SUPPLEMENTARY MATERIAL

Supplemental Methods

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Table S8. Genotype and phenotype information for 10 families with likely causative variants in genes causing a phenocopy of CAKUT.

References

SUPPLEMENTAL METHODS

Exome sequencing and variant calling

Genomic DNA was isolated from whole blood or saliva samples of all enrolled individuals according to local protocols. Generation of ES data from genomic DNA was performed at the Yale Center for Mendelian Genomics using Agilent SureSelect™ human exome capture arrays (Agilent Technologies, California, USA), followed by next generation sequencing on an Illumina HiSeq™ sequencing platform (Illumina, California, USA). Sequencing reads were mapped to the human reference genome assembly (NCBI build GRCh37/hg19) using CLC Biomedical Genomics Workbench™ (version 5.0.1) software (QIAGEN Aarhus A/S, Aarhus, Denmark). From the called variants, those with minor allele frequencies >1% in dbSNP[1] (version 147) or in the 1,000 Genomes Project[2] (1,094 subjects of various ethnicities; May 2011 data release) databases were excluded as they were considered unlikely to be deleterious, as previously described[3]. Synonymous and intronic variants located outside of splice sites were excluded, leaving non-synonymous and splice site variants for further analysis.

Homozygosity mapping

Homozygosity mapping data were generated from ES data as previously described[4] to allow identification of individuals with significant amounts of homozygosity (≥60 Mb), and to enable mapping of identified biallelic variants to homozygous regions[5].

Family analysis

In families with CAKUT, who had more than one individual enrolled in this study, segregation analysis was performed according to reported affected status and relationship. Identified variants in the index individual were examined for segregation within the relatives using CLC Biomedical Genomics Workbench™ (version 5.0.1) software (QIAGEN Aarhus A/S, Aarhus, Denmark). For multiple affected individuals within the family, only segregating variants were retained. In case of biallelic heterozygous variants, only those inherited *in trans* (assuming compound heterozygous recessive mode of inheritance) were retained.

Variant analysis in known human CAKUT genes

Following variant calling and application of the above-described filtering steps, ES data was examined for potentially deleterious variants in any of the 23 known isolated CAKUT genes (**Table S1**) and the 16 known "syndromic" CAKUT genes (**Table S2**), followed by an additional analysis for variants in the 135 genes, in which variants are known to cause syndromes with facultative CAKUT, if mutated (**Table S3**), and in 46 genes known to cause, if mutated, renal cystic ciliopathies as frequent phenocopies of CAKUT (**Table S4**). In order to assess the deleteriousness of the remaining variants, manual analysis and annotation was performed using the in-silico prediction programs Alamut Visual™ version 2.15 (Sophia Genetics, Massachusetts, USA), Sorting Intolerant form Tolerant (SIFT)[6], MutationTaster[7], and PolyPhen-2[8], the population databases Exome Variant Server (EVS) and gnomAD[9], and the variant databases HGMD® Professional 2020.3[10] (QIAGEN Aarhus A/S, Aarhus, Denmark) and ClinVar[11]. Amino acid conservation of the encoded protein among orthologues across phylogeny was analyzed using Ensembl Genome Browser (release 102)[12] and Clustal Omega[13]. Variant classification published by the American College of Medical Genetics and Genomic (ACMG) and the Association for Molecular Pathology (AMP)[14] was calculated using VarSome[15]. All database queries were last updated on December 28, 2020 and reflect this date's status. Final assessment of the identified variants was made using our previously published criteria[4].

Remaining variants were confirmed by Sanger sequencing according to local protocols in original patient DNA, if available and not otherwise specified**.** Segregation analysis was performed using all available DNA from relatives, even if not included in ES data generation.

Table S1. 23 genes known to cause isolated CAKUT in humans, if mutated.

Genes are listed by mode of inheritance and alphabetically by gene symbol.

Gene	Encoded protein	Reference	MOI	OMIM Gene number
ACE	Angiotensin I-converting enzyme	Gribouval *Nat Genet* 37:964, 2005[16]	AR	106180
AGT	Angiotensinogen	Gribouval *Nat Genet* 37:964, 2005[16]	AR	106150
AGTR1	Angiotensin II receptor, type 1	Gribouval *Nat Genet* 37:964, 2005[16]	AR	106165
FGF20	Fibroblast growth factor 20	Barak *Dev Cell* 22:1191, 2012[17]	AR	605558
ITGA8	Integrin α8	Humbert *Am J Hum Genet* 189:1260, 2014[18]	AR	604063
LRIG2	Leucine-rich repeats-and immunoglobulin-like domains-containing protein 2	Stuart *Am J Hum Genet* 92:259, 2013[19]	AR	608869
REN	Renin	Gribouval *Nat Genet* 37:964, 2005[16]	AR	179820
TRAP1	Heat-shock protein 75 (also known as TNF receptor-associated protein 1)	Saisawat *Kidney Int* 85:880, 2014[20]	AR	606219
BNC2	Basonuclin 2	Kolvenbach *Am J Hum Genet* 104:994, 2019[21]	AD	608669
CRKL	CRK Like Proto-Oncogene, adaptor protein	Lopez-Rivera *N Engl J Med* 376:742, 2017[22]	AD	602007
DSTYK	Dual serine/threonine and tyrosine protein kinase	Sanna-Cherchi *N Engl J Med* 369:621, 2013[23]	AD	612666
GREB1L	Growth regulation by estrogen in breast cancer 1-like	Brophy *Genetics* 207:215, 2017[24]	AD	617782
MUC1	Mucin 1	Kirby *Nat Genet* 45:299, 2013[25]	AD	158340
MYOCD	Myocardin	Houweling *J Clin Invest* 129:5374, 2019[26]	AD	606127
NRIP1	Nuclear receptor interacting protein 1	Vivante *J Am Soc Nephrol* 2017 28:2364, 2017[27]	AD	602490
ROBO2	Roundabout, axon guidance receptor, homolog 2 (*Drosophila*)	Hwang *Hum Genet* 134:905, 2015[28]; Lu *Am J Hum Genet* 80:616, 2007[29]	AD	602431
SIX2	SIX homeobox 2	Weber *J Am Soc Nephrol* 19:891, 2008[30]	AD	604994
SLIT2	Slit homolog 2	Hwang *Hum Genet* 134:905, 2015[28]	AD	603746
SOX17	Transcription factor SIX-17	Gimelli *Hum Mut* 31:1352, 2010[31]	AD	610928
SRGAP1	SLIT-ROBO Rho GTPase activating protein 1	Hwang *Hum Genet* 134:905, 2015[28]	AD	606523
TBX18	T-Box transcription factor	Vivante *Am J Hum Genet* 97:291, 2015[32]	AD	604613
TNXB	Tenascin XB	Gbadegesin *J Am Soc Nephrol* 24:1313, 2013[33]	AD	600985
UPK3A	Uroplakin 3A	Jenkins *J Am Soc Nephrol* 16:2141, 2005[34]	AD	611559

AD, autosomal dominant; **AR**, autosomal recessive; **MOI**, mode of inheritance; **OMIM**, Online Mendelian Inheritance in Men.

Table S2. 16 genes known to cause syndromic CAKUT in humans, if mutated.

Genes in which variants may result in a CAKUT phenotype that is accompanied by extrarenal features in ≥50% of reported cases. Genes are listed by mode of inheritance and alphabetically by gene symbol.

Gene	Encoded protein	Reference	MOI	OMIM Gene number	Phenotypes reported in HGMD® [a]			
					Total cases	CAKUT involvement reported	No CAKUT involvement reported	CAKUT involvement [%]
FRAS1	Extracellular matrix protein FRAS1	Kohl *J Am Soc Nephrol* 25:1917, 2014[35]	AR	607830	82	70[b]	12	85
FREM1	FRAS1 related extracellular matrix protein 1	Kohl *J Am Soc Nephrol* 25:1917, 2014[35]	AR	608944	37	11	26	30[c]
FREM2	FRAS1 related extracellular matrix protein 2	Kohl *J Am Soc Nephrol* 25:1917, 2014[35]	AR	608945	45	29	16	64
GRIP1	Glutamate receptor interacting protein 1	Kohl *J Am Soc Nephrol* 25:1917, 2014[35]	AR	604597	18	9	9	50
HPSE2	Heparanase 2 (Inactive)	Bulum *Nephron* 130:54, 2015[37]	AR	613469	15	15	0	100
EYA1	Eyes absent homolog 1	Abdelhak *Nat Genet* 15:157, 1997[38]	AD	601653	240	211	29	88
GATA3	GATA binding protein 3	Pandolfi *Nat Genet* 11:40, 1995[39]; Van Esch *Nature* 406:419, 2000[40]	AD	131320	118	89	29	75
HNF1B	HNF homeobox B	Lindner *Hum Mol Genet* 24:263, 1999[41]	AD	189907	301	235	66	78
PAX2	Paired box 2	Sanyanusin *Hum Mol Genet* 4:2183, 1995[42]	AD	167409	123	112	11	91
PBX1	PBX homeobox 1	Heidet *J Am Soc Nephrol* 28:2901, 2017[43]	AD	176310	37	29	8	78
SALL1	Sal-like protein 1 (also known as spalt-like transcription factor 1)	Kohlhase *Nat Genet* 18:81, 1998[44]	AD	602218	101	96	5	95
SIX1	SIX homeobox 1	Ruf *Proc Nat Acad Sci* 101:8090, 2004[45]	AD	601205	22	15	7	68
SIX5	SIX homeobox 5	Hoskins *Am J Hum Genet* 80:800, 2007[46]	AD	600963	12	11	1	92
WNT4	Protein Wnt-4	Biason-Lauber *N Engl J Med* 351:792, 2004[47]; Mandel *Am J Hum Genet* 82:39, 2008[48]; Vivante *J Am Soc Nephrol* 24:550, 2013[49]	AD	603490	9	7	2	78
ZMYM2	Zink finger, MYM-type 2	Connaughton *Am J Hum Genet* 107:727, 2020[50]	AD	602221	17	13	4	76
FAM58A	Family with sequence similarity 58 member A	Green *J Med Genet* 33:594, 1996[51]; Unger *Nat Genet* 40:287, 2008[52]	XL	300708	11	11	0	100

AD, autosomal dominant; **AR**, autosomal recessive; **MOI**, mode of inheritance; **OMIM**, Online Mendelian Inheritance in Men; **XL**, X-linked.

[a] The database HGMD® Professional 2020.3 was queried for the phenotypes reported for variants in the corresponding genes. Based on the available details, 'CAKUT involvement reported' was assumed when any CAKUT phenotype (see **Methods** for definitions) or renal involvement was specifically mentioned, and the percentage from total cases reported in this database was calculated. Last update from the database on February 25, 2021.

[b] For the genes causative of Fraser syndrome, all cases of reported Fraser syndrome without further specification were assumed to exhibit CAKUT involvement, since urogenital malformations are deemed a major diagnostic criterion (Van Haelst *Am J Med Genet A* 143A:3194, 2007[36]).

[c] This gene is listed here despite the percentage being below our 50% cutoff because it belongs to the Fraser syndrome complex, and hypomorphic variants have been shown to cause isolated CAKUT (Kohl *J Am Soc Nephrol* 25:1917, 2014[35]).

Table S3. 135 genes for syndromes with facultative CAKUT features in humans.

Genes in which variants typically result in a multi-organ syndrome with facultative CAKUT features in less than 50% of reported cases. Genes are listed by mode of inheritance and alphabetically by gene symbol.

Gene	Encoded protein	Reference	MOI	OMIM Gene number	Phenotypes reported in HGMD® [a]			
					Total cases	CAKUT involvement reported	No CAKUT involvement reported	CAKUT involvement [%]
B3GALTL	Beta 3-glucosyltransferase	Lesnik Oberstein *Am J Hum Genet* 79:562, 2006[53]	AR	610308	16	0	16	0
BMPER	Bone morphogenetic protein-binding endothelial regulator protein	Greenbaum *Eur J Med Genet* 62:167, 2019[54]	AR	608699	24	0	24	0
BSCL2	BSCL2, Seipin lipid droplet biogenesis associated	Haghighi *Clin Genet* 89: 434, 2016[55]	AR	606158	58	0	58	0
CCBE1	Collagen and calcium-binding EGF domain-containing protein 1	Van Balkom *Am J Med Genet* 112:412, 2002[56]	AR	612753	16	0	16	0
CD151	CD151 molecule (Raph blood group)	Karamatic *Blood* 104:2217, 2004[57]	AR	602243	7	0	7	0
CENPF	Centromeric protein F	Filges *Hum Mutat* 37:359, 2016[58]	AR	600236	22	1	21	5
CEP55	Centrosomal protein, 55-kD	Frosk *J Med Genet* 54:490, 2017[59]	AR	610000	6	3	3	50[b]
CHRM3	Muscarinic acetylcholine receptor M3	Weber *Am J Hum Genet* 19:634, 2011[60]	AR	118494	10	2	8	20
CHRNG	Cholinergic receptor nicotinic gamma subunit	Vogt *J Med Genet* 49:21, 2012[61]	AR	100730	42	0	42	0
CISD2	CDGSH iron sulfur domain 2	Amr *Am J Hum Genet* 81:673, 2007[62]	AR	611507	7	0	7	0
COL18A1	Collagen, type XVIII, alpha-1	Caglayan *Pediatr Neurol* 51:806, 2014[63]	AR	120328	50	0	50	0
CTU2	Cytosolic thiouridylase, subunit 2	Shaheen *Am J Med Genet* 170:3222, 2016[64]	AR	617057	6	4	2	67[b]
DHCR7	7-Dehydrocholesterol reductase	Löffler *Am J Med Genet* 95:174, 2000[65]	AR	602858	226	0	226	0
DIS3L2	DIS3 like 3'-5' exoribonuclease 2	Astuti *Nat Genet* 44:277, 2012[66]	AR	614184	21	0	21	0
DYNC2H1	Dynein cytoplasmic 2 heavy chain 1	Baujat *J Med Genet* 50:91, 2013[67]	AR	603297	233	1	232	0
EMG1	EMG1, N1-specific pseudouridine methyltransferase	Armistead *Am J Hum Genet* 84:728, 2009[68]	AR	611531	1	0	1	0
ERCC8	Excision repair cross-complementing, group 8	Bertola *J Hum Genet* 51:701, 2006[69]	AR	609412	75	0	75	0
ESCO2	Establishment of sister chromatid cohesion N-acetyltransferase 2	Vega *J Med Genet* 47:30, 2010[70]	AR	609353	33	0	33	0
ETFA	Electron transfer flavoprotein alpha subunit	Lehnert *Eur J Pediatr* 139:56, 1982[71]	AR	608053	39	0	39	0
ETFB	Electron transfer flavoprotein beta subunit	Lehnert *Eur J Pediatr* 139:56, 1982[71]	AR	130410	19	0	19	0
ETFDH	Electron transfer flavoprotein dehydrogenase	Lehnert *Eur J Pediatr* 139:56, 1982[71]	AR	231675	236	0	236	0
FANCA	Fanconi anemia complementation group A	Joenje *Nat Rev Genet* 2:466, 2001[72]	AR	607139	782	1	781	0
FANCD2	Fanconi anemia complementation group D2	Kalb *Am J Hum Genet* 80:895, 2007[73]	AR	613984	89	1	88	1
FANCE	Fanconi anemia complementation group E	Wegner *Clin Genet* 50:479, 1996[74]	AR	613976	25	0	25	0
FANCI	Fanconi anemia complementation group I	Savage *Am J Med Genet A* 170A:386, 2015[75]	AR	611360	75	4	71	5
FANCL	Fanconi anemia complementation group L	Vetro *Hum Mutat* 36:562, 2015[76]	AR	608111	35	0	35	0
FAT4	FAT atypical cadherin 4	Alders *Hum Genet* 133:1161, 2014[77]	AR	612411	45	8	37	18
FIBP	Fibroblast growth factor, acidic, intracellular binding protein	Thauvin-Robinet *Clin Genet* 89:e1-4, 2016[78]	AR	608296	2	1	1	50[b]

Gene	Encoded protein	Reference	MOI	OMIM Gene number	Phenotypes reported in HGMD® [a]			
					Total cases	CAKUT involvement reported	No CAKUT involvement reported	CAKUT involvement [%]
HAAO	3-Hydroxyanthranilate 3,4-dioxygenase	Shi *N Engl J Med* 377:544, 2017[79]	AR	604521	2	0	2	0
HYLS1	HYLS1, centriolar and ciliogenesis associated	Paetau *J Neuropathol Exp Neurol* 67:750, 2008[80]	AR	610693	2	0	2	0
ICK	Intestinal cell kinase	Lahiry *Am J Hum Genet* 84:134, 2009[81]	AR	612325	18	0	18	0
ITGA3	Integrin subunit alpha 3	Yalcin *Hum Mol Genet* 24:3679, 2015[82]	AR	605025	11	0	11	0
JAM3	Junctional adhesion molecule 3	Mochida *Am J Hum Genet* 87:882, 2010[83]	AR	606871	6	0	6	0
KYNU	Kynureninase	Shi *N Engl J Med* 377:544, 2017[79]	AR	605197	12	1	11	8
LMNA	Lamin A/C	Klupa *Endocrine* 36:518, 2009[84]	AR	150330	689	7	682	1
LRP2	LDL receptor related protein 2	Kantarci *Nat Genet* 39:957, 2007[85]	AR	600073	83	7	76	8
LRP4	LDL receptor related protein 4	Li *Am J Hum Genet* 86:696, 2010[86]	AR	604270	39	3	36	8
NADSYN1	NAD synthetase 1	Szot *Am J Hum Genet* 106:129, 2020[87]	AR	608285	6	0	6	0
NCAPG2	Non-SMC condensin II complex subunit G2	Khan *Am J Hum Genet* 104:94, 2019[88]	AR	608532	4	0	4	0
PEX1	Peroxisomal biogenesis factor 1	Crane *Hum Mutat* 26:167, 2005[89]	AR	602136	152	0	152	0
PEX5	Peroxisomal biogenesis factor 5	Sundaram *Nat Clin Pract Gastroenterol Hepatol* 5:456, 2008[90]	AR	600414	14	0	14	0
PIGL	Phosphatidylinositol glycan anchor biosynthesis class L	Schnur *Am J Med Genet* 72:24, 1997[91]	AR	605947	11	0	11	0
PIGN	Phosphatidylinositol glycan anchor biosynthesis class N	Ohba *Neurogenetics* 15:85, 2014[92]	AR	606097	60	0	60	0
PIGO	Phosphatidylinositol glycan anchor biosynthesis class O	Krawitz *Am J Hum Genet* 91:146, 2012[93]	AR	614730	21	0	21	0
PIGT	Phosphatidylinositol glycan anchor biosynthesis class T	Nakashima *Neurogenetics* 15:193, 2014[94]	AR	610272	21	0	21	0
PIGV	Phosphatidylinositol glycan anchor biosynthesis class V	Horn *Eur J Hum Genet* 22:762, 2014[95]	AR	610274	16	0	16	0
PIGY	Phosphatidylinositol glycan anchor biosynthesis class Y	Ilkovski *Hum Mol Genet* 24:6146, 2015[96]	AR	610662	2	0	2	0
PMM2	Phosphomannomutase 2	Horslen *Arch Dis Child* 66:1027, 1991[97]	AR	601785	133	1	132	1
POC1A	POC1 centriolar protein	Shaheen *Am J Hum Genet* 91:330, 2012[98]	AR	614783	12	0	12	0
RAB23	RAS-associated protein RAB23	Alessandri *Am J Med Genet A* 152A:982, 2010[99]	AR	606144	17	0	17	0
RBM8A	RNA-binding motif protein 8A	Skorka *Genet Couns* 16:377, 2005[100]	AR	605313	21	0	21	0
RECQL4	RecQ Like Helicase 4	Siitonen *Eur J Hum Genet* 17:151, 2009[101]	AR	603780	165	0	165	0
ROR2	Receptor tyrosine kinase like orphan receptor 2	Wiens *Clin Genet* 37:481, 1990[102]	AR	602337	51	3	48	6
STRA6	Stimulated by retinoic acid 6	Golzio *Am J Hum Genet* 80:1179, 2007[103]	AR	610745	36	0	36	0
TMCO1	Transmembrane and coiled-coil domains 1	Xin *Proc Natl Acad Sci U S A* 107:258, 2010[104]	AR	614123	7	0	7	0
UBR1	Ubiquitin protein ligase E3 component N-recognin 1	Vanlieferinghen *Genet Couns* 14:105, 2003[105]	AR	605981	83	0	83	0
WFS1	Wolframin ER transmembrane glycoprotein	Salih *Acta Paediatr Scand* 80:567, 1991[106]	AR	606201	454	4	450	1
WNT3	Wnt family member 3	Niemann *Am J Hum Genet* 74:558, 2004[107]	AR	165330	2	1	1	50[b]
ZMPSTE24	Zinc metallopeptidase STE24	Chen *Am J Med Genet A* 149A:1550, 2009[108]	AR	606480	36	0	36	0
ACTB	Actin beta	Rivière *Nat Genet* 44:440, 2012[109]	AD	102630	80	0	80	0

Gene	Encoded protein	Reference	MOI	OMIM Gene number	Phenotypes reported in HGMD® [a]			
					Total cases	CAKUT involvement reported	No CAKUT involvement reported	CAKUT involvement [%]
ACTG1	Actin gamma 1	Rivière *Nat Genet* 44:440, 2012[109]	AD	102560	64	0	64	0
ACTG2	Actin, gamma-2, smooth muscle, enteric	Thorson *Hum Genet* 133:737, 2014[110]	AD	102545	28	0	28	0
ARID1B	AT-Rich interaction domain 1B	Levy *J Med Genet* 28, 1991[111]	AD	614556	332	0	332	0
BMP4	Bone morphogenic protein 4	Weber *J Am Soc Nephrol* 19:891, 2008[30]	AD	112262	52	8	44	15
CD96	CD96 molecule	Kaname *Am J Hum Genet* 81:835, 2007[112]	AD	606037	5	0	5	0
CDKN1C	Cyclin dependent kinase inhibitor 1C	Mussa *Pediatr Nephrol* 27:397, 2012[113]	AD	600856	87	0	87	0
CHD7	Chromodomain helicase DNA binding protein 7	Janssen *Hum Mutat* 33:1149, 2012[114]	AD	608892	972	1	971	0
CREBBP	CREB binding protein	Kanjilal *J Med Genet* 29:669, 1992[115]	AD	600140	457	0	457	0
DACT1	Dishevelled binding antagonist of beta catenin 1	Webb *Hum Mutat* 38:373, 2017[116]	AD	607861	10	2	8	20
EP300	E1A binding protein P300	Roelfsema *Am J Hum Genet* 76:572, 2005[117]	AD	602700	133	2	131	2
FBN1	Fibrillin 1	Tokhmafshan *Pediatr Nephrol* 32:565, 2017[118]	AD	134797	3055	0	3055	0
FGF10	Fibroblast growth factor 10	Milunsky *Clin Genet* 69:349, 2006[119]; Bamforth *Am J Med Genet* 43:932, 1992[120]	AD	602115	19	0	19	0
FGF8	Fibroblast growth factor 8	Falardeau *J Clin Invest* 118:2822, 2008[121]	AD	600483	47	1	46	2
FGFR1	Fibroblast growth factor receptor 1	Farrow *Am J Med Genet A* 140:537, 2006[122]	AD	136350	301	2	299	1
FGFR2	Fibroblast growth factor receptor 2	LeHeup *Eur J Pediatr* 154:130, 1995[123]	AD	176943	167	1	166	1
FGFR3	Fibroblast growth factor receptor 3	Rohmann *Nat Genet* 38:414, 2006[124]	AD	134934	85	0	85	0
FOXF1	Forkhead box F1	Hilger *Hum Mutat* 36:1150, 2015[125]	AD	601089	149	1	148	1
FOXP1	Forkhead box P1	Bekheirnia *Genet Med* 19:412, 2017[126]	AD	605515	103	2	101	2
GDF6	Growth differentiation factor 6	Tassabehji *Hum Mutat* 29:1017, 2008[127]	AD	601147	24	0	24	0
GFRA1	GDNF family receptor alpha 1	Chatterjee *Hum Genet* 131:1725, 2012[128]	AD	601496	7	1	6	14
GLI2	GLI family zinc finger 2	Carmichael *J Urol* 190:1884, 2013[129]	AD	165230	105	3	102	3
GLI3	GLI family zinc finger 3	Cain *PLoS One* 4:e7313, 2009[130]	AD	165240	278	9	269	3
HOXA13	Homeobox A13	Halal *Am J Med Genet* 30:793, 1998[131]	AD	142959	31	2	29	6
JAG1	Jagged 1	Kamath *Nat Rev Nephrol* 9:409, 2013[132]	AD	601920	725	3	722	0
KAT6B	Lysine acetyltransferase 6B	Campeau *Am J Hum Genet* 90:282, 2012[133]	AD	605880	117	3	114	3
KCNQ1OT1	KCNQ1 opposite strand/antisense transcript 1	Chiesa *Hum Mol Genet* 21:10, 2012[134]	AD	604115	8	0	8	0
KCTD1	Potassium channel tetramerization domain containing 1	Marneros *Am J Hum Genet* 92:621, 2013[135]	AD	613420	11	0	11	0
KRAS	KRAS proto-oncogene, GTPase	Schubbert *Nat Genet* 38:331, 2006[136]	AD	190070	51	0	51	0
MLL2 / KMT2D	Myeloid/lymphoid or mixed-lineage leukemia protein 2	Banka *Eur J Hum Genet* 20:381, 2012[137]	AD	602113	921	7	914	1
MNX1	Motor neuron and pancreas homeobox 1	Hagan *Am J Hum Genet* 66:1504, 2000[138]	AD	142994	88	1	87	1
MTOR	Mechanistic target of rapamycin	Moosa *Am J Med Genet A* 173:264, 2017[139]	AD	601231	43	0	43	0
MYCN	MYCN proto-oncogene	Marcelis *Hum Mutat* 29:1125, 2008[140]	AD	164840	52	1	51	2

Gene	Encoded protein	Reference	MOI	OMIM Gene number	Phenotypes reported in HGMD® [a]			
					Total cases	CAKUT involvement reported	No CAKUT involvement reported	CAKUT involvement [%]
NFIX	Nuclear factor IX	Malan *Am J Hum Genet* 87:189, 2010[141]	AD	164005	120	0	120	0
NIPBL	NIPBL, cohesin loading factor	Rohatgi *Am J Med Genet A* 152A:1641, 2010[142]	AD	608667	488	0	488	0
NOTCH2	Notch 2	Kamath *Nat Rev Nephrol* 9:409, 2013[132]	AD	600275	105	11	94	10
PAX8	Paired box 8	Meeus *J Clin Endocrinol Metab* 89:4285, 2004[143]	AD	167415	70	0	70	0
PROK2	Prokineticin 2	Madan *Mol Genet Metab Rep* 12:57, 2017[144]	AD	607002	21	0	21	0
PROKR2	Prokineticin receptor 2	Sarfati *Front Horm Res* 39:121, 2010[145]	AD	607123	86	0	86	0
PTEN	Phosphatase and tensin homolog	Reardon *J Med Genet* 38:820, 2001[146]	AD	601728	741	0	741	0
PTPN11	Protein tyrosine phosphatase, non-receptor type 11	Bertola *Am J Med Genet A* 130A:378, 2004[69]	AD	176876	167	0	167	0
RAF1	Raf-1 proto-oncogene, serine/threonine kinase	Razzaque *Nat Genet* 39:1013, 2007[147]	AD	164760	76	0	76	0
RAI1	Retinoic acid induced 1	Vilboux *PLoS One* 6:e22861, 2011[148]	AD	607642	132	0	132	0
SALL4	Spalt like transcription factor 4	Kohlhase *GeneReviews®Book Section,* 1993[149]	AD	607343	76	6	70	8
SEMA3E	Semaphorin 3E	Lalani *J Med Genet* 41:e94, 2004[150]	AD	608166	12	1	11	8
SETBP1	SET binding protein 1	Schinzel *Am J Med Genet* 1:361, 1978[151]	AD	611060	58	0	58	0
SF3B4	Splicing factor 3b subunit 4	Bernier *Am J Hum Genet* 90:925, 2012[152]	AD	605593	44	0	44	0
SHH	Sonic hedgehog	Lurie Am *J Med Genet* 35:286, 1990[153]	AD	600725	240	1	239	0
SNRPB	Small nuclear ribonucleoprotein polypeptides B and B1	Tooley *Am J Med Genet A* 170A:1115, 2016[154]	AD	182282	7	0	7	0
SOS1	SOS Ras/Rac guanine nucleotide exchange factor 1	Ferrero *Eur J Med Genet* 51:566, 2008[155]	AD	182530	115	0	115	0
SOX9	SRY-box 9	Airik *Hum Mol Genet* 19:4918, 2010[156]	AD	608160	169	1	168	1
SRCAP	Snf2 related CREBBP activator protein	Hood *Am J Hum Genet* 90:308, 2012[157]	AD	611421	57	0	57	0
TBX1	T-box 1	Kujat *Am J Med Genet A* 140:1601, 2006[158]	AD	602054	101	0	101	0
TBX3	T-box 3	Meneghini *Eur J Med Genet* 49:151, 2006[159]	AD	601621	34	0	34	0
TFAP2A	Transcription factor AP-2 alpha	Milunsky *Am J Hum Genet* 82:1171, 2008[160]	AD	107580	50	0	50	0
TP63	Tumor protein P63	Celli *Cell* 99:143, 1999[161]	AD	603273	153	1	152	1
TSC1	Tuberous sclerosis 1	Curatolo *Lancet* 372:657, 2008[162]	AD	605284	464	3	461	1
TSC2	Tuberous sclerosis 2	Kumar *Hum Mol Genet* 4:1471, 1995[163]	AD	191092	1448	11	1437	1
TWIST2	Twist family BHLH transcription factor 2	Stevens *Am J Med Genet* 107:30, 2002[164]	AD	607556	9	0	9	0
VANGL1	VANGL planar cell polarity protein 1	Bartsch *Mol Syndromol* 3:76, 2012[165]	AD	610132	25	1	24	4
WNT5A	Wnt family member 5A	Roifman *Clin Genet* 87:34, 2015[166]; Person *Dev Dyn* 239:327, 2010[167]	AD	164975	12	2	10	17
AMER1	APC membrane recruitment protein 1	Pellegrino *Am J Med Genet* 70:159, 1997[168]	XL	300647	44	1	43	2
BCOR	BCL6 corepressor	Ng *Nat Genet* 36:411, 2004[169]	XL	300485	78	2	76	3
FANCB	Fanconi anemia complementation group B	McCauley *Am J Med Genet A* 155A:2370, 2011[170]	XL	300515	29	8	21	28
FLNA	Filamin A	Robertson *Am J Med Genet A* 140:1726, 2006[171]	XL	300017	323	3	320	1

Gene	Encoded protein	Reference	MOI	OMIM Gene number	Phenotypes reported in HGMD® [a]			
					Total cases	CAKUT involvement reported	No CAKUT involvement reported	CAKUT involvement [%]
GPC3	Glypican 3	Cottereau *Am J Med Genet C Semin Med Genet* 163:92, 2013[172]	XL	300037	105	0	105	0
KAL1	Anosmin 1	Hardelin *Proc Natl Acad Sci U S A* 89:8190, 1992[173]	XL	300836	203	0	203	0
KDM5C	Lysine-specific demethylase 5C	Jensen *Am J Hum Genet* 76:227, 2005[174]	XL	314690	72	0	72	0
KDM6A	Lysine-specific demethylase 6A	Rosenberg *Am J Med Genet* 182:85, 2020[175]	XL	300128	94	0	94	0
MID1	Midline 1	Preiksaitiene *Clin Dysmorphol* 24:7, 2015[176]	XL	300552	105	0	105	0
NSDHL	NAD(P) dependent steroid dehydrogenase-like	König *J Am Acad Dermatol* 46:594, 2002[177]	XL	300275	33	1	32	3
PIGA	Phosphatidylinositol glycan anchor biosynthesis class A	Johnston *Am J Hum Genet* 90:295, 2012[178]	XL	311770	57	0	57	0
PORCN	Porcupine O-acyltransferase	Suskan *Pediatr Dermatol* 7:283, 1990[179]	XL	300651	137	0	137	0
SMC1A	Structural maintenance of chromosomes 1A	Deardorff *GeneReviews® Book Section Seattle(WA),* 1993[180]	XL	300040	115	0	115	0
UPF3B	UPF3B, regulator of nonsense mediated MRNA decay	Lynch *Eur J Med Genet* 55:476, 2012[181]	XL	300298	25	1	24	4
ZIC3	Zic family member 3	Chung *Am J Med Genet* 155:1123, 2011[182]	XL	300265	45	0	45	0

AD, autosomal dominant; **AR**, autosomal recessive; **MOI**, mode of inheritance; **OMIM**, Online Mendelian Inheritance in Men; **XL**, X-linked.

[a] The database HGMD® Professional 2020.3 was queried for the phenotypes reported for variants in the corresponding genes. Based on the available details, 'CAKUT involvement reported' was assumed when any CAKUT phenotype (see **Methods** for definitions) or renal involvement was specifically mentioned, and the percentage from total cases reported in this database was calculated. Last update from the database on February 25, 2021.
[b] The percentage of CAKUT involvement was equal to or greater than 50% but still listed here due to the very low number of total cases.

Table S4. 46 renal cystic ciliopathy genes in which variants may cause phenocopies of CAKUT.

Genes are listed by mode of inheritance and alphabetically by gene symbol.

Gene	Disease	Reference	MOI	OMIM Gene number
AHI1	Joubert Syndrome 3	Parisi *J Med Gen* 43:334, 2005[183]	AR	608894
ARL6	Bardet-Biedl Syndrome 3	Pretorius *PLoS Genet* 6:e1000884, 2010[184]	AR	608845
BBS1	Bardet-Biedl Syndrome 1	Tieder *Int J Pediatr Nephrol* 3:199, 1982[185]	AR	209901
BBS10	Bardet-Biedl Syndrome 10	Tieder *Int J Pediatr Nephrol* 3:199, 1982[185]	AR	610148
BBS12	Bardet-Biedl Syndrome 12	Tieder *Int J Pediatr Nephrol* 3:199, 1982[185]	AR	610683
BBS2	Bardet-Biedl Syndrome 2	Tieder *Int J Pediatr Nephrol* 3:199, 1982[185]	AR	606151
BBS4	Bardet-Biedl Syndrome 4	Tieder *Int J Pediatr Nephrol* 3:199, 1982[185]	AR	600374
BBS5	Bardet-Biedl Syndrome 5	Tieder *Int J Pediatr Nephrol* 3:199, 1982[185]	AR	603650
BBS7	Bardet-Biedl Syndrome 7	Tieder *Int J Pediatr Nephrol* 3:199, 1982[185]	AR	607590
CEP290	Joubert Syndrome 5	Valente *Nat Genet* 68:623, 2006[186]	AR	610142
CPLANE1	Joubert Syndrome 17	Cleper *Am J Med Genet* 47:451, 1993[187]	AR	614571
EVC	Ellis van Creveld Syndrome	Moudgil *Pediatr Nephrol* 12:20, 1998[188]	AR	604831
EVC2	Ellis van Creveld Syndrome	Kurian *Indian J Dent Res* 18:31, 2007[189]	AR	607261
GLIS2	Nephronophthisis 7	Attanasio *Nat Genet* 39:1018, 2007[190]	AR	608539
IFT172	Jeune Syndrome	Friedland-Little *Hum Mol Genet* 20:3725, 2011[191]	AR	607386
IFT27	Bardet-Biedl Syndrome 19	Schaefer *J Hum Genet* 61:447, 2016[192]	AR	615870
IFT52	Short-rib thoracic dysplasia 16	Walczak-Sztulpa *Am J Med Genet A* 173:1364, 2017[193]; Dupont *Hum Mol Genet* 28:2720, 2019[194]	AR	617094
IFT57	Orofaciodigital Syndrome XVIII	Bruel *J Med Genet* 54:371, 2017[195]	AR	606621
IFT74	Bardet-Biedl Syndrome 20	Cevik *PLoS Genet* 9:e1003977, 2013[196]	AR	608040
IFT80	Short-rib thoracic dysplasia 2	Beales *Nat Genet* 39:727, 2007[197]	AR	611177
IFT81	Short-rib thoracic dysplasia 19	Perrault *J Med Genet* 52:657, 2015[198]	AR	605489
INPP5E	Joubert Syndrome 1	Travaglini *Eur J Hum Genet* 21:1074, 2013[199]	AR	613037
INVS	Nephronophthisis 2	Otto *Nat Genet* 34:413, 2003[200]	AR	243305
KIF14	Meckel Syndrome 12	Filges *Clin Genet* 86:220, 2013[201]	AR	611279
MKKS	Bardet-Biedl Syndrome 6	Tieder *Int J Pediatr Nephrol* 3:199, 1982[185]; Yamamura *Clin Exp Nephrol* 21:136, 2017[202]	AR	604896
MKS1	Meckel Syndrome, type 1	Kyttälä *Nat Genet* 38:155, 2006[203]	AR	609883
MKS3 / TMEM67	Nephronophthisis 11	Baala *Am J Hum Genet* 80:186, 2007[204]; Kumar *Am J Med Genet* 61:122, 1996[205]	AR	609884
NEK1	Short-rib thoracic dysplasia 6	Thiel *Am J Hum Genet* 88:106, 2011[206]	AR	604588
NPHP1	Nephronophthisis 1	Hildebrandt *Nat Genet* 17:149, 1997[207]	AR	607100
NPHP3	Nephronophthisis 3	Olbrich *Nat Genet* 34:455, 2003[208]	AR	608002
NPHP4	Nephronophthisis 4	Otto *Am J Hum Genet* 71:1161, 2002[209]	AR	607215
PKHD1	Polycystic kidney disease 4	Bergmann *Kidney Int* 67:829, 2005[210]	AR	606702
PTHB1	Bardet-Biedl Syndrome 9	Tieder *Int J Pediatr Nephrol* 3:199, 1982[185]	AR	607968
RPGRIP1L	Joubert Syndrome 7	Suzuki *Clin Genet* 90:526, 2016[211]	AR	610937
SDCCAG8	Bardet-Biedl Syndrome 16	Airik *J Am Soc Nephrol* 25:2573, 2014[212]	AR	613524
TMEM216	Joubert Syndrome 2	Edvardson *Am J Hum Genet* 86:93, 2010[213]	AR	613277
TMEM231	Joubert Syndrome 20	Shaheen *J Med Genetics* 50:160, 2013[214]	AR	614949
TMEM237	Joubert Syndrome 14	Huang *Am J Hum Genet* 89:713, 2011[215]	AR	614423

Gene	Disease	Reference	MOI	OMIM Gene number
TRIM32	Bardet-Biedl Syndrome 11	Chiang *Proc Natl Acad Sci U S A* 103:6287, 2006[216]	AR	602290
TTC21B	Nephronophthisis 12	Davis *Nat Genet* 43:189, 2011[217]	AR	612014
TTC8	Bardet-Biedl Syndrome 8	Tieder *Int J Pediatr Nephrol* 3:199, 1982[185]	AR	608132
BICC1	Renal cystic dysplasia	Kraus *Hum Mutat* 33:86, 2012[218]	AD	614295
PKD1	Polycystic kidney disease 1	Rossetti *J Am Soc Nephrol* 18:2143, 2007[219]	AD	601313
PKD2	Polycystic kidney disease 2	Rossetti *J Am Soc Nephrol* 18:2143, 2007[219]	AD	173910
UMOD	Medullary cystic kidney disease 2	Hart *J Med Genet* 39:882, 2002[220]	AD	191845
OFD1	Joubert Syndrome 10	Bisschoff *Hum Mutat* 34:237, 2013[221]	XL	300170

AD, autosomal dominant; **AR**, autosomal recessive; **MOI**, mode of inheritance; **OMIM**, Online Mendelian Inheritance in Men; **XL**, X-linked.

Table S5. Phenotypic details for 24 families in whom reverse phenotyping confirmed a likely deleterious variant as causative.

Families are listed in alphabetical order by gene symbol. Underlined text indicated signs/symptoms that yielded from reverse phenotyping.

Family	Gene	Pedigree relation Sex	*A priori* Renal phenotype	*A priori* Extrarenal phenotype	*Post ES* Renal phenotype	*Post ES* Extrarenal phenotype	Conclusion/remarks
B982	***ACTG1***	Index ind. M	BL hydronephrosis and VUR grade 1, renal dysplasia	BL optic nerve atrophy, developmental delay, abnormal brain development, dilated aortic root, bicuspid aortic valve, chronic lung disease, tracheobronchomalacy, kyphoscoliosis	BL hydronephrosis and VUR grade 1, renal dysplasia	Microcephaly, deafness, BL optic nerve atrophy, developmental delay, abnormal brain development, dilated aortic root, bicuspid aortic valve, chronic lung disease, tracheobronchomalacy, kyphoscoliosis	Additional extrarenal features consistent with syndrome caused by variants in *ACTG1* (OMIM: 102560)
B1587	***BMP4***	Index ind. M	PUV	Intellectual disability, polydactyly/syndactyly	PUV, R VUR and hydronephrosis, micropenis	Large ears, intellectual disability, psychomotor delay, polydactyly/syndactyly	Additional CAKUT and extrarenal features consistent with syndrome caused by variants in *BMP4* (OMIM: 112262)
B3542	***EYA1***	Index ind. M	BL renal hypodysplasia	-	BL renal hypodysplasia	R branchial cleft cyst	Clinical diagnosis of branchio-oto-renal syndrome (OMIM: 113650)
		Twin of index ind. M	BL renal hypodysplasia	-	BL renal hypodysplasia	R branchial cleft cyst	
B1171	***EYA1***	Index ind. M	Solitary pelvic kidney	-	Solitary pelvic kidney	R lower neck mass (consistent with branchial cleft anomaly)	Clinical diagnosis of branchio-oto-renal syndrome (OMIM: 113650)
A872	***FGFR2***	Index ind. M	L dysplastic kidney and VUR grade 1	Clubfeet	L dysplastic kidney and VUR grade 1	Unusual acne vulgaris, nasal polyposis and sinusitis, systolic murmur, L pes equinovarus, R syndactyly of toes 2/3	Additional and specific (syndactyly) extrarenal features consistent with Apert syndrome (OMIM: 101200)[a]
B3543	***GLI3***	Index ind. F	R VUR grade 5	Tracheoesophageal fistula, imperforate anus	R VUR grade 5	Tracheoesophageal fistula, esophageal atresia, atrial septal defect, patent ductus arteriosus, imperforate anus, failure to thrive	Additional extrarenal features consistent with syndrome caused by variants in *GLI3* (OMIM: 165240)
B3348	***HNF1B***	Index ind. F	BL renal hypodysplasia	-	BL renal hypodysplasia, hyperuricemia	-	Additional hyperuricemia which can be accounted to the variant detected in *HNF1B* (OMIM: 189907)

Family	Gene	Pedigree relation Sex	*A priori* Renal phenotype	*A priori* Extrarenal phenotype	*Post ES* Renal phenotype	*Post ES* Extrarenal phenotype	Conclusion/remarks
A1315	***HNF1B***	Index ind. M	L UPJO	-	L UPJO	-	Variant segregates with affected father and brother (see Table S6 for details), which was not previously known
B717	***JAG1***	Index ind. M	Renal dysplasia, echogenic kidney	Coarctation of the aorta, ventricular septal defect, peripheral pulmonary stenosis	Renal dysplasia, echogenic kidney	Developmental delay, intellectual disability, coarctation of the aorta, ventricular septal defect, peripheral pulmonary stenosis	Additional neurological features detected
B345	***KAT6B***	Index ind. F	R hypoplastic kidney with VUR	Intellectual disability, growth retardation, polydactyly/syndactyly	R hypoplastic kidney with VUR	Intellectual disability, growth retardation, hearing loss, polydactyly/syndactyly	Extrarenal features consistent with syndrome caused by variants in *KAT6B* (OMIM: 605880)
B2758	***KDM5C***	Index ind. M	Epispadias, cryptorchidism	Microcephaly, facial dysmorphism, skeletal deformity, growth retardation	Epispadias, cryptorchidism, micropenis	Microcephaly, facial dysmorphism, strabismus, skeletal deformity, growth retardation, developmental delay, clubfoot	Additional CAKUT and extrarenal features consistent with syndrome caused by variants in *KDM5C* (OMIM: 300534)
B1099	***NOTCH2***	Index ind. F	L renal agenesis, R cystic kidney, neurogenic bladder, duplicated internal genitalia	Tetralogy of Fallot, sacral agenesis, imperforate anus, hirsutism	L renal agenesis, R cystic kidney, neurogenic bladder, duplicated internal genitalia	Esophageal strictures, tetralogy of Fallot, kyphoscoliosis, sacral agenesis, imperforate anus, hirsutism	Additional CAKUT and extrarenal features detected, consistent with syndrome caused by variants in *NOTCH2* (OMIM: 600275)
B4111	***PAX2***	Index ind. M	PUV	-	PUV	Strabismus, suspected optic disc atrophy	Clinical diagnosis of papillorenal syndrome (OMIM: 120330)
B1680	***PBX1***	Index ind. F	L UVJO	-	L UVJO	Abnormally shaped ears	Additional facial features consistent with phenotype known to be caused by variants in *PBX1* (OMIM: 617641)
B3947	***PTPN11***	Index ind. F	BL hydronephrosis, L VUR grade 5, L hydroureter	-	BL hydronephrosis, L VUR grade 5, L hydroureter	Microcephaly, ptosis, myopia, widely spaced teeth, pectus carinatum	Additional extrarenal features consistent with Noonan syndrome (OMIM: 163950)
B3862	***SALL4***	Index ind. F	BL VUR	-	BL VUR	Scoliosis	Additional scoliosis detected (OMIM: 607343)
B595	***SF3B4***	Index ind. F	BL hydronephrosis, bladder exstrophy	Cloacal malformation	BL hydronephrosis, bladder exstrophy	Butterfly vertebral anomaly, short gut syndrome, omphalocele, doubling of uterus, cloacal malformation	Additional features consistent with syndrome caused by variants in *SF3B4* (OMIM: 154400)
B3182	***SRCAP***	Index ind. M	L UVJO	-	L UVJO	Low posterior hairline, triangular face, long eyelashes, prominent nose, thin lips	Additional features consistent with Floating-Harbor syndrome (OMIM: 136140)

Family	Gene	Pedigree relation Sex	*A priori* Renal phenotype	*A priori* Extrarenal phenotype	*Post ES* Renal phenotype	*Post ES* Extrarenal phenotype	Conclusion/remarks
B4148	***TP63***	Index ind. M	L renal agenesis, R VUR grade 4-5 and hydronephrosis	Low set ear, short neck, growth retardation	L renal agenesis, R VUR grade 4-5 and hydronephrosis	Photophobia, blepharitis, strabismus, low set ears, short neck, malformed auricles, growth retardation	Additional facial features consistent with syndrome caused by variants in *TP63* (OMIM: 603273)
B3618	***BBS4***	Index ind. M	L renal agenesis, R hydronephrosis	Polydactyly	L renal agenesis, R hydronephrosis, cryptorchidism	Night blindness, intellectual disability, postaxial polydactyly of foot, obesity, hypogonadism	Clinical diagnosis of Bardet-Biedl syndrome (OMIM: 615982)
B907	***PKD1***	Index ind. M	BL cystic kidneys and VUR grade 5, R duplex collecting system	-	BL cystic kidneys and VUR grade 5, R duplex collecting system	-	Variant segregates with affected father (see Table S8 for details), which was not previously known
B587	***PKD1***	Index ind. M	L MCDK	-	L MCDK, R cystic kidney with loss of corticomedullary differentiation	-	*Post ES* phenotype consistent with ADPKD (OMIM: 173900); variant segregates with affected father (see Table S8 for details), which was not previously known
A4479	***PKD2***	Index ind. F	L MCDK, BL duplex collecting system	-	L MCDK, BL duplex collecting system	-	Variant segregates with affected father (see Table S8 for details), which was not previously known
		Father of index ind. M	BL polycystic kidneys	-	BL polycystic kidneys	-	
B4070	***UMOD***	Index ind. M	PUV, BL hydronephrosis and multicystic kidneys	-	PUV, BL hydronephrosis and echogenic, multicystic kidneys	Pulmonary hypoplasia, ascites	*Post ES* confirmation of echogenic kidneys compatible with variant detected in *UMOD* (OMIM: 162000)[b]

-, not reported; **ADPKD**, autosomal dominant polycystic kidney disease; **BL**, bilateral; **ES**, exome sequencing; **F**, female; **ind**, individual; **L**, left; **M**, male; **MCDK**, multicystic dysplastic kidney; **PUV**, posterior urethral valve; **R**, right; **UPJO**, uretero-pelvic junction obstruction; **UVJO**, uretero-vesical junction obstruction; **VUR**, vesicoureterenal reflux

[a] Slaney *Am J Hum Genet* 58:923, 1996[222].
[b] Increased echogenicity is a diagnostic feature of autosomal dominant tubulointerstitial kidney disease (ADTKD); Devuyst *Nat Rev Dis Primers* 5:60, 2019[223].

Table S6. Detailed information on phenotype and genotype for 83 families with likely causative variants in genes known to cause isolated or syndromic CAKUT.

Families are listed in alphabetical order by gene symbol.

Family	Gene	Zygo-sity	Nucleotide change Protein change dbSNP	Amino acid con-serva-tion[a]	PP2 SIFT MT	gnomAD[b] EVS	HGMD[c] ClinVar[d] ACMG/ AMP[e]	Pedigree relation Sex	Homo-zygo-sity [Mb]	Segregation maternal; paternal; (other)	Renal phenotype	Extrarenal phenotype	Reference [PMID][f]
B982	***ACTG1***	*De novo* HET	c.812C>T p.Ser271Phe -	X. t.	0.722 D DC	- -	G - VUS	Index ind. M	7	WT; WT	BL hydronephrosis and VUR grade 1, renal dysplasia	Microcephaly, deafness, BL optic nerve atrophy, developmental delay, abnormal brain development, dilated aortic root, bicuspid aortic valve, chronic lung disease, tracheobronchoma-lacy, kyphoscoliosis	*Novel*
B1587[g]	***BMP4***	HET	c.1214G>A p.Cys405Tyr -	D. r.	0.999 D -	- -	G - VUS	Index ind. M	4	N/A; N/A	PUV, R VUR and hydronephrosis, micropenis	Large ears, intellectual disability, psychomotor delay, polydactyly/ syndactyly	*Novel*
B2575[g]	***BNC2***	HET	c.1296G>T p.Met432Ile rs368914032	C. i.	0.191 T DC	0/5/250630 0/1/6502	G - LB	Index ind. M	3	N/A; WT	PUV	-	*Novel*
B3372[g]	***BNC2***	HET	c.2372A>G p.Tyr791Cys rs889762379	D. r.	0.990 T DC	- -	G - VUS	Index ind. M	166	WT; HET	PUV, hypospadias, BL VUR and hydronephrosis	-	*Novel*
B3149[g]	***BNC2***	HET	c.2221G>A p.Asp741Asn rs554243088	D. r.	0.117 D DC	0/13/251098 -	G - LB	Index ind. M	6	N/A; N/A	L renal agenesis, R VUR grade 3	-	*Novel*
B3224[g]	***DSTYK***	HET	c.454C>T p.Arg152Cys rs202242580	D. r.[h]	0.719 D DC	0/3/282342 -	G - VUS	Index ind. M	26	WT; HET	BL UVJO and hydronephrosis	Facial dysmorphism	*Novel*
B3542	***EYA1***	HET	c.1081C>T p.Arg361* rs121909202	-	- - -	- -	DM PATH P	Index ind. M	19	N/A; N/A; affected twin brother: HET	BL renal hypodysplasia	R branchial cleft cyst	16691597 [224]
								Twin of index ind. M	7	N/A; N/A; affected twin brother: HET	BL renal hypodysplasia	R branchial cleft cyst	
B1481	***EYA1***	HET	c.1081C>T p.Arg361* rs121909202	-	- - -	- -	DM PATH P	Index ind. F	6	WT; HET[i]	L renal agenesis, BL VUR	Deafness, neck fistula	16691597 [224]

Family	Gene	Zygo-sity	Nucleotide change Protein change dbSNP	Amino acid con-serva-tion[a]	PP2 SIFT MT	gnomAD[b] EVS	HGMD[c] ClinVar[d] ACMG/ AMP[e]	Pedigree relation Sex	Homo-zygo-sity [Mb]	Segregation maternal; paternal; (other)	Renal phenotype	Extrarenal phenotype	Reference [PMID][f]
B3257[g]	***EYA1***	HET	c.679G>A p.Ala227Thr rs202168841	D. m.	1.000 D DC	0/14/282842 -	G - LB	Index ind. F	88	N/A; N/A	L renal agenesis (suspected aplasia or involution due to MCDK), R hypoplastic kidney	-	*Novel*
B3256[g]	***EYA1***	HET	c.689A>G p.Tyr230Cys rs1213738374	D. m.	0.998 D DC	- -	G - VUS	Index ind. F	62	WT; HET	R UPJO and hydronephrosis	-	*Novel*
B1024[g]	***EYA1***	HET	c.83C>G p.Ser28Cys rs558089479	D. r.	0.998 D DC	0/1/251488 -	G - VUS	Index ind. M	16	N/A; N/A	L MCDK	-	*Novel*
B1171[g]	***EYA1***	HET	c.809T>C p.Val270Ala rs1342127067	X. t.	0.008 T DC	0/1/251464 -	G - VUS	Index ind. M	1	N/A; N/A	Solitary pelvic kidney	R lower neck mass (consistent with branchial cleft anomaly)	*Novel*
B3817[g]	***EYA1***	HET	c.700C>A p.Pro234Thr -	D. r.	0.997 T DC	- -	G - VUS	Index ind. F	15	WT; N/A	BL VUR grade 2	-	*Novel*
A3342[g]	***FGFR1***	HET	c.2152C>T p.Arg718Cys -	D. m.	1.000 D DC	- -	R - LP	Index ind. M	26	N/A; N/A	R renal agenesis	Otapostasis, malformed auricles, intergluteal cleft, hydrocele, intrauterine growth retardation	*Novel*
A872[g]	***FGFR2***	HET	c.1608G>A p.Met536Ile rs1057519800	D. r.	0.991 D DC	- -	G LP P	Index ind. M	8	N/A; N/A	L dysplastic kidney and VUR grade 1	Unusual acne vulgaris, nasal polyposis and sinusitis, systolic murmur, L pes equinovarus, R syndactyly of toes 2/3	*Novel*
B2675	***FRAS1***	HET	c.4579C>T p.Arg1527Trp rs1872267	D. r.[j]	0.724 D DC	2/759/280412 0/24/6196	DM US VUS	Index ind. M	3	N/A; N/A	PUV, secondary neurogenic bladder	-	24700879 35
	FRAS1	HET	c.9364C>T p.Arg3122Trp rs200346497	D. r.	1.000 D DC	0/84/278976 -	DM US/LB VUS			N/A; N/A			24700879 35
B3860	***FRAS1***	HET	c.9521A>C p.Asp3174Ala -	G. g.	1.000 D DC	- -	R - VUS	Index ind. M	2	WT; HET	BL enlarged echogenic kidneys, oligohydramnios	-	*Novel*
	FRAS1	HET	c.4028G>C p.Gly1343Ala rs182375530	C. i.	1.000 D DC	1/5/248208 -	G - VUS			HET; WT			*Novel*

Family	Gene	Zygo-sity	Nucleotide change Protein change dbSNP	Amino acid con-serva-tion[a]	PP2 SIFT MT	gnomAD[b] EVS	HGMD[c] ClinVar[d] ACMG/ AMP[e]	Pedigree relation Sex	Homo-zygo-sity [Mb]	Segregation maternal; paternal; (other)	Renal phenotype	Extrarenal phenotype	Reference [PMID][f]
B2418	***FRAS1***	HOM	c.8486C>A p.Ser2829Tyr rs376788346	D. r.	0.965 D DC	4/147/248942 0/2/6052	G US B	Index ind. M	122	HET; HET; unaffected sister: WT	R renal agenesis	-	*Novel*
B3519	***FREM2***	HET	c.4030C>A p.Arg1344Ser rs114409305	D. r.	0.587 D -	0/18/251384 -	R - VUS	Index ind. F	15	WT; HET	BL VUR grade 2	-	*Novel*
	FREM2	HET	c.4512G>A p.Met1504Ile -	D. r.	0.022 D -	- -	G - LB			HET; WT			*Novel*
B1784[g]	***GLI2***	HET	c.1418G>A p.Arg473His rs150170739	D. m.[k]	0.118 D DC	0/46/282812 0/2/6501	G - B	Index ind. F	157	N/A; N/A	L hydronephrosis and VUR grade 5, R MCDK	Cleft lip, inguinal hernia	*Novel*
B3543[g]	***GLI3***	HET	c.308C>T p.Pro103Leu rs755154814	D. r.	0.998 D DC	0/3/279724 -	G - VUS	Index ind. F	133	WT; HET	R VUR grade 5	Tracheoesophageal fistula, esophageal atresia, atrial septal defect, patent ductus arteriosus, imperforate anus, failure to thrive	*Novel*
B3258[g]	***GREB1L***	HET	c.2939A>G p.Asp980Gly -	D. r.	0.998 D DC	- -	G - VUS	Index ind. F	55	N/A; N/A	Unilateral MCDK	-	*Novel*
B3652[g]	***GREB1L***	HET	c.1241T>C p.Val414Ala rs777013152	D. r.	0.998 D DC	0/16/188370 -	G - B	Index ind. M	12	HET; WT	BL echogenic kidneys with cysts, R VUR	-	*Novel*
B3233[g]	***GREB1L***	HET	c.2992G>A p.Glu998Lys rs758445815	D. r.	1.000 D DC	0/14/186570 -	G - B	Index ind. M	6	HET; WT	R ectopic and hypoplastic kidney	-	*Novel*
B3165[g]	***GREB1L***	HET[l]	c.2768C>T p.Thr923Ile rs1382291794	D. r.	1.000 D DC	0/1/157380 -	G - VUS	Index ind. M	5	WT; HET	R VUR grade 2	-	*Novel*
B3523[g]	***GREB1L***	HET	c.2360C>T p.Thr787Met rs144678858	D. r.	0.999 D DC	0/3/162894 -	G - VUS	Index ind. M	7	WT; HET	L hydronephrosis	-	*Novel*
B4048[g]	***GREB1L***	HET	c.722G>A p.Arg241Gln rs147048716	D. r.[m]	0.986 D DC	0/16/157328 0/1/2282	G - B	Index ind. M	18	HET; WT	R VUR grade 3-4, BL hydronephrosis	-	*Novel*
B808[g]	***GREB1L***	HET	c.100C>T p.Arg34Trp rs559234950	X. t.	0.971 D DC	0/6/188054 -	G - B	Index ind. M	1	N/A; N/A	BL VUR grade 2-3	-	*Novel*

Family	Gene	Zygo-sity	Nucleotide change Protein change dbSNP	Amino acid con-serva-tion[a]	PP2 SIFT MT	gnomAD[b] EVS	HGMD[c] ClinVar[d] ACMG/ AMP[e]	Pedigree relation Sex	Homo-zygo-sity [Mb]	Segregation maternal; paternal; (other)	Renal phenotype	Extrarenal phenotype	Reference [PMID][f]
B1083[g]	***GREB1L***	HET	c.5486A>G p.Tyr1829Cys rs769118539	D. r.	0.999 D DC	0/2/154038 -	G - VUS	Index ind. F	12	N/A; N/A	R hypodysplastic kidney with VUR	-	*Novel*
B462[g]	***GREB1L***	HET	c.2510G>A p.Arg837His rs1297427942	D. r.[n]	0.897 D DC	0/2/156490 -	G - VUS	Index ind. F	11	N/A; N/A	L non-obstructive duplex collecting system	Polythelia	*Novel*
B3749	***GREB1L***	HET	c.5323G>A p.Asp1775Asn -	D. r.	1.000 D DC	- -	DM - LP	Index ind. M	20	N/A; N/A	BL VUR	-	29100091 [225]
B3348	***HNF1B***	*De novo* HET	c.840_844del CTCCA p.Lys282Pro fs*10 -	-	- - -	- -	G - P	Index ind. F	9	WT; WT	BL renal hypodysplasia, hyperuricemia	-	*Novel*
A1315	***HNF1B***	HET	c.1006C>G p.His336Asp rs138986885	D. r.	0.182 T -	1/59/281558 0/3/6500	DM US/B VUS	Index ind. M	7	WT; HET; affected brother: HET[o]	L UPJO	-	16971658 [226]
B3830_ B3948	***HPSE2***	HOM	Exon 9 deletion[p]					Index ind. M	134	N/A; N/A	Neurogenic bladder, BL renal pelvis dilation	Inverted smile, hemoglobin H disease	*Novel*
B717[g]	***JAG1***	HET	c.2413C>G p.Arg805Gly -	D. r.	0.996 D DC	- -	G - VUS	Index ind. M	3	N/A; N/A	Renal dysplasia, echogenic kidney	Developmental delay, intellectual disability, coarctation of the aorta, ventricular septal defect, peripheral pulmonary stenosis	*Novel*
B345[g]	***KAT6B***	HET	c.3994C>T p.Pro1332Ser rs764565963	G. g.	0.986 D DC	0/6/251384 -	G - LB	Index ind. F	4	N/A; N/A	R hypoplastic kidney with VUR	Intellectual disability, growth retardation, hearing loss, polydactyly/ syndactyly	*Novel*
B2758	***KDM5C***	HEMI	c.938G>A p.Arg313Gln -	D. r.[q]	0.980 D DC	0/2/241938 -	G - VUS	Index ind. M	246	N/A; N/A	Epispadias, cryptorchidism, micropenis	Microcephaly, facial dysmorphism, strabismus, skeletal deformity, growth retardation, developmental delay, clubfoot	*Novel*
B2587[g]	***MYCN***	HET	c.816_821del TGAAGA p.Asp272_ Glu273del rs1267141762	-	- - -	0/1/246346 -	G - VUS	Index ind. M	203	N/A; N/A	Horseshoe kidney	Microcephaly, developmental delay, growth retardation	*Novel*

Family	Gene	Zygo-sity	Nucleotide change Protein change dbSNP	Amino acid con-serva-tion[a]	PP2 SIFT MT	gnomAD[b] EVS	HGMD[c] ClinVar[d] ACMG/ AMP[e]	Pedigree relation Sex	Homo-zygo-sity [Mb]	Segregation maternal; paternal; (other)	Renal phenotype	Extrarenal phenotype	Reference [PMID][f]
B1099[g]	***NOTCH2***	HET	c.2906A>G p.Asn969Ser rs142978777	D. r.	0.119 D DC	0/5/251436 0/1/6502	R - VUS	Index ind. F	5	WT; N/A	L renal agenesis, R cystic kidney, neurogenic bladder, duplicated internal genitalia	Esophageal strictures, tetralogy of Fallot, kyphoscoliosis, sacral agenesis, imperforate anus, hirsutism	*Novel*
B3775	***PAX2***	*De novo* HET	c.76dup p.Val26Glyfs*28 rs768607170	-	- - -	0/7/246960 -	DM[r] PATH P	Index ind. F	5	WT; WT; two unaffected siblings: WT	R MCDK	Retinal coloboma, morbid obesity	8589702[42]
B3358	***PAX2***	HET	c.76dup p.Val26Glyfs*28 rs768607170	-	- - -	0/7/246960 -	DM[r] PATH P	Index ind. F	7	N/A; N/A	L MCDK, R hydronephrosis	-	8589702[42]
B1677	***PAX2***	HET	c.76dup p.Val26Glyfs*28 rs768607170	-	- - -	0/7/246960 -	DM[r] PATH P	Index ind. M	133	N/A; N/A	BL MCDK	Optic disc coloboma, myopia, nystagmus, blindness	8589702[42]
B4069[g]	***PAX2***	HET	c.1123C>A p.Pro375Thr rs745392326	D. m.	0.169 D -	0/1/249426 -	G - VUS	Index ind. M	98	HET; N/A	L duplex collecting system and ureter with hydroureters and hydronephrosis	Skeletal deformity, growth retardation, Fanconi anemia	*Novel*
B4111	***PAX2***	HET	c.183C>A p.Ser61Arg -	D. m.	0.998 D -	- -	DM - LP	Index ind. M	7	WT; HET	PUV	Strabismus, suspected optic disc atrophy	28566479[43]
B2446	***PAX2***	HET	c.213-1G>A p.? -	-	- - -	- -	R - P	Index ind. M	10	HET; WT	BL renal hypodysplasia	BL optic disc coloboma, global developmental delay	*Novel*
								Mother of index ind. F	9	N/A; N/A; affected son: HET	End-stage renal disease of unknown cause	-	
B1680	***PBX1***	*De novo* HET	c.862C>T p.Arg288* rs1259895025	-	- - -	0/1/31382 -	DM - P	Index ind. F	332	WT; WT	L UVJO	Abnormally shaped ears	29036646[227]
B1127	***PTEN***	HET	c.492+1G>T p.? -	-	- - -	- -	DM PATH P	Index ind. F	4	HET; N/A	Crossed fused ectopia with small and scarred L moiety, BL VUR, vaginal agenesis, Mayer-Rockitansky-Kuster syndrome (OMIM: 277000)	Facial dysmorphism, progressive macrocephaly, tracheo-esophageal fistula, esophageal atresia, vertebral anomalies, tethered cord	28677221[228]
A608	***PTPN11***	HET	c.1226G>C p.Gly409Ala rs201247699	D. r.	0.054 D DC	0/16/250808 0/2/6501	DM US VUS	Index ind. F	19	WT; HET	R VUR grade 3	L auricular cyst	17052965[229]

Family	Gene	Zygo-sity	Nucleotide change Protein change dbSNP	Amino acid con-serva-tion[a]	PP2 SIFT MT	gnomAD[b] EVS	HGMD[c] ClinVar[d] ACMG/ AMP[e]	Pedigree relation Sex	Homo-zygo-sity [Mb]	Segregation maternal; paternal; (other)	Renal phenotype	Extrarenal phenotype	Reference [PMID][f]
B3947	***PTPN11***	HET	c.5C>T p.Thr2Ile rs267606990	X. t.	0.031 T -	- -	DM PATH P	Index ind. F	50	HET; WT	BL hydronephrosis, L VUR grade 5, L hydroureter	Microcephaly, ptosis, myopia, widely spaced teeth, pectus carinatum	12960218[230]
B3546x[g]	***ROBO2***	HET	c.2261C>G p.Ala742Gly rs750635483	D. r.	- T DC	0/1/249024 -	G - VUS	Index ind. M	12	N/A; N/A	BL VUR and hydronephrosis	-	*Novel*
B2626[g]	***ROBO2***	HET	c.1331C>T p.Thr444Met rs755515210	D. r.	- D DC	0/2/248992 -	G - VUS	Index ind. M	8	N/A; N/A	BL VUR	-	*Novel*
B592[g]	***ROBO2***	HET	c.3677C>G p.Ser1226Cys rs755603547	D. r.	0.999 D DC	0/4/249412 -	G - VUS	Index ind. M	7	N/A; N/A	BL VUR grade 4	-	*Novel*
B2813[g]	***ROBO2***	HET	c.1468C>A p.Gln490Lys rs774652786	D. r.[s]	0.106 T DC	0/12/279878 -	G - LB	Index ind. M	6	HET; N/A	R VUR and hydronephrosis	-	*Novel*
B2419[g]	***ROBO2***	HET	c.3394C>A p.Gln1132Lys rs777186201	D. r.	0.155 T DC	0/1/249500 -	G - VUS	Index ind. M	17	HET; WT; unaffected sister: WT	L UPJO	-	*Novel*
B2411[g]	***ROBO2***	HET	c.598C>T p.Arg200Cys rs763574051	D. r.	0.997 T DC	0/1/249134 -	G - VUS	Index ind. F	4	WT; HET	L renal agenesis, R UPJO	-	*Novel*
A4855[g]	***ROBO2***	HET	c.3280C>A p.Pro1094Thr rs200040879	D. r.	- T DC	0/5/280854 0/2/5916	G - VUS	Index ind. M	9	WT; HET	L renal agenesis	-	*Novel*
B3608[g]	***SALL1***	HET	c.3802G>A p.Gly1268Ser rs764123321	D. r.	0.588 D DC	0/6/282850 -	G - B	Index ind. F	2	HET; N/A	L renal agenesis, R renal hypoplasia and VUR with hydronephrosis, hypotrophic genitalia	Patent ductus arteriosus, dilated L ventricle, imperforate anus, cloacal malformation	*Novel*
B656[g]	***SALL1***	HET	c.2941A>G p.Ile981Val rs772457413	X. t.	0.184 D DC	0/3/282574 -	G - LB	Index ind. M	6	N/A; N/A	L VUR grade 5 and hydronephrosis, R atrophic kidney	Patent ductus arteriosus, atrial septal defect, chronic ventriculomegaly, chronic lung disease, ileal atresia, congenital hernia, hip abnormalities, BL clubfeet	*Novel*

Family	Gene	Zygo-sity	Nucleotide change Protein change dbSNP	Amino acid con-serva-tion[a]	PP2 SIFT MT	gnomAD[b] EVS	HGMD[c] ClinVar[d] ACMG/ AMP[e]	Pedigree relation Sex	Homo-zygo-sity [Mb]	Segregation maternal; paternal; (other)	Renal phenotype	Extrarenal phenotype	Reference [PMID][f]
B2583	***SALL1***	*De novo* HET	c.1508dup p.Tyr503* -	-	- - -	- -	DM[t] - P	Index ind. M	136	WT; WT; three unaffected siblings: WT	BL VUR, L UPJO	Facial dysmorphism, low set ears, developmental delay, ventricular septal defect, imperforate anus, clubfoot	*Novel*
B1770	***SALL1***	HET	c.1209del p.Ser404Ala fs*13 -	-	- - -	- -	G - P	Index ind. F	7	WT; N/A	L hypoplastic ectopic kidney	Low set ears, patent ductus arteriosus, R preaxial thumb polydactyly, imperforate anus	*Novel*
B961[g]	***SALL1***	HET	c.1129G>C p.Ala377Pro -	X. t.	0.012 D DC	- -	G - LB	Index ind. F	16	HET; N/A	BL dysplastic and echogenic kidneys	Townes-Brocks syndrome (OMIM: 107480)	*Novel*
B3862[g]	***SALL4***	HET	c.986G>A p.Arg329His rs376519013	C. i.	1.000 T -	0/26/282110 0/2/6501	G - B	Index ind. F	3	N/A; N/A	BL VUR	Scoliosis	*Novel*
B595[g]	***SF3B4***	HET	c.231C>G p.Ile77Met -	D. m.	0.771 D DC	- -	G - LB	Index ind. F	1	N/A; N/A	BL hydronephrosis, bladder exstrophy	Butterfly vertebral anomaly, short gut syndrome, omphalocele, doubling of uterus, cloacal malformation	*Novel*
B594[g]	***SIX1***	HET	c.37C>A p.Gln13Lys rs1480942237	D. m.	0.937 D DC	- -	G - VUS	Index ind. M	8	N/A; N/A	L hypoplastic kidney	Tetralogy of Fallot	*Novel*
B3353[g]	***SIX1***	HET	c.191G>A p.Arg64His rs1051653507	C. i.	0.071 D DC	0/5/282762 -	G US VUS	Index ind. F	6	WT; N/A	BL VUR	-	*Novel*
B3892[g]	***SLIT2***	HET	c.705G>T p.Gln235His -	C. e.	0.980 T -	- -	G - VUS	Index ind. M	18	WT; HET	L renal agenesis, malrotated R kidney with ureterocele	-	*Novel*
B332[g]	***SOX17***	HET	c.322G>A p.Ala108Thr rs1309570757	D. r.	0.907 D DC	- -	G - VUS	Index ind. M	5	HET; WT	Megaureter, BL VUR	-	*Novel*
B3501[g]	***SOX17***	HET	c.188A>G p.Lys63Arg rs754603226	C. i.[u]	0.959 D DC	0/2/240692 -	G - VUS	Index ind. F	5	N/A; N/A	L VUR grade 3	-	*Novel*
B3182[g]	***SRCAP***	HET	c.3694C>T p.Arg1232Cys rs1324080441	C. i.[v]	0.972 D DC	0/1/250984 -	G - VUS	Index ind. M	8	WT; HET	L UVJO	Low posterior hairline, triangular face, long eyelashes, prominent nose, thin lips	*Novel*

Family	Gene	Zygo-sity	Nucleotide change Protein change dbSNP	Amino acid con-serva-tion[a]	PP2 SIFT MT	gnomAD[b] EVS	HGMD[c] ClinVar[d] ACMG/ AMP[e]	Pedigree relation Sex	Homo-zygo-sity [Mb]	Segregation maternal; paternal; (other)	Renal phenotype	Extrarenal phenotype	Reference [PMID][f]
B3112[g]	***SRGAP1***	HET	c.550G>A p.Glu184Lys -	D. r.	0.229 T DC	- -	G - VUS	Index ind. M	174	N/A; N/A	BL hydrouretero-nephrosis	-	*Novel*
A3889[g]	***SRGAP1***	HET	c.268G>A p.Asp90Asn -	C. i.	0.936 T DC	- -	G - VUS	Index ind. M	5	N/A; N/A	PUV	-	*Novel*
B3621[g]	***SRGAP1***	HET	c.2197G>T p.Gly733Cys -	D. r.[w]	0.627 D DC	- -	G - VUS	Index ind. F	10	N/A; N/A	L MCDK, R renal stones	Femoral facial syndrome (OMIM: 134780), cleft palate, skeletal dysplasia	*Novel*
A1958	***SRGAP1***	HET	c.806G>A p.Cys269Tyr -	D. r.	0.840 T DC	- -	DM PATH LP	Index ind. M	28	WT; HET	R VUR grade 3	-	26026792 [28]
B806[g]	***SRGAP1***	HET	c.1850G>A p.Arg617His rs201404379	C. i.	1.000 T DC	0/31/280932 0/2/6501	G - VUS	Index ind. F	4	N/A; N/A	R UPJO	-	*Novel*
B3057[g]	***SRGAP1***	HET	c.1762G>A p.Glu588Lys rs371344520	C. e.	0.665 T DC	0/4/251014 0/1/4299	G - VUS	Index ind. F	10	HET; WT	BL VUR	-	*Novel*
B3119[g]	***TBX18***	HET	c.787A>G p.Met263Val rs1465314738	D. m.	0.991 D DC	0/1/249930 -	G - VUS	Index ind. F	5	HET; N/A	BL VUR	-	*Novel*
B3628[g]	***TBX18***	HET	c.821G>T p.Arg274Leu rs200317774	D. r.	0.983 D DC	0/20/282454 -	G - LB	Index ind. F	13	HET; N/A	BL VUR grade 3	-	*Novel*
B4079[g]	***TBX18***	HET	c.1179_1181del CTC p.Ser394del rs1459853324	-	- - -	- -	G - VUS	Index ind. F	11	WT; HET	R VUR grade 3	-	*Novel*
B4148[g]	***TP63***	HET	c.473C>T p.Ala158Val rs767384779	D. r.	0.447 D DC	0/3/251428 -	G - VUS	Index ind. M	104	WT; HET	L renal agenesis, R VUR grade 4-5 and hydronephrosis	Photophobia, blepharitis, strabismus, low set ears, short neck, malformed auricles, growth retardation	*Novel*
B1825	***TRAP1***	HET	c.1018C>T p.Arg340Cys rs775599442	C. e.	0.985 D DC	0/4/250926 -	G - VUS	Index ind. M	66	WT; HET	Prenatal BL hydronephrosis	-	*Novel*
		HET	c.383G>A p.Arg128His rs61758086	S. c.	0.991 D DC	6/848/282796 0/19/6478	G LB B			HET; WT			*Novel*

Family	Gene	Zygo-sity	Nucleotide change Protein change dbSNP	Amino acid con-serva-tion[a]	PP2 SIFT MT	gnomAD[b] EVS	HGMD[c] ClinVar[d] ACMG/ AMP[e]	Pedigree relation Sex	Homo-zygo-sity [Mb]	Segregation maternal; paternal; (other)	Renal phenotype	Extrarenal phenotype	Reference [PMID][f]
B3253	***UPK3A***	HET	c.227C>A p.Ser76* rs202189234	-	- - -	0/23/251206 0/1/6502	DM - LB	Index ind. F	10	HET; N/A	BL VUR	-	26489027 232
B3283[g]	***WNT4***	HET	c.125C>T p.Thr42Met rs1453786532	D. r.	0.759 D DC	0/1/251440 -	G - VUS	Index ind. M	9	HET; WT	PUV, L UPJO and VUR grade 3-4	-	*Novel*
B3545x	***WNT4***	HET	c.992A>T p.His331Leu rs1292945005	D. r.	0.577 T DC	- -	DM - VUS	Index ind. F	10	N/A; N/A	R renal agenesis, L hydronephrosis	Hirsutism, acne	31130284 233

-, not available/not reported; **BL**, bilateral; **DC**, disease-causing; **D**, deleterious; **EVS**, Exome Variant Server; **F**, female; **gnomAD**, Genome Aggregation Database; **HOM**, homozygous; **HET**, heterozygous; **ind**, individual; **L**, left; **M**, male; **MCDK**, multicystic dysplastic kidney; **MT**, MutationTaster; **N/A**, DNA for segregation analysis not available; **PMID**, PubMed Identifier; **PP2**, PolyPhen-2 **PUV**, posterior urethral valve; **R**, right; **SIFT**, Sorting intolerant from tolerant; **T**, tolerated; **UPJO**, uretero-pelvic junction obstruction; **UVJO**, uretero-vesical junction obstruction; **VUR**, vesicoureterenal reflux; **WT**, wild type.

[a] Evolutionary amino acid conservation across phylogeny was assessed over *Mus musculus* (M. m.), *Gallus gallus* (G. g.), *Xenopus tropicalis* (X. t.), *Danio rerio* (D. r.), *Ciona intestinalis* (C. i.), *Caenorhabditis elegans* (C. e.), *Drosophila melanogaster* (D. m.), and *Saccharomyces cerevisiae* (S. c.). If continuous conservation is interrupted but otherwise preserved across phylogeny, additional information is provided.
[b] Allele frequencies in gnomAD and EVS are indicated with homozygous/hemizygous (if applicable)/heterozygous/total alleles detected.
[c] Indicates presence status in the Human Gene Mutation Database (HGMD®): **DM**, variant reported as disease-causing (reference for primary literature report is provided in 'Reference' column; **G**, the particular variant was not reported in the database but other disease-causing variants in the gene were previously reported; **R**, disease-causing variants were reported in the ±10 nucleotides vicinity of the nucleotide that harbors a variant here.
[d] ClinVar classification indicates that the variant has been reported to the ClinVar database as follows: **B**, benign; **LB**, likely benign; **US**, uncertain significance; **LP**, likely pathogenic; **PATH**, pathogenic.
[e] Indicates variant classification published by the American College of Medical Genetics and Genomics (ACMG) and the Association for Molecular Pathology (AMP): **B**, benign; **LB**, likely benign; **VUS**, variant of uncertain significance; **LP**, likely pathogenic; **P**, pathogenic.
[f] *Novel* indicates that, to our knowledge, the variant has not been reported in the literature before.
[g] In a clinical diagnostic setting, this variant would be classified as "variant of unknown significance" due to difficultly assessable pathogenicity (non-truncating heterozygous variant in a dominant gene with unproven *de novo* status and not previously reported in the literature).
[h] Interruption of conservation due to lysine present in *D. r.*
[i] The father was reported to be affected from deafness.
[j] Interruption of conservation due to proline present in *X. t.*
[k] Interruption of conservation due to leucine present in *C. e.*
[l] Variant confirmation with Sanger sequencing was not performed due to insufficient remaining DNA.
[m] Interruption of conservation due to phenylalanine present in *G. g.*
[n] Interruption of conservation due to lysine present in *X. t.*
[o] The father and paternal grandfather were reported to be affected from severe gout; the older brother of the proband was reported to be affected from left hydronephrosis, chronic kidney disease, and hyperuricemia.
[p] Homozygous exon deletion, which is predicted to result in no functional protein, was detected by absent ES sequencing coverage in this area and was confirmed by a polymerase chain reaction-based analysis.
[q] No existing orthologous gene in *G. g.*

[r] This variant is located within a stretch of seven consecutive G-C base pairs, thus the exact nucleotide in which this variant arose cannot be ascertained. Since the variant in family B3775 proved to be *de novo* and as several different truncating variants within this region were previously reported to be disease-causing, the area probably denotes a mutational hotspot.
[s] Interruption of conservation due to cysteine present in *X. t.*
[t] A truncating single nucleotide variant c.1509C>A that is predicted to result in the same protein change p.Y503* was reported previously (PMID 10819639[231]).
[u] Interruption of conservation due to glycine present in *X. t.*
[v] Interruption of conservation due to leucine present in *G. g.*
[w] Interruption of conservation due to serine present in *G. g.*

Table S7. 32 Families with isolated CAKUT and likely non-causative variants in candidate genes for syndromes with facultative CAKUT.

Families are listed in alphabetical order by gene symbol.

Family	Gene	Zygo-sity	Nucleotide change Protein change dbSNP	Amino acid con-serva-tion[a]	PP2 SIFT MT	gnomAD[b] EVS	HGMD[c] ClinVar[d] ACMG/ AMP[e]	Pedigree relation Sex	Homo-zygo-sity [Mb]	Segregation maternal; paternal; (other)	Renal phenotype	Extrarenal phenotype	Reference [PMID][f]
B3506	***ACTG1***	HET[g]	c.389C>T p.Pro130Leu -	D. m.	1.000 D DC	0/1/31404 -	- - VUS	Index ind. M	10	HET; WT	L UPJO	-	*Novel*
A3464	***ACTG2***	HET	c.752T>C p.Ile251Thr rs201286699	X. t.	0.999 D DC	0/5/249150 0/1/6502	- - VUS	Index ind. F	12	N/A; N/A	L renal agenesis	-	*Novel*
B720	***ARID1B***	HET	c.2675G>A p.Gly892Asp rs780312215	D. r.[h]	1.000 T -	0/2/31402 -	G - VUS	Index ind. M	2	WT; N/A	PUV, R dysplastic kidney with VUR grade 5 and megaureters	-	*Novel*
B3399	***BCOR***	HEMI	c.4631A>G p.Glu1544Gly -	C. i.[i]	0.866 D DC	- -	G - VUS	Index ind. M	15	HET; WT	BL VUR and hydronephrosis	-	*Novel*
B2501	***CHD7***	HET	c.6335C>T p.Thr2112Met rs758409717	D. r.	0.781 T DC	0/4/248948 -	G - VUS	Index ind. M	16	HET; WT	PUV, BL VUR	-	*Novel*
B1778	***CHD7***	HET	c.4870A>G p.Ile1624Val -	C. e.	0.898 D DC	- -	G - VUS	Index ind. M	175	N/A; N/A	PUV, neurogenic bladder	-	*Novel*
B3118	***DACT1***	HET	c.7C>T p.Pro3Ser rs1247520462	D. r.	0.998 D DC	- -	G - LB	Index ind. M	2	N/A; N/A	L duplex kidney, R renal hypodysplasia	-	*Novel*
B37	***GLI3***	HET	c.892C>G p.Pro298Ala -	C. i.	0.975 D DC	- -	G - VUS	Index ind. F	4	HET; WT; affected sister: HET	BL ureterocele	-	*Novel*
								Sister of index ind. F	9	HET; WT; affected sister: HET	BL UVJO	-	
								Mother of index ind. F	4	N/A; N/A; two affected daughters: HET	R duplex collecting system	-	
B1684	***GLI3***	HET	c.1954C>A p.Pro652Thr rs552333286	D. r.	0.940 D DC	0/3/251278 -	G - VUS	Index ind. F	7	HET; N/A	BL VUR, L hydronephrosis and renal cysts	-	*Novel*
B3403	***GLI3***	HET	c.2965C>T p.Arg989Trp rs1313713644	D. r.[j]	0.582 D DC	- -	G - VUS	Index ind. F	7	HET; N/A	BL VUR	-	*Novel*

Family	Gene	Zygo-sity	Nucleotide change Protein change dbSNP	Amino acid con-serva-tion[a]	PP2 SIFT MT	gnomAD[b] EVS	HGMD[c] ClinVar[d] ACMG/ AMP[e]	Pedigree relation Sex	Homo-zygo-sity [Mb]	Segregation maternal; paternal; (other)	Renal phenotype	Extrarenal phenotype	Reference [PMID][f]
B4106	***GLI3***	HET	c.2584C>G p.Arg862Gly -	C. e.	1.000 D DC	- -	G - VUS	Index ind. M	5	HET; N/A	BL VUR	-	*Novel*
B3181	***GLI3***	HET	c.1424A>T p.Glu475Val -	D. r.	0.159 D DC	- -	G - VUS	Index ind. M	20	HET; WT	R hypoplastic kidney and VUR grade 2	-	*Novel*
B694	***JAG1***	HET	c.2150G>C p.Gly717Ala rs200473477	C. i.	0.988 D DC	0/1/251488 -	R - LP	Index ind. M	10	N/A; N/A	BL VUR	-	*Novel*
B2314	***KAL1***	HEMI	c.1345A>C p.Lys449Gln -	D. r.[k]	0.888 D P	0/0/2/183354 -	G - VUS	Index ind. M	9	HET; WT	BL renal hypodysplasia	-	*Novel*
B573	***KCTD1***	HET	c.1963A>G p.Thr655Ala rs771086832	C. i.	0.997 D DC	0/1/251040 -	G - LP	Index ind. M	6	HET; WT	R anterior ureteral obstruction	-	*Novel*
B561	***KDM6A***	HEMI	c.1954G>T p.Ala652Ser -	D. r.	0.011 D DC	- -	G - LB	Index ind. M	8	N/A; N/A	BL echogenic kidneys	-	*Novel*
B2790	***MTOR***	HET	c.6856G>C p.Val2286Leu -	C. i.	1.000 D DC	- -	G - VUS	Index ind. F	11	HET; WT	R ureterohydronephrosis	-	*Novel*
								Mother of index ind. F	6	N/A; N/A; affected daughter: HET	L non-obstructive duplex collecting system	-	
B2448	***MTOR***	HET	c.2762A>G p.Lys921Arg -	D. r.	0.973 T DC	- -	G - VUS	Index ind. M	11	HET; WT	R renal agenesis, L hydronephrosis	-	*Novel*
B807	***NIPBL***	HET	c.8329G>T p.Ala2777Ser rs200872976	D. r.	0.978 D DC	0/6/282784 -	R - VUS	Index ind. M	7	N/A; N/A	PUV, R renal agenesis, L UPJO	-	*Novel*
B3242	***NIPBL***	HET[g]	c.5700G>C p.Glu1900Asp -	D. r.	0.847 D DC	- -	R - VUS	Index ind. M	7	HET; N/A	PUV	-	*Novel*
A560	***NIPBL***	HET	c.2521C>G p.Arg841Gly -	X. t.	0.319 D DC	- -	G - VUS	Index ind. F	17	N/A; N/A	PUV	-	*Novel*

Family	Gene	Zygo-sity	Nucleotide change Protein change dbSNP	Amino acid con-serva-tion[a]	PP2 SIFT MT	gnomAD[b] EVS	HGMD[c] ClinVar[d] ACMG/ AMP[e]	Pedigree relation Sex	Homo-zygo-sity [Mb]	Segregation maternal; paternal; (other)	Renal phenotype	Extrarenal phenotype	Reference [PMID][f]
B4112	***PIGT***	HET	c.934C>T p.Arg312Trp rs1377337561	C. i.[l]	0.659 D DC	0/2/251490 -	G - VUS	Index ind. M	12	HET; WT	PUV, BL VUR and hydronephrosis	-	*Novel*
		HET	c.575T>A p.Leu192His -	S. c.	0.990 D DC	- -	G - VUS			WT; HET			*Novel*
A3465	***PROKR2***	HET	c.759G>C p.Lys253Asn rs945720170	D. r.	1.000 D DC	- -	R - VUS	Index ind. M	22	N/A; N/A	L renal agenesis	-	*Novel*
B3235	***PTPN11***	HET	c.1048T>G p.Ser350Ala rs146571700	D. r.	0.744 D -	0/3/251460 0/1/6502	G US VUS	Index ind. F	11	WT; HET	BL VUR	-	*Novel*
A3282	***RAI1***	HET	c.1379C>T p.Pro460Leu rs749537955	X. t.	0.998 D DC	0/4/281476 -	G - VUS	Index ind. M	174	N/A; N/A	R renal agenesis, L renal stone	-	*Novel*
B2677	***RECQL4***	HOM	c.1090G>A p.Val364Met rs144637135	D. r.[m]	0.998 D -	1/405/278948 0/1/12454	G B LB	Index ind. M	80	N/A; N/A	L VUR	-	*Novel*
A1069	***SALL4***	HET	c.1243T>C p.Cys415Arg -	D. m.	1.000 D -	- -	G - VUS	Index ind. M	6	N/A; N/A	L renal hypoplasia and ureterocele	-	*Novel*
B3175	***SOS1***	HET	c.2728G>C p.Asp910His rs369277679	D. r.	0.906 T DC	0/7/250834 0/2/6498	G US/LB VUS	Index ind. M	11	N/A; N/A	BL VUR	-	*Novel*
B3366	***SOX9***	HET	c.233G>A p.Ser78Asn rs1175328216	C. i.	0.996 T DC	0/1/226684 -	R - LP	Index ind. F	10	N/A; HET	BL VUR	-	*Novel*
								Father of index ind. M	4	N/A; N/A; affected daughter: HET	BL VUR	-	
B3744	***TBX1***	HET	c.610G>A p.Ala204Thr rs748232668	G. g.	0.337 D DC	0/6/250736 -	G - LB	Index ind. M	15	HET; WT	L hydroureter and hydronephrosis	-	*Novel*
B4063	***TP63***	HET	c.865C>T p.Pro289Ser rs757045273	C. i.	0.937 D DC	0/10/251324 -	G - B	Index ind. F	14	HET; WT	R UVJO	-	*Novel*
B2324	***TP63***	HET	c.1313A>G p.Gln438Arg -	D. r.	0.996 D DC	- -	G - VUS	Index ind. M	10	WT; HET; unaffected sibling: WT	BL hydronephrosis	-	*Novel*

-, not available/not reported; **BL**, bilateral; **DC**, disease-causing; **D**, deleterious; **EVS**, Exome Variant Server; **F**, female; **gnomAD**, Genome Aggregation Database; **HOM**, homozygous; **HEMI**, hemizygous; **HET**, heterozygous; **ind**, individual; **L**, left; **M**, male; **MT**, MutationTaster; **N/A**, DNA for segregation analysis not available; **P**, polymorphism; **PMID**, PubMed Identifier; **PP2**, PolyPhen-2 **PUV**, posterior urethral valve; **R**, right; **SIFT**, Sorting intolerant from tolerant; **T**, tolerated; **UPJO**, uretero-pelvic junction obstruction; **UVJO**, uretero-vesical junction obstruction; **VUR**, vesicoureterenal reflux; **WT**, wild type.

[a] Evolutionary amino acid conservation across phylogeny was assessed over *Mus musculus* (M. m.), *Gallus gallus* (G. g.), *Xenopus tropicalis* (X. t.), *Danio rerio* (D. r.), *Ciona intestinalis* (C. i.), *Caenorhabditis elegans* (C. e.), *Drosophila melanogaster* (D. m.), and *Saccharomyces cerevisiae* (S. c.). If continuous conservation is interrupted but otherwise preserved across phylogeny, additional information is provided.
[b] Allele frequencies in gnomAD and EVS are indicated with homozygous/hemizygous (if applicable)/heterozygous/total alleles detected.
[c] Indicates presence status in the Human Gene Mutation Database (HGMD®): **DM**, variant reported as disease-causing (reference for primary literature report is provided in 'Reference' column; **G**, the particular variant was not reported in the database but other disease-causing variants in the gene were previously reported; **R**, disease-causing variants were reported in the ±10 nucleotides vicinity of the nucleotide that harbors a variant here.
[d] ClinVar classification indicates that the variant has been reported to the ClinVar database as follows: **B**, benign; **LB**, likely benign; **US**, uncertain significance; **LP**, likely pathogenic; **PATH**, pathogenic.
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[f] *Novel* indicates that, to our knowledge, the variant has not been reported in the literature before.
[g] Variant confirmation with Sanger sequencing was not performed due to insufficient remaining DNA.
[h] The orthologous gene in *X. t.* does not align at this position.
[i] Interruption of conservation due to aspartate present in *D. r.*
[j] Interruption of conservation due to glycine present in *M. m.*
[k] Interruption of conservation due to asparagine present in *M. m.*
[l] Interruption of conservation due to lysine present in *G. g.*
[m] The orthologous gene in *G. g.* does not align at this position.

Table S8. Genotype and phenotype information for 10 families with likely causative variants in genes causing a phenocopy of CAKUT.

Families are listed in alphabetical order by gene symbol.

Family	Gene	Zygo-sity	Nucleotide change Protein change dbSNP	Amino acid con-serva-tion[a]	PP2 SIFT MT	gnomAD[b] EVS	HGMD[c] ClinVar[d] ACMG/ AMP[e]	Pedigree relation Sex	Homo-zygo-sity [Mb]	Segregation maternal; paternal; (other)	Renal phenotype	Extrarenal phenotype	Reference [PMID][f]
B3618	*BBS4*	HOM	c.157-2A>G p.? rs113994192	-	- - -	0/1/251008 -	DM PATH P	Index ind. M	231	N/A; N/A	L renal agenesis, R hydronephrosis, cryptorchidism	Night blindness, intellectual disability, postaxial polydactyly of foot, obesity, hypogonadism	12016587 234
B780	*BBS12*	HET	c.1531C>T p.Gln511* -	-	- - -	- -	G - P	Index ind. F	2	HET; N/A	BL cystic kidney disease	Bardet-Biedl syndrome (OMIM: 615982)	*Novel*
		HET	c.2023C>T p.Arg675* rs752202089	-	- - -	0/2/246292 -	DM PATH P			WT; N/A			20827784 235
B1255[g]	*BICC1*	HET	c.797A>G p.Glu266Gly -	C. i.[h]	0.890 D DC	- -	G - LP	Index ind. M	14	HET; WT	PUV, R hypoplastic kidney, L dysplastic kidney, BL hydronephrosis	-	*Novel*
B2378	*KIF14*	HOM	c.1603T>G p.Ser535Ala rs868084071	D. r.[i]	0.380 D DC	0/2/245972 -	G - VUS	Index ind. M	154	N/A; N/A; affected brother: HOM	R VUR, L UPJO, R cystic dysplasia	-	*Novel*
								Brother of index ind. M	154	N/A; N/A; affected brother: HOM	L hypoplastic kidney, R renal pelvis dilation	-	
B907	*PKD1*	HET[j]	c.6487C>T p.Arg2163* -	-	- - -	- -	DM PATH P	Index ind. M	12	N/A; N/A	BL cystic kidneys and VUR grade 5, R duplex collecting system	-	11115377 236
B587	*PKD1*	HET[j]	c.303_305del CAA p.Asn101del -	-	- - -	- -	DM - VUS	Index ind. M	1	N/A; N/A	L MCDK, R cystic kidney with loss of corticomedullary differentiation	-	17574468 237
B3777	*PKD1*	HET	c.11944C>T p.Gln3982* -	-	- - -	- -	DM PATH P	Index ind. F	5	WT; HET; two unaffected siblings: WT	BL polycystic kidneys	-	17582161 219
								Father of index ind. M	153	N/A; N/A; affected daughter: HET	BL polycystic kidneys	-	

Family	Gene	Zygo-sity	Nucleotide change Protein change dbSNP	Amino acid con-serva-tion[a]	PP2 SIFT MT	gnomAD[b] EVS	HGMD[c] ClinVar[d] ACMG/ AMP[e]	Pedigree relation Sex	Homo-zygo-sity [Mb]	Segregation maternal; paternal; (other)	Renal phenotype	Extrarenal phenotype	Reference [PMID][f]
A4479	***PKD2***	HET[j]	c.916C>T p.Arg306* -	-	- - -	0/1/251172 -	DM PATH P	Index ind. F	19	WT; HET	L MCDK, BL duplex collecting system	-	9326320 [238]
								Father of index ind. M	30	N/A; N/A; affected son: HET	BL polycystic kidneys	-	
B3906	***PKHD1***	HOM	c.5601-1G>A p.? -	-	- - -	- -	R - P	Index ind. M	154	HET; HET	BL polycystic kidneys	Pulmonary hypoplasia	*Novel*
B4070	***UMOD*** [k]	HET	c.306delC p.Gly136Val fs*141 -	-	- - -	- -	DM - P	Index ind. M	87	N/A; N/A	PUV, BL hydronephrosis and echogenic, multicystic kidneys	Pulmonary hypoplasia, ascites	28600779 [239]

-, not available/not reported; **BL**, bilateral; **DC**, disease-causing; **D**, deleterious; **EVS**, Exome Variant Server; **F**, female; **gnomAD**, Genome Aggregation Database; **HOM**, homozygous; **HEMI**, hemizygous; **HET**, heterozygous; **ind**, individual; **L**, left; **M**, male; **MCDK**, multicystic dysplastic kidney; **MT**, MutationTaster; **N/A**, DNA for segregation analysis not available; **PMID**, PubMed Identifier; **PP2**, PolyPhen-2 **PUV**, posterior urethral valve; **R**, right; **SIFT**, Sorting intolerant from tolerant; **T**, tolerated; **UPJO**, uretero-pelvic junction obstruction; **UVJO**, uretero-vesical junction obstruction; **VUR**, vesicoureterenal reflux; **WT**, wild type.

[a] Evolutionary amino acid conservation across phylogeny was assessed over *Mus musculus* (M. m.), *Gallus gallus* (G. g.), *Xenopus tropicalis* (X. t.), *Danio rerio* (D. r.), *Ciona intestinalis* (C. i.), *Caenorhabditis elegans* (C. e.), *Drosophila melanogaster* (D. m.), and *Saccharomyces cerevisiae* (S. c.). If continuous conservation is interrupted but otherwise preserved across phylogeny, additional information is provided.
[b] Allele frequencies in gnomAD and EVS are indicated with homozygous/hemizygous (if applicable)/heterozygous/total alleles detected.
[c] Indicates presence status in the Human Gene Mutation Database (HGMD®): **DM**, variant reported as disease-causing (reference for primary literature report is provided in 'Reference' column; **G**, the particular variant was not reported in the database but other disease-causing variants in the gene were previously reported; **R**, disease-causing variants were reported in the ±10 nucleotides vicinity of the nucleotide that harbors a variant here.
[d] ClinVar classification indicates that the variant has been reported to the ClinVar database as follows: **B**, benign; **LB**, likely benign; **US**, uncertain significance; **LP**, likely pathogenic; **PATH**, pathogenic.
[e] Indicates variant classification published by the American College of Medical Genetics and Genomics (ACMG) and the Association for Molecular Pathology (AMP): **B**, benign; **LB**, likely benign; **VUS**, variant of uncertain significance; **LP**, likely pathogenic; **P**, pathogenic.
[f] *Novel* indicates that, to our knowledge, the variant has not been reported in the literature before.
[g] In a clinical diagnostic setting, this variant would be classified as "variant of unknown significance" due to difficultly assessable pathogenicity (non-truncating heterozygous variant in a dominant gene with unproven *de novo* status and not previously reported in the literature).
[h] Interruption of conservation due to arginine present in *D. r.*
[i] Interruption of conservation due to threonine present in *G. g.*
[j] Variant confirmation with Sanger sequencing was not performed due to insufficient remaining DNA.
[k] The variant detected in *UMOD* can explain the bilateral echogenic kidneys in the patient; however, the CAKUT phenotype besides that (PUV, VUR) is most likely due to another cause.

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