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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

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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), *CHD1L* (5), *EYA1* (3), *GATA3* (2), *HNF1B* (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 penetrance[10]. 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 patient[15]. 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 phenotype[35].

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 believed[35]. 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* deletion[35]. 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 imbalances[43].

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 $MgCl_2$, 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 group[35]. 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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References

1. Hildebrandt F. Genetic kidney diseases. Lancet. 2010; 375:1287–1295. [PubMed: 20382325]
2. North American Pediatric Renal Transplant Cooperative Study (NAPRTCS). 2008 Annual report. Vol. 2008. The EMMES Corporation; Rockville, MD: 2008.
3. Dressler GR. The cellular basis of kidney development. Annu Rev Cell Dev Biol. 2006; 22:509–529. [PubMed: 16822174]
4. Ichikawa I, Kuwayama F, Pope JC IV, et al. Paradigm shift from classic anatomic theories to contemporary cell biological views of CAKUT. Kidney Int. 2002; 61:889–898. [PubMed: 11849443]
5. Sanna-Cherchi S, Caridi G, Weng PL, et al. Genetic approaches to human renal agenesis/hypoplasia and dysplasia. Pediatr Nephrol. 2007; 22:1675–1684. [PubMed: 17437132]
6. Eccles MR, Schimmenti LA. Renal-coloboma syndrome: a multi-system developmental disorder caused by PAX2 mutations. Clin Genet. 1999; 56:1–9. [PubMed: 10466411]
7. Bingham C, Bulman MP, Ellard S, et al. Mutations in the hepatocyte nuclear factor-1beta gene are associated with familial hypoplastic glomerulocystic kidney disease. Am J Hum Genet. 2001; 68:219–224. [PubMed: 11085914]
8. Roodhooft AM, Birnholz JC, Holmes LB. Familial nature of congenital absence and severe dysgenesis of both kidneys. N Engl J Med. 1984; 310:1341–1345. [PubMed: 6717505]
9. Bulum B, Ozcakar ZB, Ustuner E, et al. High frequency of kidney and urinary tract anomalies in asymptomatic first-degree relatives of patients with CAKUT. Pediatr Nephrol. 2013 Epub ahead of print.
10. McPherson E, Carey J, Kramer A, et al. Dominantly inherited renal adysplasia. Am J Med Genet. 1987; 26:863–872. [PubMed: 3591828]
11. Chen F. Genetic and developmental basis for urinary tract obstruction. Pediatr Nephrol. 2009; 24:1621–1632. [PubMed: 19085015]
12. Schedl A. Renal abnormalities and their developmental origin. Nat Rev Genet. 2007; 8:791–802. [PubMed: 17878895]

13. Song R, Yosypiv IV. Genetics of congenital anomalies of the kidney and urinary tract. Pediatr Nephrol. 2011; 26:353–364. [PubMed: 20798957]
14. Chen T, Li Q, Xu J, et al. Mutation screening of BMP4, BMP7, HOXA4 and HOXB6 genes in Chinese patients with hypospadias. Eur J Hum Genet. 2007; 15:23–28. [PubMed: 17003840]
15. Weber S, Taylor JC, Winyard P, et al. SIX2 and BMP4 mutations associate with anomalous kidney development. J Am Soc Nephrol. 2008; 19:891–903. [PubMed: 18305125]
16. Groenen PM, Vanderlinden G, Devriendt K, et al. Rearrangement of the human CDC5L gene by a t(6;19)(p21;q13. 1) in a patient with multicystic renal dysplasia. Genomics. 1998; 49:218–229. [PubMed: 9598309]
17. Brockschmidt A, Chung B, Weber S, et al. CHD1L: a new candidate gene for congenital anomalies of the kidneys and urinary tract (CAKUT). Nephrol Dial Transplant. 2012; 27:2355–2364. [PubMed: 22146311]
18. Abdelhak S, Kalatzis V, Heilig R, et al. A human homologue of the Drosophila eyes absent gene underlies branchio-oto-renal (BOR) syndrome and identifies a novel gene family. Nat Genet. 1997; 15:157–164. [PubMed: 9020840]
19. Horikawa Y, Iwasaki N, Hara M, et al. Mutation in hepatocyte nuclear factor-1 beta gene (TCF2) associated with MODY. Nat Genet. 1997; 17:384–385. [PubMed: 9398836]
20. Lindner TH, Njolstad PR, Horikawa Y, et al. 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; 8:2001–2008. [PubMed: 10484768]
21. Sanyanusin P, Schimmenti LA, McNoe LA, et al. Mutation of the PAX2 gene in a family with optic nerve colobomas, renal anomalies and vesicoureteral reflux. Nat Genet. 1995; 9:358–364. [PubMed: 7795640]
22. Skinner MA, Safford SD, Reeves JG, et al. Renal aplasia in humans is associated with RET mutations. Am J Hum Genet. 2008; 82:344–351. [PubMed: 18252215]
23. Lu W, van Eerde AM, Fan X, et al. Disruption of ROBO2 is associated with urinary tract anomalies and confers risk of vesicoureteral reflux. Am J Hum Genet. 2007; 80:616–632. [PubMed: 17357069]
24. Kohlhase J, Wischermann A, Reichenbach H, et al. Mutations in the SALL1 putative transcription factor gene cause Townes-Brocks syndrome. Nat Genet. 1998; 18:81–83. [PubMed: 9425907]
25. Ruf RG, Berkman J, Wolf MT, et al. A gene locus for branchio-otic syndrome maps to chromosome 14q21.3–q24. 3. J Med Genet. 2003; 40:515–519. [PubMed: 12843324]
26. Hoskins BE, Cramer CH, Silvius D, et al. Transcription factor SIX5 is mutated in patients with branchio-oto-renal syndrome. Am J Hum Genet. 2007; 80:800–804. [PubMed: 17357085]
27. Gimelli S, Caridi G, Beri S, et al. Mutations in SOX17 are associated with congenital anomalies of the kidney and the urinary tract. Hum Mutat. 2010; 31:1352–1359. [PubMed: 20960469]
28. Hart TC, Gorry MC, Hart PS, et al. Mutations of the UMOD gene are responsible for medullary cystic kidney disease 2 and familial juvenile hyperuricaemic nephropathy. J Med Genet. 2002; 39:882–892. [PubMed: 12471200]
29. Jenkins D, Bitner-Glindzicz M, Malcolm S, et al. De novo Uroplakin IIIa heterozygous mutations cause human renal adysplasia leading to severe kidney failure. J Am Soc Nephrol. 2005; 16:2141–2149. [PubMed: 15888565]
30. Van Esch H, Groenen P, Nesbit MA, et al. GATA3 haplo-insufficiency causes human HDR syndrome. Nature. 2000; 406:419–422. [PubMed: 10935639]
31. Gbadegesin RA, Brophy PD, Adeyemo A, et al. TNXB Mutations Can Cause Vesicoureteral Reflux. J Am Soc Nephrol. 2013; 24:1313–1322. [PubMed: 23620400]
32. Vivante A, Mark-Danieli M, Davidovits M, et al. Renal hypodysplasia associates with a WNT4 variant that causes aberrant canonical WNT signaling. J Am Soc Nephrol. 2013; 24:550–558. [PubMed: 23520208]
33. Sanna-Cherchi S, Sampogna RV, Papeta N, et al. Mutations in DSTYK and dominant urinary tract malformations. N Engl J Med. 2013; 369:621–629. [PubMed: 23862974]
34. Barak H, Huh SH, Chen S, et al. FGF9 and FGF20 maintain the stemness of nephron progenitors in mice and man. Dev Cell. 2012; 22:1191–1207. [PubMed: 22698282]

35. Weber S, Moriniere V, Knuppel 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; 17:2864–2870. [PubMed: 16971658]
36. Thomas R, Sanna-Cherchi S, Warady BA, et al. HNF1B and PAX2 mutations are a common cause of renal hypodysplasia in the CKiD cohort. Pediatr Nephrol. 2011; 26:897–903. [PubMed: 21380624]
37. Madariaga L, Moriniere V, Jeanpierre C, et al. Severe Prenatal Renal Anomalies Associated with Mutations in HNF1B or PAX2 Genes. Clin J Am Soc Nephrol. 2013; 8:1179–1187. [PubMed: 23539225]
38. Heidet L, Decramer S, Pawtowski A, et al. Spectrum of HNF1B mutations in a large cohort of patients who harbor renal diseases. Clin J Am Soc Nephrol. 2010; 5:1079–1090. [PubMed: 20378641]
39. Ulinski T, Lescure S, Beaufils S, et al. Renal phenotypes related to hepatocyte nuclear factor-1beta (TCF2) mutations in a pediatric cohort. J Am Soc Nephrol. 2006; 17:497–503. [PubMed: 16371430]
40. Edghill EL, Bingham C, Ellard S, et al. Mutations in hepatocyte nuclear factor-1beta and their related phenotypes. J Med Genet. 2006; 43:84–90. [PubMed: 15930087]
41. Bell CJ, Dinwiddie DL, Miller NA, et al. Carrier testing for severe childhood recessive diseases by next-generation sequencing. Sci Transl Med. 2011; 3:65ra64.
42. Xue Y, Chen Y, Ayub Q, et al. Deleterious- and disease-allele prevalence in healthy individuals: insights from current predictions, mutation databases, and population-scale resequencing. Am J Hum Genet. 2012; 91:1022–1032. [PubMed: 23217326]
43. Sanna-Cherchi S, Kiryluk K, Burgess KE, et al. Copy-number disorders are a common cause of congenital kidney malformations. Am J Hum Genet. 2012; 91:987–997. [PubMed: 23159250]
44. Hoskins BE, Cramer CH II, Tasic V, et al. Missense mutations in EYA1 and TCF2 are a rare cause of urinary tract malformations. Nephrol Dial Transplant. 2008; 23:777–779. [PubMed: 18065799]
45. Bingham C, Bulman MP, Ellard S, et al. Mutations in the hepatocyte nuclear factor-1beta gene are associated with familial hypoplastic glomerulocystic kidney disease. Am J Hum Genet. 2001; 68:219–24. [PubMed: 11085914]
46. Amiel J, Audollent S, Joly D, et al. PAX2 mutations in renal-coloboma syndrome: mutational hotspot and germline mosaicism. Eur J Hum Genet. 2000; 11:820–6. [PubMed: 11093271]
47. Saisawat P, Tasic V, Vega-Warner V, et al. Identification of two novel CAKUT-causing genes by massively parallel exon resequencing of candidate genes in patients with unilateral renal agenesis. Kidney Int. 2012; 81:196–200. [PubMed: 21900877]

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				EVS alleles[2]	SIFT[3]	Mutation- Taster[4]	PP- 2[5]	References
							Mm	Gg	Xt	Dr					
BMP7	A3068-21	M	EE	R UVJO	c.661G>A	p.E221K	E	E	E	E	0/13,006	T	DC	0.192	
	A3068-22	M		L HD											
CDC5L	A4171-11	M	EE	L RA	c.2014C>T	p.P672S	P	P	P	/	0/13,006	T	DC	0.393	
	A4171-21	M		L RA											
CHD1L	A5061-21	M	WE	R MCDK, L UVJO	c.998C>G	p.P333R	P	P	/	P	0/13,006	D	DC	0.953	
CHD1L	A549-21	F	Asi	B kidney malrotation	c.1199A>G	p.E400G	E	E	/	E	0/13,006	D	DC	0.997	
CHD1L	A3902-21[a]	M	Ind	PUV	c.1551A>G	p.I517M	I	I	/	I	0/13,006	D	DC	0.505	
CHD1L	A3925-21	F	Ind	R RD	c.1551A>G	p.I517M	I	I	/	I	0/13,006	D	DC	0.505	
CHD1L	A3219-21	M	Ind	Horseshoe kidneys, R DS	c.1551A>G	p.I517M	I	I	/	I	0/13,006	D	DC	0.505	
EYA1	A1522-21[b]	M	Ara	R UPJO	c.647C>T	p.P216L	P	P	P	P	0/13,006	D	DC	0.079	44*
EYA1	A1438-21[c]	F	WE	B VUR, B RHD	c.966+1G>A	NA					0/13,006				
EYA1	A1542-21[d]	M	Ara	L UPJO	c.1733C>T	p.S578L	S	S	S	S	0/13,006	D	DC	0.984	
GATA3	A4733-21	F	EE	B VUR	c.766C>G	p.R256G	R	R	R	R	0/12,988	D	DC	0.404	
GATA3	A1319-21	F	EE	B VUR	c.889C>A	p.Q297K	Q	Q	Q	Q	0/13,006	D	DC	0.439	
HNF1B	A3967-21	M	Ind	B VUR, NB	c.234G>C	p.E78D	E	E	E	E	0/13,004	D	DC	0.992	
HNF1B	A2921-21	M	EE	L RHD, R MCDK	c.477delT	p.M160*					0/13,006				
	A2921-12	F		Unspecified CAKUT											45
HNF1B	A3069-21	F	EE	L VUR	c.499G>A	p.A167T	A	A	A	A	0/13,006	D	DC	0.999	
HNF1B	A3840-21	M	Ind	VUR, PUV	c.542G>A	p.R181Q	R	R	R	R	0/13,006	D	DC	0.888	
HNF1B	A2326-21	M	WE	L UPJO, subcapsular cysts	c.823C>T	p.Q275*					0/13,006				
	A2326-11	M		subcapsular cysts											
HNF1B	A4672-21[e]	F	EE	R RHD, cystinuria	c.1024T>C	p.S342P	S	S	S	S	0/13,006	D	DC	0.767	
PAX2	A3148-21	M	WE	B RHD, RCT	c.76dup	p.V26Gfs*28					0/12,980				46
PAX2	A2334-21[f]	F	WE	B RHD	c.211A>G	p.R71G	R	R	R	R	0/12,958	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- 2[5]	Refe
							Mm	Gg	Xt	Dr					
PAX2	A1087-21	M	EE	B UVJO	c.320C>T	p.P107L	P	P	P	P	0/13,006	D	DC	0.999	
PAX2	A3872-21	M	Ind	B RHD	c.343C>T	p.R115X					0/13,006				
PAX2	A1743-12	F	WE	RCT	c.408del	p.N136Kfs*23					0/13,006				
	A1743-21	F		RCT											
RET	A3836-21[g]	F	Ind	B RHD	c.667G>A	p.V223M	V	V	V	V	0/12,958	D	DC	0.642	
RET	A1077-21[b]	F	Ara	L RA, R UPJO	c.2110G>T	p.V704F	V	V	V	V	0/13,006	T	DC	0.901	
RET	A1318-21	F	EE	L DS, VUR, ureterocele	c.3079C>G	p.L1027V	L	L	L	L	0/13,006	D	DC	0.996	
ROBO2	A1220-21	F	Ind	R UPJO, stone	c.340G>T	p.G114W	G	G	G	G	0/12,438	D	DC	1	
ROBO2	A3839-21	M	Ind	PUV	c.724A>G	p.T242A	T	T	T	T	0/11,902	D	DC	0.224	
ROBO2	A3372-21	M	EE	R MCDK	c.808C>G	p.P270A	P	P	P	P	0/11,930	D	DC	0.988	
ROBO2	A521-11	M	EE	B VUR	c.3712G>A	p.D1238N	D	D	D	D	0/12,130	D	DC	0.251	
SALL1	A3935-21	M	Ind	PUV	c.220G>A	p.V74I	V	V	V	V	0/12,996	D	DC	0.007	
SALL1	A2333-21	M	WE	B VUR, MCDK	c.548C>G	p.T183R	T	T	T	T	0/12,996	D	DC	0.296	
SALL1	A2898-21	F	EE	L UPJO	c.602A>G	p.Q201R	Q	Q	Q	Q	0/12,996	D	DC	0.968	
SALL1	A617-21	F	EE	B VUR gr III, Rt duplex	c.703G>A	p.A235T	A	A	A	A	0/12,996	D	DC	0.782	
SALL1	A3070-21	M	EE	L UPJO											
SALL1	A4448-21	F	EE	B VUR	c.1738A>G	p.I580V	I	I	I	I	0/12,996	D	DC	0.035	
SALL1	A5083-21	F	EE	L VUR	c.1738A>G	p.I580V	I	I	I	I	0/12,996	D	DC	0.035	
SALL1	A3687-12[h]	F	EE	L DS	c.2582C>A	p.S861*					0/12,996				
	A3687-21	M		R RHD											
SALL1	F1434-21[i]	M	WE	R RA, L VUR	c.3006_3009del	p.C1003Tfs*41					0/12,996				
SIX2	A3904-21	M	Ind	PUV	c.859G>A	p.V287M	V	V	V	V	0/13,006	D	DC	0.987	
SIX5	A959-21	M	EE	R DS, VU, L UVJO	c.1817C>T	p.P606L	P	/	-	P	0/12,946	D	DC	0.994	