resequencing

Primers were pooled to generate 6-plex primer pools per PCR with a final concentration of 1 QM per primer. Every sample master mix contained 50 ng genomic DNA, 1X FastStart High Fidelity Reaction Buffer with MgCl₂, 5 % DMSO, dNTPs (200 μM each), “FastStart High Fidelity Enzyme Blend” and 1X “Access Array” loading reagent (Roche, Indianapolis, IN). 48 different DNA samples were mixed with 48 different 6-plex primer pools on one 48.48 Access Array™ followed by thermal cycling. Subsequently harvested amplicon pools were submitted to another PCR-step to tag PCR products with 48 different barcodes and Illumina sequence-specific adaptors as previously described^{35, 39}. Barcoded PCR products were pooled from 125 individuals and submitted to next-generation resequencing on an Illumina MiSeq platform. A total of six 2 x 250 bp paired-end runs of Illumina MiSeq were performed according to manufacturer’s protocol. Detected variants were confirmed by Sanger sequencing. Segregation analysis was performed if DNA from family members was available.

Mutation calling of autosomal dominant genetic variants as likely disease-causing

Read alignment and variant detection was done using CLC Genomics Workbench software (CLC-bio, Aarhus, Denmark) as described previously by our group³⁵. After applying filtering criteria, the number of remaining variants (in parenthesis) were as follows: 1) minor variant frequency <10% (56,410), 2) dbSNP135 with minor allele frequency (MAF) < 1% (23,491), 3) non-synonymous changes and splice variants (7,252), 4) variant with minor variant frequency > 30% (2,511), 5) same variant presents in < 5% of the study cohort (341).

We considered variants as probably disease-causing according to the following inclusion and exclusion criteria:

Inclusion criteria: (1) truncating mutation (stop-gained, abrogation of obligatory splice site, frameshift); OR (2) missense mutation if one of the following applied: (a) continuous evolutionary conservation to *D. rerio*; OR (b) the given disease causing allele is supported by functional data.

Exclusion criteria (superseding inclusion criteria): (1) lack of segregation of a “mutant” allele to all affected family members; (2) no continuous evolutionary conservation to *D. rerio* (3) allele is present in the Exome Variant Server (EVS) database.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Genotypes and phenotypes of 41 families with mutations in 17 known autosomal dominant CAKUT-causing genes.

Gene	Family- Individual	Sex	Ethnicity	Renal Phenotype	Nucleotide Change ¹	Amino Acid Change	Conservation				SIFT ³	Mutation- Taster ⁴	PP-2 ⁵	References
							Mm	Gg	Xt	Dr				
<i>BMP7</i>	A3068-21	M	EE	R UVJO	c.661G>A	p.E221K	E	E	E	E	T	DC	0.192	
	A3068-22	M		L HD										
<i>CDC5L</i>	A4171-11	M	EE	L RA	c.2014C>T	p.P672S	P	P	/	/	T	DC	0.393	
	A4171-21	M		L RA										
<i>CHD1L</i>	A3061-21	M	WE	R MCDK, L UVJO	c.998C>G	p.P333R	P	P	/	P	DC	DC	0.953	
<i>CHD1L</i>	A349-21	F	Asi	B kidney malrotation	c.1199A>G	p.E400G	E	E	/	E	D	DC	0.997	
<i>CHD1L</i>	A3902-21 ^a	M	Ind	PUV	c.1551A>G	p.I517M	I	I	/	I	D	DC	0.505	
<i>CHD1L</i>	A3925-21	F	Ind	R RD	c.1551A>G	p.I517M	I	I	/	I	D	DC	0.505	
<i>CHD1L</i>	A3219-21	M	Ind	Horseshoe kidneys, R DS	c.1551A>G	p.I517M	I	I	/	I	D	DC	0.505	
<i>EYAI</i>	A1522-21 ^b	M	Ara	R UPIO	c.647C>T	p.P216L	P	P	P	P	D	DC	0.079	44*
<i>EYAI</i>	A4438-21 ^c	F	WE	B VUR, B RHD	c.966+1G>A	NA								
<i>EYAI</i>	A1542-21 ^d	M	Ara	L UPIO	c.1733C>T	p.S578L	S	S	S	S	D	DC	0.984	
<i>GATA3</i>	A4733-21	F	EE	B VUR	c.766C>G	p.R256G	R	R	R	R	D	DC	0.404	
<i>GATA3</i>	A1319-21	F	EE	B VUR	c.889C>A	p.Q297K	Q	Q	Q	Q	D	DC	0.439	
<i>HNF1B</i>	A3967-21	M	Ind	B VUR, NB	c.234G>C	p.E78D	E	E	E	E	D	DC	0.992	
<i>HNF1B</i>	A2921-21	M	EE	L RHD, R MCDK	c.477delT	p.M160*								45
	A2921-12	F		Unspecified CAKUT										
<i>HNF1B</i>	A3069-21	F	EE	L VUR	c.499G>A	p.A167T	A	A	A	A	D	DC	0.999	
<i>HNF1B</i>	A3840-21	M	Ind	VUR, PUV	c.542G>A	p.R181Q	R	R	R	R	D	DC	0.888	
<i>HNF1B</i>	A2326-21	M	WE	L UPIO, subcapsular cysts	c.823C>T	p.Q275*								
	A2326-11	M		subcapsular cysts										
<i>HNF1B</i>	A4672-21 ^e	F	EE	R RHD, cystinuria	c.1024T>C	p.S342P	S	S	S	S	D	DC	0.767	
<i>PAX2</i>	A3148-21	M	WE	B RHD, RCT	c.76dup	p.V26Gfs*28								46
<i>PAX2</i>	A2334-21 ^f	F	WE	B RHD	c.211A>G	p.R71G	R	R	R	R	D	DC	0.888	

Gene	Family- Individual	Sex	Ethnicity	Renal Phenotype	Nucleotide Change ¹	Amino Acid Change	Conservation				EVS alleles ²	SIFT ³	Mutation- Taster ⁴	PP- Z ⁵	Refseq	
							Mm	Gg	Xt	Dr						
<i>PAX2</i>	A1087-21	M	EE	B UVJO	c.320C>T	p.P107L	P	P	P	P	D	DC	0/13,006	D	0.999	
<i>PAX2</i>	A3872-21	M	Ind	B RHD	c.343C>T	p.R115X							0/13,006			
<i>PAX2</i>	A1743-12	F	WE	RCT	c.408del	p.N136Kfs*23							0/13,006			
	A1743-21	F		RCT												
<i>RET</i>	A3836-21 ^g	F	Ind	B RHD	c.667G>A	p.V223M	V	V	V	V	D	DC	0/12,958	D	0.642	
<i>RET</i>	A1077-21 ^b	F	Ara	L RA, R UPJO	c.2110G>T	p.V704F	V	V	V	V	T	DC	0/13,006	T	0.901	
<i>RET</i>	A1318-21	F	EE	L DS, VUR, ureteroceles	c.3079C>G	p.L1027V	L	L	L	L	D	DC	0/13,006	D	0.996	
<i>ROBO2</i>	A1220-21	F	Ind	R UPJO, stone	c.340G>T	p.G114W	G	G	G	G	D	DC	0/12,438	D	I	
<i>ROBO2</i>	A3839-21	M	Ind	PUV	c.724A>G	p.T242A	T	T	T	T	D	DC	0/11,902	D	0.224	
<i>ROBO2</i>	A3372-21	M	EE	R MCDK	c.808C>G	p.P270A	P	P	P	P	D	DC	0/11,930	D	0.988	
<i>ROBO2</i>	A521-11	M	EE	B VUR	c.3712G>A	p.D1238N	D	D	D	D	D	DC	0/12,130	D	0.251	
<i>SALL1</i>	A3935-21	M	Ind	PUV	c.220G>A	p.V74I	V	V	V	V	D	DC	0/12,996	D	0.007	
<i>SALL1</i>	A2333-21	M	WE	B VUR, MCDK	c.548C>G	p.T183R	T	T	T	T	D	DC	0/12,996	D	0.296	
<i>SALL1</i>	A2898-21	F	EE	L UPJO	c.602A>G	p.Q201R	Q	Q	Q	Q	D	DC	0/12,996	D	0.968	
<i>SALL1</i>	A617-21	F	EE	B VUR gr III, Rt duplex	c.703G>A	p.A235T	A	A	A	A	D	DC	0/12,996	D	0.782	
<i>SALL1</i>	A3070-21	M	EE	L UPJO												
<i>SALL1</i>	A4448-21	F	EE	B VUR	c.1738A>G	p.1580V	I	I	I	I	D	DC	0/12,996	D	0.035	
<i>SALL1</i>	A5083-21	F	EE	L VUR	c.1738A>G	p.1580V	I	I	I	I	D	DC	0/12,996	D	0.035	
<i>SALL1</i>	A3687-12 ^h	F	EE	L DS	c.2582C>A	p.S861*							0/12,996			
	A3687-21	M		R RHD												
<i>SALL1</i>	F1434-21 ⁱ	M	WE	R RA, L VUR	c.3006_3009del	p.C1003Tfs*41							0/12,996			
<i>SIX2</i>	A3904-21	M	Ind	PUV	c.859G>A	p.V287M	V	V	V	V	D	DC	0/13,006	D	0.987	
<i>SIX5</i>	A959-21	M	EE	R DS, VU, L UVJO	c.1817C>T	p.P606L	P	/	-	P	D	DC	0/12,946	D	0.994	