Supplemental methods

Targeted exome sequencing: design, sequencing, and prioritization of the variants

We developed a targeted exome sequencing strategy focusing on 330 genes (Table S2) including (a) known causative or likely causative genes, with mutations reported in the literature in cases with isolated and/or syndromic CAKUT (55 genes),[1-50] (b) genes whose knock-out in mouse lead to kidney developmental defects (104 genes),[51-142] (c) genes involved in cellular processes/signaling pathways relevant for kidney development (84 genes),[143-200] (d) genes with a role in ureter/bladder development (11 genes),[201,202] (e) potential targets of transcription factors WT1 or HNF1B (57 genes),[204-206] and (f) gene related to gene(s) in group (a) to (e), expressed during kidney/LUT development (19 genes). A custom SureSelect gene panel was designed using the SureDesign software (Agilent). The target regions covered 1.38 Mb, including coding exons and splice junctions of the 330 genes. Illumina compatible precapture barecoded genomic DNA libraries were constructed according to the manufacturer's protocol (Ovation Ultralow, Nugen Technologies). Briefly, 1 to 3 µg of each double strand genomic DNA was mechanically fragmented to a median size of 200 pb using a Covaris, 100 ng was end-repaired and Illumina compatible adaptors containing a specific 8 bases barecode were ligated to the repaired ends (one specific barecode per patient). DNA fragments were PCR amplified to get the final precapture barecoded libraries and series of 16 or 36 barecoded libraries were pooled at equimolar concentrations. The capture process was performed according to the SureSelect protocol (Agilent) using 750 ng of the pool and 2µl or 3µl of biotinylated probes from the SureSelect panel (for pools of 16 or 36 libraries respectively). The barecoded libraries molecules complementary to the biotinylated probes retained by streptavidine coated magnetic beads were PCR amplified to generate a final pool of postcapture libraries. Sequencing was performed on an Illumina HiSeq2500 (Paired-End sequencing 130 x130 bases, High

Throughput Mode, 36 libraries per lane). After demultiplexing, sequences were aligned to the reference human genome hg19 using the Burrows-Wheeler Aligner. Downstream processing was carried out with the Genome Analysis Toolkit (GATK), SAMtools and Picard, following documented best practices (https://software.broadinstitute.org/gatk/best-practices/). Variant calls were made with the GATK Unified Genotyper. The annotation process was based on the latest release of the Ensembl database. Variants were annotated and analysed using the Polyweb software interface designed by the Bioinformatics platform of University Paris Descartes.

Prioritization of the variants was performed thanks to the polyweb interface. For known CAKUT genes, we filtered the variants whose frequency in ExAC was higher than 0,02% for genes reported in dominant CAKUT, or higher than 0,1% for those reported in recessive forms. For candidate genes, more stringent criteria were used in order to focus on the most promising genes and only variants absent in ExAC were retained. In addition, all variants identified in our in-house database (> 8000 exomes) in more than 5 independent sequencing projects of patients with various non-CAKUT phenotypes were eliminated. For missense variants, prediction of damaging effect was based on PolyPhen2,[207] Sift,[208] Mutation Taster,[209] Grantham score,[210] and GVGD.[211] Prediction of the effect of variants on splicing were based on SpliceSiteFinder, MaxEntScan, NNSPLICE, GeneSplicer and HumanSplicingFinder through Alamut.[212]

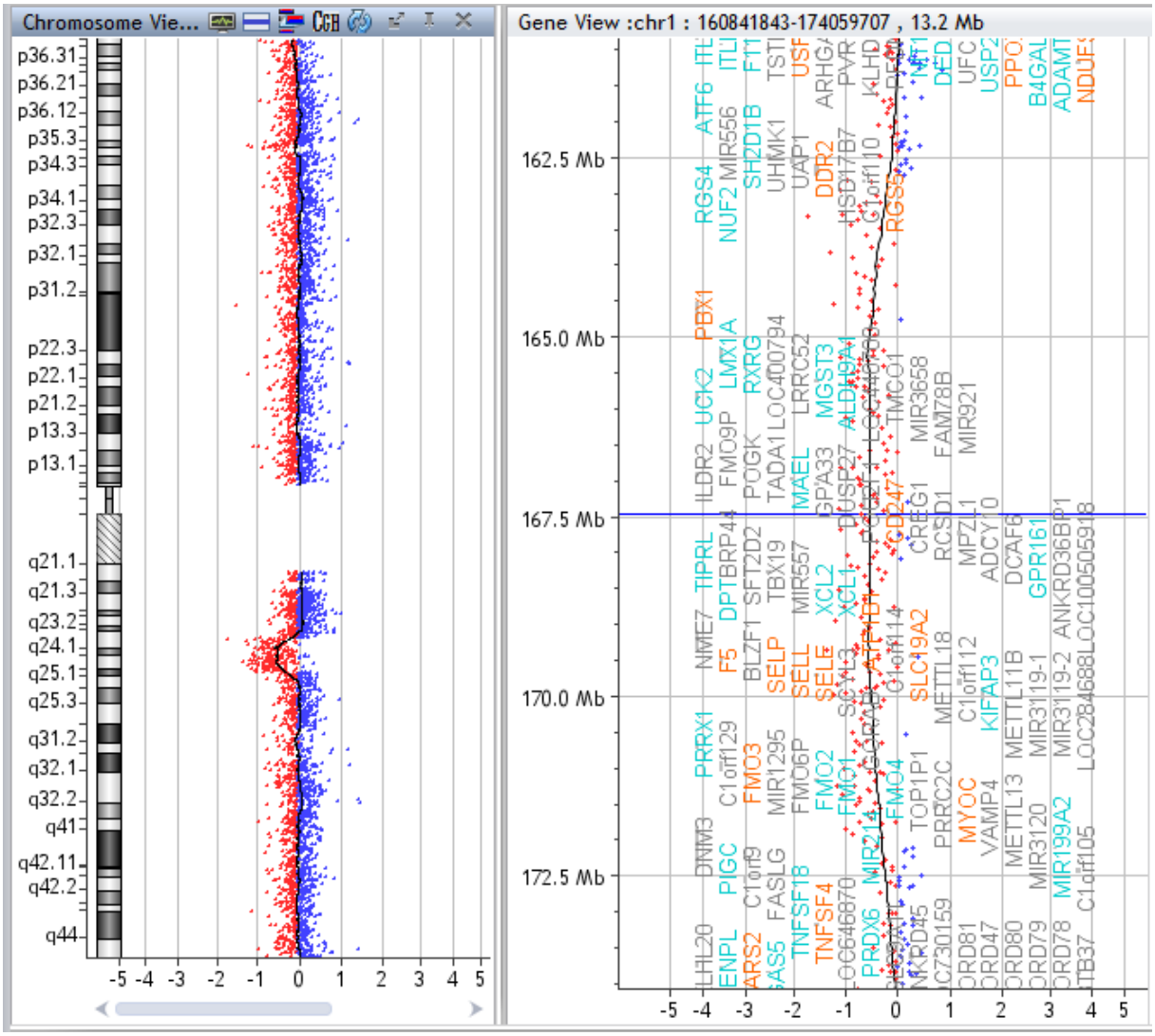

Figure S1 : Identification of a mosaic deletion including *PBX1* in the long arm of chromosome 1 in case K136 by CGH array

Array CGH analysis of DNA extracted from lymphocytes of case K136 was performed on an Agilent 60K oligonucleotide microarray (Agilent Technologies, Santa Clara, CA, USA). Result showing the 1q23.3q24.3 deletion (left). Vertical and horizontal axes indicate the genomic location and signal log2 ratio, respectively. The mean log2 ratio of the aberration region is −0.465, indicating mosaic deletion (right). The aneusomic segment was approximately 9.1 Mb in size, with proximal and distal breakpoints at 162,824,523 bp and 172,011,180 bp (GRCh 37, Hg19). This region includes *PBX1* and ~ 130 other genes.

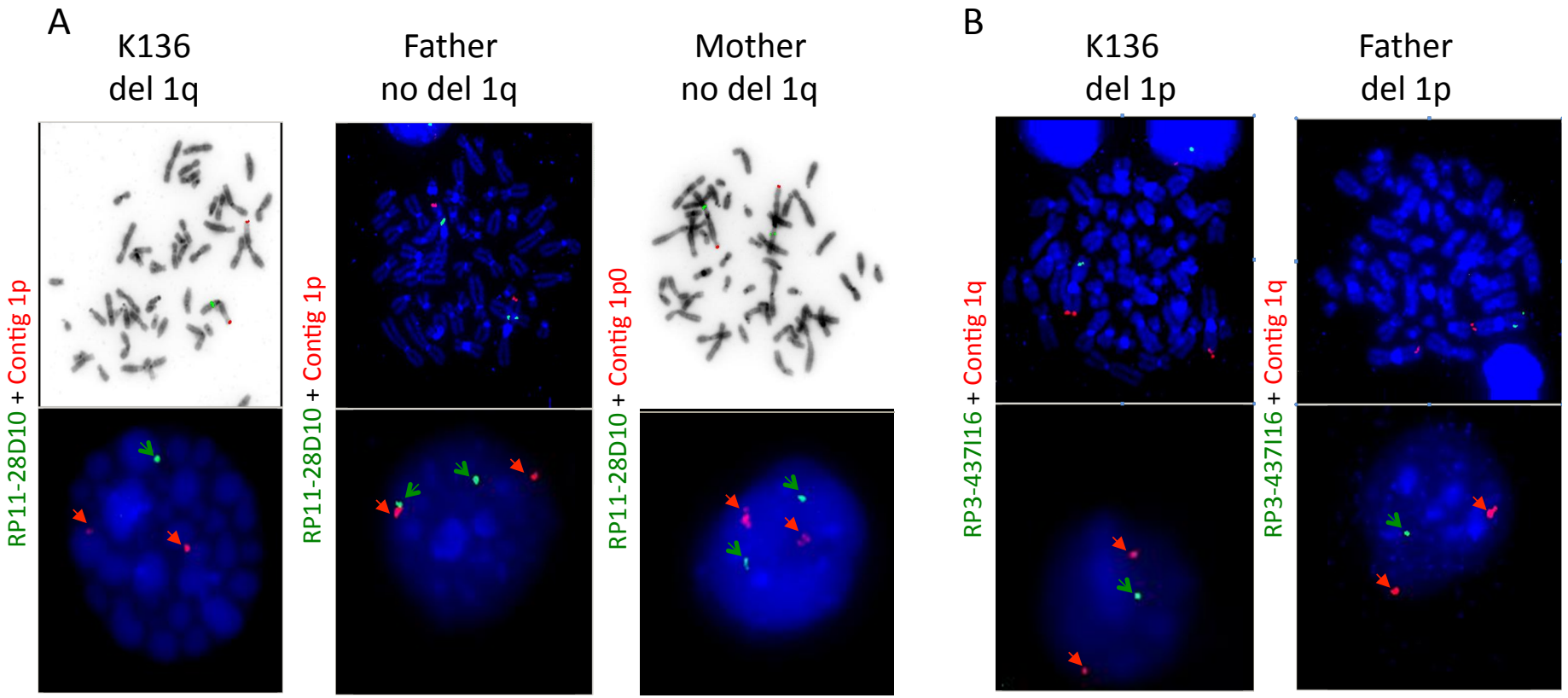

Figure S2: Fluorescent in situ hybridization experiments showing (A) *de novo* occurrence of the 1q deletion including *PBX1* and (B) inheritance of a paternal 1p deletion in case K136 (family 5)

BAC clones RP11-28D10 located in chr1:167,722,147 - 167,722,642; RP3-437I16 located in chr1:29,528,719-29,549,213

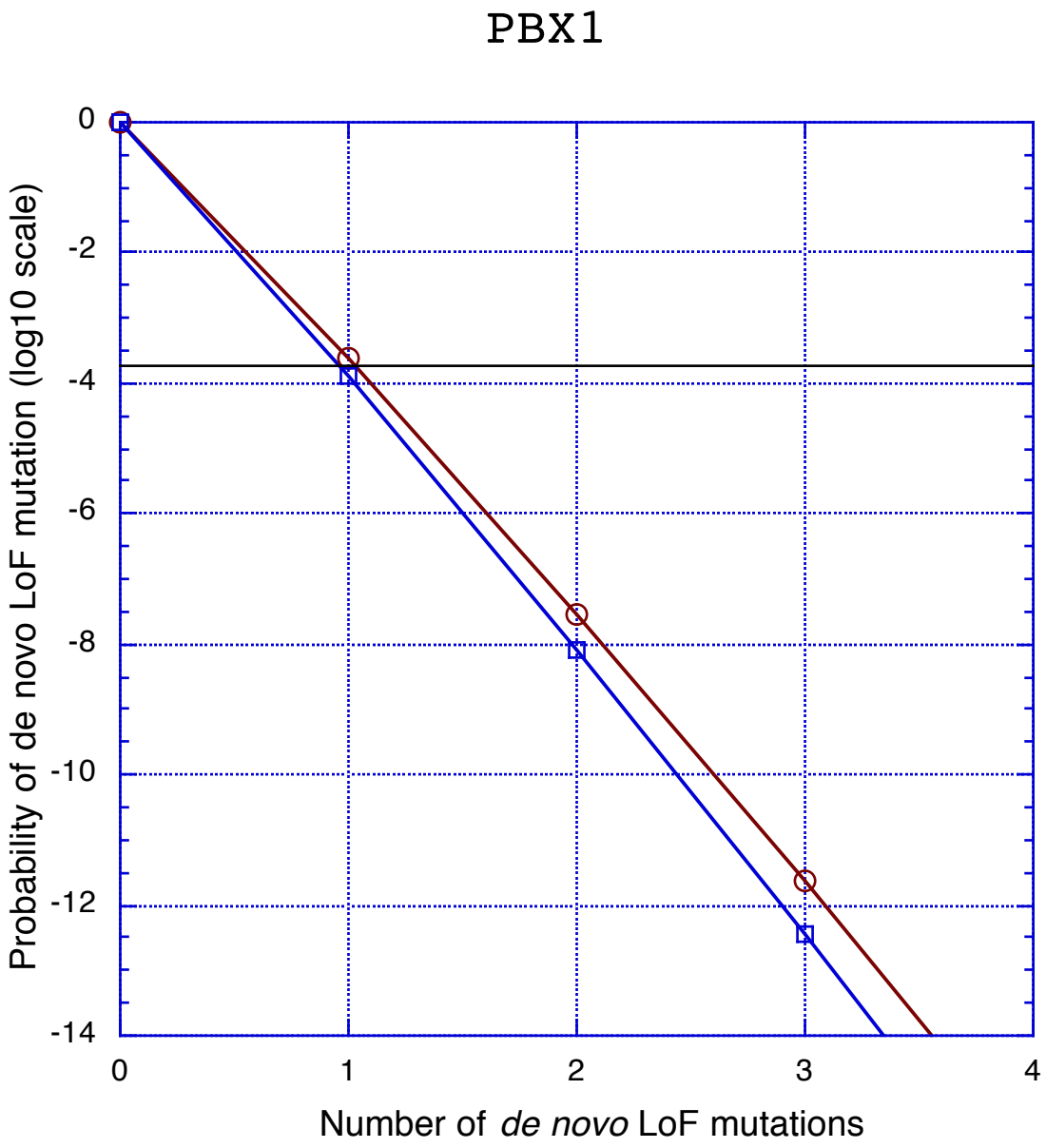

Figure S3: Result of a binomial test showing the probability that one or more *de novo* loss of function mutations in *PBX1* would occur by chance only in a cohort of 204 CAKUT cases.

Calculated and empirical values of probability for *de novo* loss-of-function mutations in *PBX1* were considered: (1) blue line: $p = 6.4 \times 10^{-7}$ = mean of values computed by Samocha et al for nonsense (7.8×10^{-7}), frameshift (8.2×10^{-7}) and splice site mutations (3.3×10^{-7}) in *PBX1*;[213] (2) red line: $p = 1.2 \times 10^{-6}$, corresponding to empirical frequency of *de novo* loss of function mutations per exome per generation (0.03 per-generation),[214] according to the size of the coding sequence of *PBX1* (1293 bp). The black line indicates the Bonferroni corrected significance threshold (1.5×10^{-4}) for 330 genes. The p-value for 3 mutations is 3.6×10^{-13}.

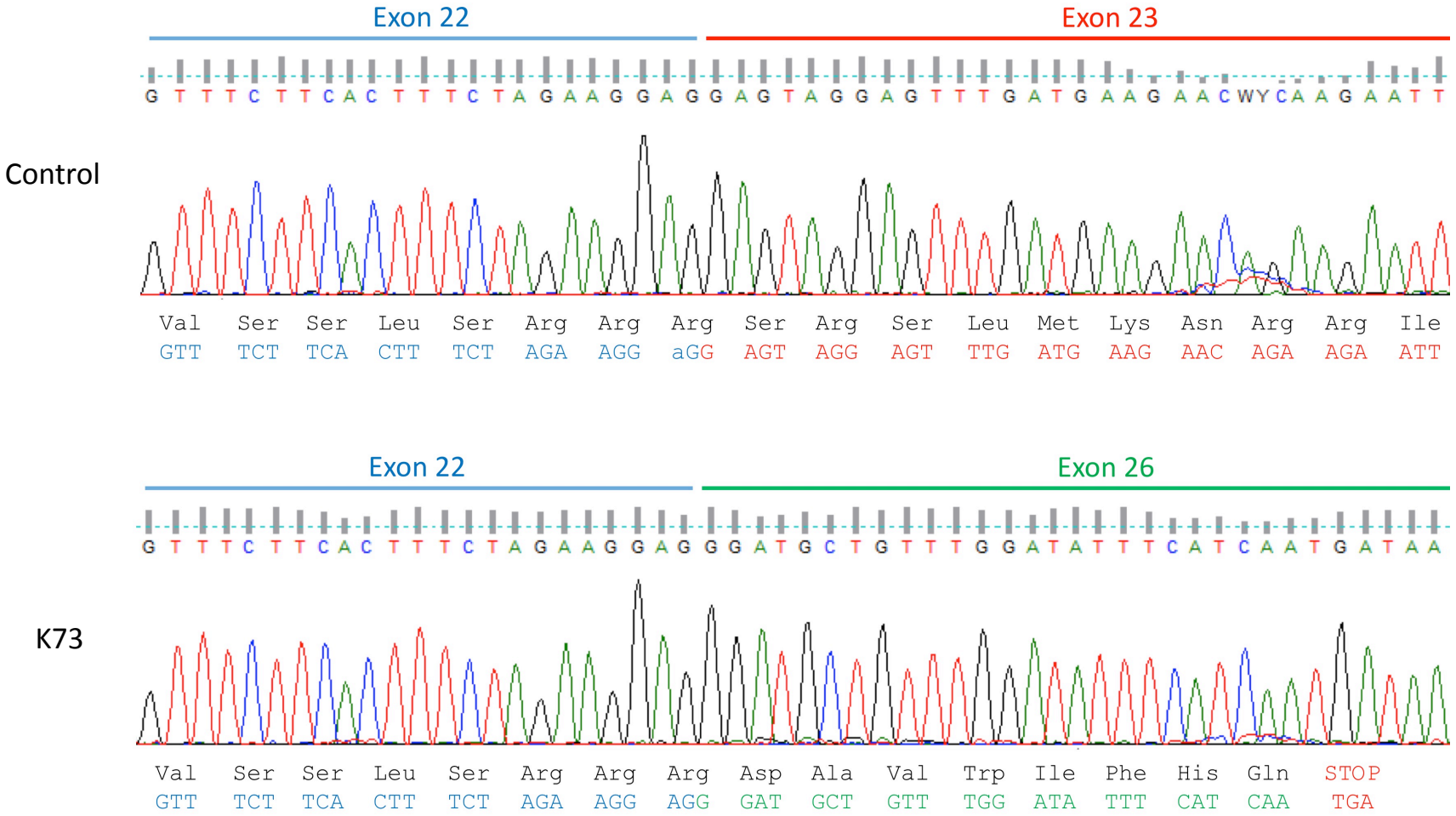

Figure S4: cDNA sequencing showing deletion of exons 23-25 with creation of a premature stop codon in case K73

Table S1. Phenotypes of all cases and variants identified																							
Case	Sex	Fetus	Renal phenotype acronym	RHa	RDb	Cysts	UMDc	BMDd	UKAe	BKAf	VURg	ObMegaUh	Duplexi	PUOj	Unprecised hydronephrosis	Renal ectopy	Family (1st degree)k	Family (other)l	Extra-renal phenotype	Causative mutations	Rare damaging variants in dominant CAKUT genes(<1/5000 in ExAC)	Reported variants in dominant CAKUT genes (>1/5000, <1/100 in ExAC)	Rare damaging variants in candidate genes[m] (absent from ExAC)
Cases with CAKUT phenotype																							
K1	F		RH	1																			MMP9, p.[Arg322Trp];[=] PDE3B, p.[Leu92Argfs*241];[=] HIC1, p.[Pro230Ser];[=]
K2	M		RH	1															hypospadias + polydactyly				CDKN1C, p.[Leu6Pro];[=]
K3	M	fetus	BKA							1							1		rigth ventricular dilation			RET, p.[Asp567Asn];[=]	
K4	F		RH	1															bifid uterus	HNF1B, c.[(?_-30)_(*220_?)del];[=]			
K5	M	fetus	BKA							1													LHX1, p.[Thr90Ile];[=]
K6	F		UKA						1										mullerian duplication				
K7	M	fetus	BKA							1									aortic stenosis				
K8	F	fetus	BKA							1									ephageal atresia + imperforate anus + 13th pair of ribs + vertebral fusion				
K9	M	fetus	BKA							1							1						SHH, p.[Val366Ala];[=]
K10	M	fetus	BKA							1													SPOCK2, p.[Lys398Glu];[=]
K11	M	fetus	UKA+				1		1														KIF3A, p.[Glu379Lys];[=]
K12	M	fetus	BKA							1													
K13	NA	fetus	BMD					1															DCHS1, p.[Ala2216Val];[=]
K14	F		RH	1													1		urogenital sinus				MAGED1, p.[Ala738Val];[=]
K15	M	fetus	BKA							1							1		pulmonary isomerisme + 11 pairs of ribs				
K16	M	fetus	BKA							1													
K17	F		UKA+						1		1		1				1						FRY, p.[Ala1643Val];[=]
K18	M	fetus	BMD					1															
K19	F	fetus	BKA							1									uterus and fallopian tubes agenesis				
K20	M	fetus	RD		1	1													liver cysts + pancreatitis				ENC1, p.[Tyr220His];[=]
K21	M	fetus	BMD					1													TBX18, p.[His204Tyr];[=]		
K22	M		RH+	1	1						1						1						
K23	F	fetus	BKA							1									left diaphragmatic hernia				
K24	M	fetus	BKA							1													
K25	M	fetus	UKA+				1		1										intrauterine growth retardation				
K26	M	fetus	BKA							1										ANOS1, p.[Arg257*];[=]			
K27	M	fetus	UKA+		1	1			1										left diaphragmatic hernia + imperforate anus + hypospadias				
K28	M	fetus	BKA							1									ear tag				LHX1, p.[Asn230His];[=] WNT6, p.[Gly196Alafs*123];[=]
K29	M	fetus	BKA							1											SIX5, p.[Ser730Leu];[=]		
K30	M		UMD+		1		1																
K31	M		RH+	1	1												1						WNT9B, p.[Cys145Tyr];[=]
K32	F	fetus	RH	1																	NOTCH2, p.[Asp355Asn];[=]	RET, p.[Arg694Gln];[=]	
K33	M		UMD+		1	1	1							1									
K34	M	fetus	BKA							1									testis agenesis				CRIM1, p.[Gly634Glu];[=]
K35	M		RH+	1							1						1						
K36	F		UKA+	1					1														
K37	F	fetus	UKA+				1		1														
K38	M	fetus	UKA+				1		1														
K39	F	fetus	UKA+				1		1								1	1	megalourethra				PIK3C3, p.[Phe597His];[=] RSPO3, p.[Lys161Gln];[=]
K40	F	fetus	BKA							1													
K41	M	fetus	BKA							1													
K42	F	fetus	Oth												1		1						
K43	F	fetus	RH+	1	1														heart defect + partial pancreas agenesis				ETV4, p.[Tyr209Cys];[=]
K44	NA	fetus	UKA+						1							1							GNB3, p.[Val276Gly];[=]
K45	F	fetus	BMD					1											accessory spleen				TGM5, p.[Thr590Arg];[=]
K46	M	fetus	BMD					1															KISS1R, p.[Ala135Ser];[=]
K47	M		RH+	1	1						1						1						
K48	M	fetus	RH+	1	1	1														GATA3, p.[Arg277*];[=]	TBX18, p.[Gln495Lys];[=]		
K49	M	fetus	BKA							1													
K50	F		UMD+				1				1						1			HNF1B, c.[(?_-30)_(*220_?)del];[=]			
K51	F	fetus	BMD					1											unicornuate uterus				SULF2, p.[Thr766Ile];[=]
K52	F	fetus	RD		1	1																	
K53	NA	fetus	UKA+	1					1								1						GREM1, p.[Gly9Cysfs*16];[=]

K54	NA	fetus	RD		1																		
K55	M		UKA						1									1					SOX4, p.[Phe334His];[=] WNT2B, p.[Ser136Ile];[=]
K56	NA	fetus	RD		1														interventricular communication + intrauterine growth retardation		TBC1D1, p.[Met930Ile];[=]		
K57	F	fetus	BKA							1													
K58	M	fetus	BKA							1								1					SPOCK2, p.[Gly372Trp];[=]
K59	F	fetus	RH+	1	1	1													uterus hypoplasia				
K60	F	fetus	RD		1	1													pancreas hypoplasia				DCHS1, p.[Thr930Ser];[=]
K61	NA	fetus	BKA							1													ECM1, p.[Asn176Ile];[=]
K62	M		RH	1															eye coloboma	PAX2, c.[?-30_305+?];[=]			
K63	F	fetus	BKA							1													
K64	M		Oth								1							1					KIF26B, p.[Arg1930Gly];[=]
K65	M	fetus	BMD					1															LAMC1, c.[1427+1G>C];[=] DACT1, p.[Glu57Lys];[=]
K66	M	fetus	BKA							1													
K67	M	fetus	UMD+				1								1				interventricular communication + single ombilical artery + small gallblader				
K68	M		RH+	1	1													1					
K69	F	fetus	BMD					1													SALL1, p.[Asn1257Lys];[=]		
K70	M	fetus	BMD					1													CHD1L, p.[Lys519Asn];[=] NOTCH2, p.[Arg1719Gln];[=] SALL4, p.[Arg831Gln];[=]		
K71	M	fetus	UMD				1											1					HIC1, p.[Gly702Asp];[=]
K72	M		RH	1														1	papillary excavation	PAX2, c.[(?_-30)_(*220_?)del];[=]			
K73	F	fetus	RH+	1	1	1													lissencephaly + agenesis of corpus callosum	KIF14, p.[1189Argfs*9];[(1189Argfs*9)]			CRLF1, p.[Lys285Glu];[=]
K74	M	fetus	BKA							1													HOXB1, p.[Ala294Val];[=]
K75	F		RH+	1	1	1																	
K76	M		RD		1	1													hypertelorism				
K77	F		RH	1														1					MDM4, p.[Ala398Thr];[=]
K78	NA	fetus	BKA							1								1	external ear anomaly	EYA1, c.[967-1G>C]:[=],			SOX4, p.[Ser136Ala];[=]
K79	F		RD		1	1													papillary coloboma	PAX2, c.[26-?_503+?del];[=]			
K80	F		UKA+		1	1			1									1 (BO)	preauricular pit + ear tag	EYA1, c.[557-?_1597+?del];[=]			GBX2, p.[Arg51Gly];[=]
K81	F	fetus	BKA							1													AMOTL1, p.[Glu507Lys];[=]
K82	M	fetus	BKA							1								1	1				HOXC11, p.[Pro62Arg];[=] SULF2, p.[Arg656Leu];[=]
K83	M		BMD					1											1			RET, p.[Ser688Phe];[=]		
K84	F	fetus	UKA+	1					1														AMOT, p.[Arg534Lys];[=]
K85	M		UKA						1									1	abnormal teeth				
K86	M		UMD+				1				1								morning glory syndrome + intellectual disability				DCHS1, p.[Val290Leu];[=]
K87	NA	fetus	BKA							1									1				HOXB5, p.[Arg181Trp];[=] HCN3, p.[Arg685Trp];[=]
K88	F	fetus	BKA							1								1					
K89	F		RH	1															1				
K90	F	fetus	RH+	1	1	1																	
K91	M		UKA						1									1			RET, p.[Arg635Cys];[=]		
K92	M	fetus	BKA							1													RCSD1, p.[Arg167Lys];[=]
K93	F		RH+	1	1														intellectual disability				LAMA5, p.[Leu1930Pro];[=] NTN1, p.[605Trpext*84];[=]
K94	M	fetus	UKA+				1		1										didelphys uterus		BICC1, p.[Thr755Arg];[=]		
K95	F	fetus	BKA							1													MET, p.[Ala119Val];[=]
K96	F		Oth											1				1	persistent left vena cava				HPSE, p.[Met1?];[=]
K97	F		Oth								1								optic atrophia + hyperlaxity				
K98	M	fetus	BKA							1								1	1				
K99	F	fetus	RH	1																			
K100	M		RD		1																		BMPR1A, p.[Phe397Ser];[=]
K101	F		UKA						1									1 (deafness)	ear tag + external ear canal stenosis	GATA3, c.[(?_-30)_(*220_?)del];[=]			
K102	M		RD		1	1																	MMP9, p.[Arg267Glyfs*71];[=]
K103	M		RD+		1										1			1		HNF1B, c.[(?_-30)_(*220_?)del];[=]			
K104	F		RH+	1	1	1																	
K105	M		RH+	1	1						1										TBC1D1, p.[Arg718Cys];[=]		
K106	M		RH+	1	1	1																	FAT4, p.[Ala2178Val];[=] FOXC1, p.[Ser339Phe];[=]

K107	F		RH	1															preauricular pits				ZEB2, p.[Thr350Met];[=] MYOCD, p.[Lys241Arg(;)Ser435Phe] GPR173, p.[Val143Ala];[=]
K108	M		RD		1	1											1							
K109	M		RH+	1	1	1								1										
K110	M		RD		1	1											1							
K111	F	fetus	BKA							1														
K112	M		RH+	1	1	1																		
K113	F		Oth								1						1		preauricular pits + deafness				GRHL2, p.[Lys419Glu];[=] PTGIR, p.[Pro17Argfs*6];[=]
K114	M		Oth									1							preauricular pits + cryptorchidy				AMOTL1, p.[Pro420Ser];[=]
K115	M		UMD				1												retina and iris coloboma					
K116	F	fetus	RH	1															intrauterine growth retardation + aortic anomaly				SCRIB, p.[Ser118Pro];[=]
K117	M	fetus	RH	1																PAX2, p.[Ser61Arg];[=]			CRLF1, p.[Trp144*];[=]
K118	F		RD		1	1																		
K119	F		RH	1													1 (BO)		branchial defect + deafness	EYA1, p.[Ser487Pro];[=]			LGR4, p.[Phe864*];[=] FAT1, p.[Glu1920Ala];[=] GAS1, p.[Ala216Glyfs*52];[=]
K120	M		RD		1														preauricular pit + deafness + growth retardation				NPNT, p.[Arg484Cys];[=]
K121	M	fetus	BKA							1									anus atresia + 13th pair of ribs					
K122	M	fetus	RD		1	1																		
K123	M		RH+	1	1														deafness					
K124	M		RD+		1	1								1						HNF1B, c.[(?_-30)_(*220_?)del];[=]			SCRIB, p.[Ala1516Val];[=]
K125	M		Oth												1			1					MATN4, p.[Ser44Asn];[=]
K126	NA	fetus	BKA							1													FAT4, p.[Glu3862Gln];[=] HOXD13, p.[Glu81*];[=]
K127	M		UKA+				1		1								1				BICC1, p.[Cys351Tyr];[=] DSTYK, p.[Asp892Asn];[=]	SOX17, p.[Tyr259Asn];[=]	
K128	F		UKA						1										bicornuate uterus					
K129	F		RD		1	1													diabetes				EGFR, p.[Gly573Arg];[=] FOXC2, p.[Pro204Ser];[=] HOXA11, p.[Met294Thr];[=]
K130	F	fetus	BMD					1									1							
K131	M		RD+		1	1									1		1						FZD7, p.[Pro217Leu];[=]
K132	F		UKA+		1	1			1										mullerian duplication				MMP9, p.[Ser335*];[=]
K133	F		RH+	1	1						1						1 (coloboma)		papillary coloboma	PAX2, p.[Val26Cysfs*3];[=]				
K134	F	fetus	BKA							1									cardiomyopathy + didelphys uterus					
K135	M		UKA						1								1 (BO)		preauricular pit	EYA1, p.[Gln185*];[=]			FZD4, p.[Leu443Met];[=]
K136	M		UKA+		1				1								1		dysmorphic features + intellectual disability + microcephaly	**PBX1, c.[(?_-30)_(*220_?)del];[=]**				
K137	M		RD+		1											1			papillary excavation				TFCP2L1, p.[Cys52Phe];[=]
K138	M		UKA+						1		1						1						SPOCK2, p.[Leu207Arg];[=]
K139	M		UKA						1								1							
K140	F		UMD+	1	1		1												dysmorphic features + intellectual disability					
K141	M		UMD+				1					1					1							
K142	M		RH+	1	1																			
K143	M		RD+		1										1					HNF1B, c.[(?_-30)_(*220_?)del];[=]				
K144	F	fetus	BMD					1											pulmonary cystic adenomatoid malformation				LAMA5, p.[Gly3067Alafs*40];[=] LAMC1, c.[3850-1G>A];[=] IRX2, p.[Leu398Ser];[=]
K145	M		RH	1													1		branchial defect	EYA1, p.[Asn446_Tyr448del];[=]			FZD8, p.[Pro105Arg];[=] ZNF106, p.[Phe1857Leu];[=] WNT6, p.[Glu221Asp];[=]
K146	F		RH+	1	1	1														PAX2, p.[Pro149Glnfs*10];[=]				
K147	F	fetus	UKA+				1		1															
K148	F	fetus	RH	1																PAX2, p.[Val26Glyfs*28];[=]				
K149	M		Oth									1											FAT4, p.[Arg1804Gly];[=]
K150	F		UKA						1										branchial defect					
K151	M		RH+	1	1	1																		
K152	M		UMD				1												preauicular pit				FAT3, p.[Thr3272Ser];[=]
K153	F		UKA+						1					1										
K154	M	fetus	BKA							1														
K155	F		UKA						1								1							
K156	M		RD+		1	1					1												TJP2, p.[Pro826Gln];[=]

K157	F		UKA						1											deafness				
K158	M	fetus	BKA							1								1			ANOS1, c.[?-30_255+?del]				
K159	M		UKA+		1	1			1																DCHS1, p.[Gln1714*];[=]
K160	F		UKA						1											deafness + branchial defect + colobomatous microphtalmia	CHD7, p.[Gly1684Ser];[=]	CDC5L, p.[Leu747Trp];[=]		
K161	F		RH	1																					MMP9, p.[Gly605Alafs*9];[=]
K162	F		RH+	1							1							1	1	palate cleft + preauticular pit		CDC5L, p.[Thr84Ser];[=]		FGFR1, p.[Arg91Trp];[=]
K163	M	fetus	BKA							1									1	interventricular communication				
K164	M	fetus	UMD+		1	1	1																		
K165	F	fetus	UKA+	1					1																
K166	F		Oth														1			deafness + preauricular pit				
K167	M		UKA						1											deafness + intellectual disability	GATA3, c.[(?_-30)_(*220_?)del];[=]			HIC1, p.[Gly386Arg];[=]
K168	M	fetus	BKA							1										intrauterine growth retardation				
K169	M	fetus	UKA+				1		1													TNXB, p.[Pro188Leu];[=]		
K170	M		RH+	1	1	1															HNF1B, c.[344+2_+5del];[=]			
K171	M		RD		1	1												1						
K172	M	fetus	UMD+		1	1	1											1 (diabetes)		diabetes + cryptorchidy	HNF1B, c.[(?_-30)_(*220_?)del];[=]			
K173	M		RH+	1	1	1												1	1	hypomagnesemia				FGF8, p.[Thr121Ser];[=] SLC6A18, p.[Thr221Ser];[=] FAT3, p.[Leu577Val];[=]
K174	NA	fetus	BKA							1														FRY, p.[Thr2366Ile];[=]
K175	F		RH	1																deafness + scoliosis	**PBX1, p.[Asn143Thrfs*37];[=]**			HOXD11, p.[Gly87Arg];[=]
K176	M		RH+	1	1	1												1			PAX2, p.[Ala111Thr];[=]			SCRIB, p.[Leu396Phe];[=]
K177	F		Oth												1					preauricular pit				ROBO1, p.[Ala1414Asp];[=] HS6ST1, p.[Lys84Asn];[=]
K178	F		RH+	1									1											
K179	F		RH+	1	1	1														dysmorphic features + intellectual disability	**PBX1, p.[Arg184*];[=]**			
K180	M		RH	1														1						NR2F2, p.[Gly44Ser];[=] WNT11, p.[Glu345Ala];[=] MECOM, p.[Ala311Val];[=]
K181	F		RH+	1	1												1			deafness	**PBX1, c.[(?_-30)_(*220_?)del];[=]**			
K182	F		RD		1	1												1		interauricular communication + osophageal atresia				SEMA3A, p.[Thr134Met];[=]
K183	M	fetus	UKA+				1		1								1							FAT1, p.[His2123Tyr];[=] GLI1, p.[Arg323Gln];[=]
K184	M		RH+	1	1						1									ear tag				ADCY8, p.[Ile868Ser];[=]
K185	F		RD		1																HNF1B, c.[(?_-30)_(*220_?)del];[=]			CITED1, p.[Gln6*];[=]
K186	M	fetus	RH	1																	**PBX1, c.[511-2A>G];[=],**			
K187	M	fetus	BKA							1								1	1					
K188	M		RD		1	1												1	1					FAT3, p.[Val1242Leu];[=]
K189	F		RD		1													1						ZNF106, p.[Ser482Phefs*17];[=]
K190	F		RH+	1	1	1												1 (deafness)				NOTCH2, p.[Ala1968Val];[Arg285His]		GRHL2, p.[Gly386Arg];[=] PAXIP1, p.[His358Gln];[=] DEAF1, p.[Glu232Glyfs*10];[=]
K191	F		RH+	1	1	1																		GBX2, p.[Pro62Leu];[=]
K192	F	fetus	BKA							1												TBX18, p.[Ile258Val];[=]		
K193	M		RH	1																				
K194	M		RH	1																				
K195	F	fetus	BKA							1								1		craniostenosis + microcephaly + agenesis of corpus callosum	KIF14, p.[Gln1304*];[Arg364Cys]			FAT4, p.[Glu4734Gly];[=]
K196	F		UMD				1													diabetes				GLI1, p.[Pro1080Leu];[=] HNF1A, p.[Gly319Ser];[=]
K197	M		UKA						1										1					RAI2, p.[Leu169Pro]
K198	F		UKA						1										1	VACTER syndrome				
K199	M		Oth								1							1		papillary coloboma	PAX2, p.[Arg71Lys];[=]			
K200	M		UMD				1											1						
K201	F	fetus	BKA							1								1						LAMA5, p.[Pro1082Leu];[=]
K202	M		RH+	1										1										
K203	F		RD		1	1												1			HNF1B, c.[(?_-30)_(*220_?)del];[=]			RARG, p.[Pro82Leu];[=]
K204	M		RH+	1	1													1		diabetes				
Cases with branchial signs and/or ear defect without CAKUT phenotype																								
BO1	F																			branchial defect + deafness				
BO2	F																			deafness				WNT11, p.[Cys59Alafs*19];[=]
BO3	F																			ear tag + ear tag + intellectual diability + thumb hypoplasia		WNT4, p.[Arg83Gln];[=]		PAXIP1, p.[Gln404_Ala407del];[=]

BO4	F																	branchial defect + preauricular pit + deafness	EYA1, p.[Arg361*];[=]			
BO5	M																	branchial defect + deafness	SIX1, p.[Tyr92Leufs*62];[=]			SCRIB, p.[Arg1641Cys];[=] FAT1, p.[His1190Tyr];[=]
BO6	M																	ear tag + deafness				
BO7	M																	preauricular pit + deafness		TNXB, p.[Pro2490Arg];[=]		
BO8	M																	external ear hypoplasia				
BO9	F																	branchial defect				
BO10	F																	external ear defect + preauricular pit + ear tag				
BO11	M																	deafness			DSTYK, c.[654+1G>A];[=]	

(a) Renal Hypoplasia
(b) Renal Dysplasia
(c) Unilateral Multicystic Dysplasia
(d) Bilateral Multicystic Dysplasia
(e) Unilateral Kidney Agenesis
(f) Bilateral Kidney Agenesis
(g) Vesico-Ureteral Reflux
(h) Obstructive Megaureter
(i) Duplex kidney
(j) Pelvi-ureteric junction Obstruction
(k) Parents, children and/or siblings
(l) Grand parents, uncles, aunts, cousins
(m) *PBX1* mutations are in the "Causative mutations" column

Table S2.List of genes for targeted exome sequencing

gene	Name	Phenotype/Syndrome	OMIM#	MGI#	References
a- Human mutations in CAKUT +/- syndrome					
ACE	angiotensin I converting enzyme (peptidyl-dipeptidase A) 1	Renal tubular dysgenesis	106180		1
ACTA2	actin, alpha 2, smooth muscle, aorta	Prune Belly			2
ACTG2	actin, gamma 2, smooth muscle, enteric	Megacystis Microcolon Intestinal Hypoperistalsis	155310		3
AGT	angiotensinogen (serpin peptidase inhibitor, clade A, member 8)	Renal tubular dysgenesis	106165		1
AGTR1	angiotensin II receptor, type 1a	Renal tubular dysgenesis	106180		1
ANOS1	Anosmin	Kallmann	308700		4
BICC1	BicC family RNA binding protein 1	Cystic renal dysplasia	601331		5
BMP4	bone morphogenetic protein 4	Isolated CAKUT			6
CDC5L	cell division cycle 5-like (S. pombe)	Isolated CAKUT			7
CHD1L	chromodomain helicase DNA binding protein 1-like	Isolated CAKUT			8
CHD7	chromodomain helicase DNA binding protein 7	Charge/Kallmann	214880/612370		9
CHRM3	cholinergic receptor, muscarinic 3, cardiac	Prune belly like	100100		10
DACH1	dachshund 1 (Drosophila)	Cystic renal dysplasia			11
DHCR7	7-dehydrocholesterol reductase	Smith-Lemli-Opitz	270400		12
DSTYK	dual serine/threonine and tyrosine protein kinase	Isolated CAKUT	610805		13
ESRRG	estrogen-related receptor gamma	Kidney agenesis			14
EYA1	EYA transcriptional coactivator and phosphatase 1	Branchio oto renal	113650		15
FAM58A	family with sequence similarity 58, member B	Toe syndactyly, telecanthus, anogenital and renal malformations	300707		16
FGF20	fibroblast growth factor 20	Kidney agenesis	615721		17
FRAS1	Fraser extracellular matrix complex subunit 1	Fraser/isolated CAKUT	219000		18
FREM1	Fras1 related extracellular matrix protein 1	Bifid nose, renal agenesis & anorectal malformations syndrome/isolated CAKUT	608980		19
FREM2	Fras1 related extracellular matrix protein 2	Fraser/isolated CAKUT	219000		18
GATA3	GATA binding protein 3	Hypoparathyroidism, sensorineural deafness and renal dysplasia	146255		20
GDF6	growth differentiation factor 6	Klippel-Feil	118180		21
GLI3	GLI-Kruppel family member GLI3	Pallister Hall	146510		22
GPC3	glypican 3	Simpson Golabi Behmel	312870		23
GRIP1	glutamate receptor interacting protein 1	Fraser/isolatedCAKUT	219000		24
HNF1B	HNF1 homeobox B	Renal cysts and diabetes	137920		25
HPSE2	heparanase 2	Urofacial	236730		26
ITGA3	integrin alpha 3	nephrotic syndrome	614748		27
ITGA8	integrin alpha 8	Kidney agenesis	191830		28
JAG1	jagged 1	Allagile	118450		29
KIF14	kinesin family member 14	Multicystic renal dysplasia/renal agenesis and microcephaly	616258		30
LRIG2	leucine-rich repeats and immunoglobulin-like domains 2	Urofacial	615112		31
LRP4	low density lipoprotein receptor-related protein 4	Cenani-Lenz	212780		32
NEK8	NIMA (never in mitosis gene a)-related expressed kinase 8	Renal cystic dysplasia, situs inversus, cardiopathy, bile duct paucity	615415		33
NOTCH2	notch 2	Allagille/Hadju Cheney	610205		34
PAX2	paired box 2	Renal coloboma	120330		35
REN	renin 1 structural	Renal tubular dysgenesis	179820		36
RET	ret proto-oncogene	Kidney agenesis, Hirschsprung	142623		37
ROBO2	roundabout guidance receptor 2	Vesico ureteral reflux	610878		38
SALL1	sal-like 1 (Drosophila)	Townes Brocks	107480		39
SALL4	sal-like 4 (Drosophila)	Duane-radial ray	607323		40
SIX1	sine oculis-related homeobox 1	Branchio oto renal	608389		41
SIX2	sine oculis-related homeobox 2	Isolated CAKUT			6
SIX5	sine oculis-related homeobox 5	Branchio oto renal	610896		42
SLIT2	slit homolog 2 (Drosophila)	Vesico ureteral reflux			38
SOX17	SRY (sex determining region Y)-box 17	isolated CAKUT	613674		43
TBC1D1	TBC1 domain family, member 1	isolated CAKUT			44
TBX18	T-box18	pelvi-ureteric jonction obstruction	143400		45
TNXB	tenascin XB	Vesico ureteral reflux	615963		46
TRAP1	TNF receptor-associated protein 1	VACTERL/isolated CAKUT			47
UMOD	uromodulin	Hyperuricemia, Medullary cystic kidney disease	162000, 603860		48
UPK3A	uroplakin 3A	Vesico ureteral reflux			49
WNT4	wingless-type MMTV integration site family, member 4	Hypodysplasia			50
b- Mouse models with kidney developmental defects					
AGTR2	angiotensin II receptor, type 2			MGI:87966	51
ALDH1A2	aldehyde dehydrogenase family 1, subfamily A2			MGI:107928	52
AMER1	APC membrane recruitment 1			MGI:1919595	53
AQP2	aquaporin 2			MGI:1096865	54

ATMIN	ATM interactor			MGI:2682328	55
BCL2	B cell leukemia/lymphoma 2			MGI:88138	56
BDKRB2	bradykinin receptor, beta 2			MGI:102845	57
BMP7	bone morphogenetic protein 7			MGI:103302	58
BMPER	BMP-binding endothelial regulator			MGI:1920480	59
CDH6	cadherin 6			MGI:107435	60
CER1	alkaline ceramidase 1				61
CFL1	cofilin 1				62
CRIM1	cysteine rich transmembrane BMP regulator 1 (chordin like)			MGI:1354756	63
CTNNB1	catenin (cadherin associated protein), beta 1			MGI:88276	64
CTNNBIP1	catenin beta interacting protein 1			MGI:1915756	65
CXCR4	chemokine (C-X-C motif) receptor 4			MGI:109563	66
DACT1	dishevelled-binding antagonist of beta-catenin 1			MGI:1891740	67
DCHS1	dachsous 1 (Drosophila)			MGI:2685011	68
DCN	decorin			MGI:94872	69
DLG1	discs, large homolog 1 (Drosophila)			MGI:107231	70
DLL1	delta-like 1 (Drosophila)			MGI:104659	71
DSTN	destrin				62
ECM1	extracellular matrix protein 1				72
EGFR	epidermal growth factor receptor			MGI:95294	73
EMX2	empty spiracles homeobox 2			MGI:95388	74
EPHA4	Eph receptor A4				75
EPHA7	Eph receptor A7				75
ETV4	ets variant 4			MGI:99423	76
ETV5	ets variant 5			MGI:1096867	76
EXOC5	exocyst complex component 5			MGI:2145645	77
FAT1	FAT atypical cadherin 1			MGI:109168	78
FAT4	FAT atypical cadherin 4			MGI:3045256	79
FGF10	fibroblast growth factor 10			MGI:1099809	80
FGF7	fibroblast growth factor 7			MGI:95521	81
FGF8	fibroblast growth factor 8			MGI:99604	82
FGF9	fibroblast growth factor 9				17
FGFR1	fibroblast growth factor receptor 1	Kallmann	147950		83
FGFR2	fibroblast growth factor receptor 2			MGI:95523	83
FGFRL1	fibroblast growth factor receptor-like 1			MGI:2150920	84
FMN1	formin 1			MGI:101815	85
FOXC1	forkhead box C1			MGI:1347466	86
FOXC2	forkhead box C2			MGI:1347481	86
FOXD1	forkhead box D1			MGI:1347463	87
FSTL1	follistatin-like 1			MGI:102793	88
GATA2	GATA binding protein 2			MGI:95662	89
GDF11	growth differentiation factor 11			MGI:1338027	90
GDNF	glial cell line derived neurotrophic factor			MGI:107430	91
GFRA1	glial cell line derived neurotrophic factor family receptor alpha 1			MGI:1100842	92
GLCE	glucuronyl C5-epimerase			MGI:2136405	93
GREM1	gremlin 1, DAN family BMP antagonist			MGI:1344337	94
GRHL2	grainyhead-like 2 (Drosophila)				95
HOXA11	homeobox A10				96
HOXD11	homeobox D11				96
HS2ST1	heparan sulfate 2-O-sulfotransferase 1			MGI:1346049	97
ILK	integrin linked kinase			MGI:1195267	98
ISL1	ISL1 transcription factor, LIM/homeodomain				99
ITGB1	integrin beta 1 (fibronectin receptor beta)			MGI:96610	100
KIF26B	kinesin family member 26B			MGI:2447076	101
KIF3A	kinesin family member 3A			MGI:107689	102
KISS1R	KISS1 receptor			MGI:2148793	103
LAMA5	laminin, alpha 5			MGI:105382	104
LAMC1	laminin, gamma 1			MGI:99914	105
LGR4	leucine-rich repeat-containing G protein-coupled receptor 4			MGI:1891468	106
LHX1	LIM homeobox protein 1			MGI:99783	107
LZTS2	leucine zipper, putative tumor suppressor 2			MGI:2385095	108
MMP9	matrix metallopeptidase 9				109
MYCN	v-myc avian myelocytomatosis viral related oncogene, neuroblastoma derived			MGI:97357	110
NFIA	nuclear factor I/A			MGI:108056	111
NPNT	nephronectin			MGI:2148811	112
NR2F2	nuclear receptor subfamily 2, group F, member 2				113
OSR1	odd-skipped related 1 (Drosophila)			MGI:1344424	114
PARVA	parvin, alpha			MGI:1931144	115
PAX8	paired box 8				116
PBX1	pre B cell leukemia homeobox 1			MGI:97495	117
POU3F3	POU domain, class 3, transcription factor 3			MGI:102564	118
PPP3R1	protein phosphatase 3, regulatory subunit B, alpha isoform (calcineurin B, type I)			MGI:107172	119
PTCH1	patched 1			MGI:105373	120
PTGS2	prostaglandin-endoperoxide synthase 2			MGI:97798	121
RARA	retinoic acid receptor, alpha				122

RARB	retinoic acid receptor, beta				122
RBPJ	recombination signal binding protein for immunoglobulin kappa J region			MGI:96522	123
RERE	arginine glutamic acid dipeptide (RE) repeats			MGI:2683486	124
ROBO1	roundabout guidance receptor 1			MGI:1274781	66
SEMA3A	sema domain, immunoglobulin domain (Ig), short basic domain, secreted, (semaphorin) 3A	Kallmann	614897	MGI:107558	125
SHH	sonic hedgehog			MGI:98297	126
SMAD4	SMAD family member 4			MGI:894293	127
SOX11	SRY (sex determining region Y)-box 11				128
SOX12	SRY (sex determining region Y)-box 12				129
SOX4	SRY (sex determining region Y)-box 4				129
SOX8	SRY (sex determining region Y)-box 8				130
SOX9	SRY (sex determining region Y)-box 9			MGI:98371	130
SPRY1	sprouty homolog 1 (Drosophila)			MGI:1345139	131
TCF21	transcription factor 21			MGI:1202715	132
TFCP2L1	transcription factor CP2-like 1			MGI:2444691	133
TGFB2	transforming growth factor, beta 2			MGI:98726	134
TGFBR3	transforming growth factor, beta receptor III				135
TRPS1	trichorhinophalangeal syndrome I (human)			MGI:1927616	136
TSHZ3	teashirt zinc finger family member 3			MGI:2442819	137
WNT11	wingless-type MMTV integration site family, member 11			MGI:101948	138
WNT5A	wingless-type MMTV integration site family, member 5A			MGI:98958	66
WNT7B	wingless-type MMTV integration site family, member 7B			MGI:98962	139
WNT9B	wingless-type MMTV integration site family, member 9B			MGI:1197020	140
WT1	Wilms tumor 1 homolog	Denys Drash syndrome	194080/256370		141
YAP1	yes-associated protein 1			MGI:103262	142

c- Relevant functional data (cellular and/or non-mouse models)

ALCAM	activated leukocyte cell adhesion molecule	143
ALX1	ALX homeobox 1	144
AMOT	angiomotin	145
AMOTL1	angiomotin-like 1	145
AMOTL2	angiomotin-like 2	145
ATF2	glial cell line derived neurotrophic factor	143
BCL2L11	BCL2-like 11 (apoptosis facilitator)	146
CD151	CD151 antigen	147
CDKN1C	cyclin-dependent kinase inhibitor 1C (P57)	148
CITED1	Cbp/p300-interacting transactivator with Glu/Asp-rich carboxy-terminal domain 1	149
CRLF1	cytokine receptor-like factor 1	150
DCHS2	dachsous 2 (Drosophila)	151
DKK1	dickkopf WNT signaling pathway inhibitor 1	64
ELF5	E74-like factor 5	152
ESRP1	epithelial splicing regulatory protein 1	unpublished
ESRP2	epithelial splicing regulatory protein 2	unpublished
FJX1	four jointed box 1 (Drosophila)	79
FRS2	fibroblast growth factor receptor substrate 2	153
FRY	FRY microtubule binding protein	unpublished
FZD3	frizzled class receptor 9	143
FZD4	frizzled class receptor 4	154
FZD7	frizzled class receptor 7	155
FZD8	frizzled class receptor 8	154
GLI1	GLI-Kruppel family member GLI1	156
GNB3	guanine nucleotide binding protein (G protein), beta 3	49
GPC1	glypican 1	157
HAS3	hyaluronan synthase 3	158
HCN3	hyperpolarization-activated, cyclic nucleotide-gated K+ 3	159
HGF	interleukin 6	160
HOXB5	homeobox B5	161
HOXB6	homeobox B6	161
HOXC11	homeobox C11	96
HOXD10	homeobox D10	162
HOXD3	homeobox D3	161
HOXD8	homeobox D8	161
HOXD9	homeobox D9	161
IRX3	Iroquois related homeobox 3	163
KDR	kinase insert domain protein receptor	164
KEAP1	kelch-like ECH-associated protein 1	unpublished
KIT	kit oncogene	165
LATS1	large tumor suppressor	166
LLGL1	lethal giant larvae homolog 1 (Drosophila)	167
MAGED1	melanoma antigen, family D, 1	168
MDM2	transformed mouse 3T3 cell double minute 2	169
MDM4	transformed mouse 3T3 cell double minute 4	unpublished
MECOM	MDS1 and EVI1 complex locus	170
MEOX2	mesenchyme homeobox 2	171

MET	met proto-oncogene				172
MMP13	matrix metallopeptidase 13				173
NCAM1	neural cell adhesion molecule 1				174
NF2	neurofibromatosis 2				175
NKX2-1	NK2 homeobox 1				176
NR2F1	nuclear receptor subfamily 2, group F, member 2				177
NR4A2	nuclear receptor subfamily 4, group A, member 2				178
OSR2	odd-skipped related 2				179
PAXIP1	PAX interacting (with transcription-activation domain) protein 1				180
Pik3c3	phosphoinositide-3-kinase, class 3				unpublished
PLAC8	placenta-specific 8				181
PPM1B	protein phosphatase 1B, magnesium dependent, beta isoform				182
PRKX	protein kinase, X-linked				183
PTPN11	protein tyrosine phosphatase, non-receptor type 11				184
RARG	retinoic acid receptor, gamma				122
RSPO3	R-spondin 3				185
RXRA	retinoid X receptor alpha				177
SCRIB	scribbled planar cell polarity				186
SH2B1	SH2B adaptor protein 1				187
SHOX2	short stature homeobox 2				188
SIM1	single-minded homolog 1 (Drosophila)				189
SMO	smoothened, frizzled class receptor				190
SNAI1	snail family zinc finger 1				191
SOST	sclerostin				192
SPRY2	sprouty homolog 2 (Drosophila)				193
SULF1	sulfatase 1				194
SULF2	sulfatase 2				194
TAZ	WW domain containing transcription regulator 1				178
TBX1	T-box 1				162
TBX3	T-box 3	Ulnar mammary	181450		195
TIMP1	tissue inhibitor of metalloproteinase 1				173
TJP2	tight junction protein 2				196
USF2	upstream transcription factor 2				14
VEGFA	vascular endothelial growth factor A				197
VSNL1	visinin-like 1				198
WNT5B	wingless-type MMTV integration site family, member 5B				199
ZEB2	zinc finger E-box binding homeobox 2				200

d- Role in ureter/bladder development

ADAMTS1	a disintegrin-like and metallopeptidase (reprolysin type) with thrombospondin type 1 motif, 1			MGI:109249	201
AHR	aryl-hydrocarbon receptor			MGI:105043	202
BMP5	bone morphogenetic protein 5			MGI:88181	202
BMPR1A	bone morphogenetic protein receptor, type 1A				202
BMPR1B	bone morphogenetic protein receptor, type 1B				202
BMPR2	bone morphogenetic protein receptor, type II (serine/threonine kinase)			MGI:1095407	202
HOXD13	homeobox D13				202
ID2	inhibitor of DNA binding 2			MGI:96397	202
KLF5	Kruppel-like factor 5				203
MYOCD	myocardin				202
SCARB2	scavenger receptor class B, member 2			MGI:1196458	202

e- Potential targets of WT1 or HNF1B

ACTN3	actinin alpha 3				204
ADCY8	adenylate cyclase 8				204
Aip	aryl-hydrocarbon receptor-interacting protein				204
ASIC4	acid-sensing (proton-gated) ion channel family member 4				204
C1QTNF3	C1q and tumor necrosis factor related protein 3				204
CALCR	calcitonin receptor				204
CEBPA	CCAAT/enhancer binding protein (C/EBP), alpha				204
CHST9	carbohydrate (N-acetylgalactosamine 4-0) sulfotransferase 9				204
CRYM	crystallin, mu				204
DEAF1	asparagine-linked glycosylation 10B (alpha-1,2-glucosyltransferase)				204
DES	desmin				204
DUSP6	dual specificity phosphatase 6				204
EGR1	early growth response 1				204
ENC1	ectodermal-neural cortex 1				204
FGF14	fibroblast growth factor 14				204
FGF16	fibroblast growth factor 16				204
FGF18	fibroblast growth factor 18				204
FST	follistatin				204
GAS1	growth arrest specific 1				205
GBX2	gastrulation brain homeobox 2				204
GPR173	G-protein coupled receptor 173				204
GPX6	glutathione peroxidase 7				204

HIC1	hypermethylated in cancer 1	204
HOXA3	homeobox A3	204
HOXB1	homeobox B1	204
HOXB3	homeobox B3	204
HS3ST6	heparan sulfate (glucosamine) 3-O-sulfotransferase 6	204
IRX1	Iroquois related homeobox 1 (Drosophila)	206
IRX2	Iroquois related homeobox 2 (Drosophila)	206
KRT23	keratin 23	204
LRFN2	leucine rich repeat and fibronectin type III domain containing 2	204
MATN4	matrilin 2	204
Mybph	myosin binding protein H	204
NRXN3	neurexin III	204
NTN1	netrin 1	204
PDE3B	phosphodiesterase 3B, cGMP-inhibited	204
PHF19	PHD finger protein 19	204
PPP1R1B	protein phosphatase 1, regulatory (inhibitor) subunit 1B	204
PTGIR	prostaglandin I receptor (IP)	204
RAI2	retinoic acid induced 2	204
RCSD1	RCSD domain containing 1	204
REM1	rad and gem related GTP binding protein 1	204
RORA	RAR-related orphan receptor alpha	204
RSPO1	R-spondin 1	204
SLC16A6	solute carrier family 16 (monocarboxylic acid transporters), member 6	204
SLC6A18	solute carrier family 6 (neurotransmitter transporter), member 18	204
SNAP91	synaptosomal-associated protein 91	204
SPACA4	sperm acrosome associated 4	204
SPOCK2	sparc/osteonectin, cwcv and kazal-like domains proteoglycan 2	204
STMN4	stathmin-like 4	204
SYPL2	synaptophysin-like 2	204
TGM5	transglutaminase 5	204
TNNT2	troponin T2, cardiac	204
TRAF1	TNF receptor-associated factor 1	204
UNCX	UNC homeobox	204
WNT8B	wingless-type MMTV integration site family, member 8B	204
ZNF106	zinc finger protein 106	204

f- gene related to gene(s) in group (a) to (e), expressed during kidney/LUT development

ALDH1A3	aldehyde dehydrogenase family 1, subfamily A3
BMP2	bone morphogenetic protein 2
BMP6	bone morphogenetic protein 6
FAT3	FAT atypical cadherin 3
FGF1	fibroblast growth factor 1
FGF2	fibroblast growth factor 13
GRIP2	glutamate receptor interacting protein 2
HNF1A	HNF1 homeobox A
HNF4A	hepatic nuclear factor 4, alpha
HPSE	heparanase
HS6ST1	heparan sulfate 6-O-sulfotransferase 1
SIX4	sine oculis-related homeobox 4
TBX2	T-box 2
UPK1A	uroplakin 1A
UPK1B	uroplakin 1B
UPK2	uroplakin 2
UPK3B	uroplakin 3B
WNT2B	wingless-type MMTV integration site family, member 2B
WNT6	wingless-type MMTV integration site family, member 6

Table S3. List of the 120 variants of unknown significance identified in candidate genes in CAKUT cases, that are absent in ExAC and our in-house database

Gene	Ref seq	Nucleotide change	Protein change	Number of damaging scores for missense variants [a]
ADCY8	NM_001115	c.2603T>G	p.Ile868Ser	4/5
AMOT	NM_001113490	c.1601G>A	p.Arg534Lys	3/5
AMOTL1	NM_130847	c.1519G>A	p.Glu507Lys	5/5
AMOTL1	NM_130847	c.1258C>T	p.Pro420Ser	3/5
BMPR1A	NM_004329	c.1189C>T	p.Phe397Ser	5/5
CDKN1C	NM_000076	c.17T>C	p.Leu6Pro	3/5
CITED1	NM_001144885	c.16C>T	p.Gln6*	
CRIM1	NM_016441	c.1901G>A	p.Gly634Glu	5/5
CRLF1	NM_004750	c.853A>G	p.Lys285Glu	3/5
CRLF1	NM_004750	c.431G>A	p.Trp144*	
DACT1	NM_016651	c.169G>A	p.Glu57Lys	5/5
DCHS1	NM_003737	c.6647C>T	p.Ala2216Val	3/5
DCHS1	NM_003737	c.5140C>T	p.Gln1714*	
DCHS1	NM_003737	c.2789C>G	p.Thr930Ser	4/5
DCHS1	NM_003737	c.868G>T,	p.Val290Leu	4/5
DEAF1	NM_021008	c.694dup	p.Glu232Glyfs*10	
ECM1	NM_004425	c.527A>T	p.Asn176Ile	4/5
EGFR	NM_005228	c.1717G>A	p.Gly573Arg	5/5
ENC1	NM_003633	c.658T>C	p.Tyr220His	4/5
ETV4	NM_001986	c.626A>G	p.Tyr209Cys	5/5
FAT1	NM_005245	c.5759A>C	p.Glu1920Ala	4/5
FAT1	NM_005245	c.6367C>T	p.His2123Tyr	5/5
FAT3	NM_001008781	c.1729C>G	p.Leu577Val	3/5
FAT3	NM_001008781	c.9814A>T	p.Thr3272Ser	3/5
FAT3	NM_001008781	c.3724G>C	p.Val1242Leu	3/5
FAT4	NM_001291303	c.6533C>T	p.Ala2178Val	4/4
FAT4	NM_001291303	c.5410A>G	p.Arg1804Gly	4/4
FAT4	NM_001291303	c.11584G>C	p.Glu3862Gln	4/4
FAT4	NM_001291303	c.14201A>G	p.Glu4734Gly	4/5
FGF8	NM_033163	c.362C>G	p.Thr121Ser	3/5
FGFR1	NM_001174067	c.271C>T	p.Arg91Trp	4/5
FOXC1	NM_001453	c.1016C>T	p.Ser339Phe	3/5
FOXC2	NM_005251	c.610C>T	p.Pro204Ser	3/5
FRY	NM_023037	c.4928C>T	p.Ala1643Val	3/5
FRY	NM_023037	c.7097C>T	p.Thr2366Ile	4/5
FZD4	NM_012193	c.1327C>A	p.Leu443Met	3/5
FZD7	NM_003507	c.650C>T	p.Pro217Leu	4/5
FZD8	NM_031866	c.314C>G	p.Pro105Arg	3/5
GAS1	NM_002048	c.644dup	p.Ala216Glyfs*52	
GBX2	NM_001485	c.151C>G	p.Arg51Gly	4/5
GBX2	NM_001485	c.185C>T	p.Pro62Leu	3/5
GLI1	NM_005269	c.968G>A	p.Arg323Gln	4/5
GLI1	NM_005269	c.3239C>T	p.Pro1080Leu	4/5

GNB3	NM_002075	c.827T>G	p.Val276Gly	4/5
GPR173	NM_018969	c.428T>C	p.Val143Ala	4/5
GREM1	NM_013372	c.24-25insTGTA	p.Gly9Cysfs*16	
GRHL2	NM_024915	c.1156G>A	p.Gly386Arg	5/5
GRHL2	NM_024915	c.1255A>G	p.Lys419Glu	5/5
HCN3	NM_020897	c.2053C>T	p.Arg685Trp	4/5
HIC1	NM_006497	c.1099G>C	p.Gly386Arg	3/5
HIC1	NM_006497	c.2105G>A	p.Gly702Asp	4/5
HIC1	NM_006497	c.688C>T	p.Pro230Ser	3/5
HNF1A	NM_001306179	c.955G>A	p.Gly319Ser	3/4
HOXA11	NM_005523	c.881T>C	p.Met294Thr	3/5
HOXB1	NM_002144	c.881C>T	p.Ala294Val	4/5
HOXB5	NM_002147	c.542G>C	p.Arg181Trp	5/5
HOXC11	NM_014212	c.185C>G	p.Pro62Arg	4/5
HOXD11	NM_021192	c.259G>C	p.Gly87Arg	3/5
HOXD13	NM_000523	c.241G>T	p.Glu81*	
HPSE	NM_006665	c.2T>C	p.Met1?	
HS6ST1	NM_004807	c.252G>T	p.Lys84Asn	3/5
IRX2	NM_033267	c.1193T>C	p.Leu398Ser	3/5
KIF26B	NM_018012	c.5788C>G	p.Arg1930Gly	4/5
KIF3A	NM_007054	c.1135G>A	p.Glu379Lys	3/5
KISS1R	NM_032551	c.403G>T	p.Ala135Ser	5/5
LAMA5	NM_005560	c.9200del	p.Gly3067Alafs*40	
LAMA5	NM_005560	c.5789T>C	p.Leu1930Pro	3/5
LAMA5	NM_005560	c.3245C>T	p.Pro1082Leu	4/5
LAMC1	NM_002293	c.1427+1G>C	c.1427+1G>C	
LAMC1	NM_002293	c.3850-1G>A	c.3850-1G>A	
LGR4	NM_018490	c.2590_2591insAA	p.Phe864*	
LHX1	NM_005568	c.688A>C	p.Asn230His	4/4
LHX1	NM_005568	c.269C>T	p.Thr90Ile	4/4
MAGED1	NM_001005333	c.2213C>T	p.Ala738Val	4/5
MATN4	NM_003833	c.131G>A	p.Ser44Asn	3/5
MDM4	NM_002393	c.1192G>A	p.Ala398Thr	3/5
MECOM	NM_001105077	c.932C>T	p.Ala311Val	3/5
MET	NM_001127500	c.356C>T	p.Ala119Val	5/5
MMP9	NM_004994	c.798delC	p.Arg267Glyfs*71	
MMP9	NM_004994	c.964C>T	p.Arg322Trp	3/5
MMP9	NM_004994	c.1814del	p.Gly605Alafs*9	
MMP9	NM_004994	c.1004C>A	p.Ser335*	
MYOCD	NM_001146312	c.722A>G	p.Lys241Arg	3/5
MYOCD	NM_001146312	c.1304C>T	p.Ser435Phe	4/5
NPNT	NM_001184690	c.1450C>T	p.Arg484Cys	4/5
NR2F2	NM_021005	c.130G>A	p.Gly44Ser	3/5
NTN1	NM_004822	c.1814A>G	p.605Trpext*84	
PAXIP1	NM_007349	c.1074T>G	p.His358Gln	3/5
PDE3B	NM_000922	c.275_194del	p.Leu92Argfs*241	
PIK3C3	NM_002647	c.1790C>A	p.Phe597His	4/4
PTGIR	NM_000960	c.48del	p.Pro17Argfs*6	
RAI2	NM_001172739	c.506T>C	p.Leu169Pro	4/5

RARG	NM_000966	c.245C>T	p.Pro82Leu	4/5
RCSD1	NM_052862	c.500G>A	p.Arg167Lys	4/5
ROBO1	NM_002941	c.4241C>A	p.Ala1414Asp	3/5
RSPO3	NM_032784	c.481A>C	p.Lys161Gln	3/5
SCRIB	NM_182706	c.4547C>T	p.Ala1516Val	5/5
SCRIB	NM_182706	c.1186C>T	p.Leu396Phe	3/5
SCRIB	NM_182706	c.352T>C	p.Ser118Pro	3/5
SEMA3A	NM_006080	c.401C>T	p.Thr134Met	4/5
SHH	NM_000193	c.1097T>C	p.Val366Ala	3/5
SLC6A18	NM_182632	c.661A>T	p.Thr221Ser	3/5
SOX4	NM_003107	c.1001C>A	p.Phe334His	3/5
SOX4	NM_003107	c.406T>G	p.Ser136Ala	3/5
SPOCK2	NM_014767	c.1114G>T	p.Gly372Trp	4/5
SPOCK2	NM_014767	c.620T>G	p.Leu207Arg	4/5
SPOCK2	NM_014767	c.1192A>G	p.Lys398Glu	4/5
SULF2	NM_018837	c.1967G>T	p.Arg656Leu	4/5
SULF2	NM_018837	c.2297C>T	p.Thr766Ile	5/5
TFCP2L1	NM_014553	c.155G>T	p.Cys52Phe	4/5
TGM5	NM_201631	c.1769C>G	p.Thr590Arg	4/5
TJP2	NM_001170416	c.2477C>A	p.Pro826Gln	3/5
WNT11	NM_004626	c.1034A>C	p.Glu345Ala	3/5
WNT2B	NM_024494	c.407G>T	p.Ser136Ile	5/5
WNT6	NM_006522	c.663G>C	p.Glu221Asp	4/5
WNT6	NM_006522	c.568_586dup	p.Gly196Alafs*123	
WNT9B	NM_003396	c.434G>A	p.Cys145Tyr	5/5
ZEB2	NM_014795	c.1049C>T	p.Thr350Met	3/5
ZNF106	NM_022473	c.5569T>C	p.Phe1857Leu	3/5
ZNF106	NM_022473	c.1444dup	p.Ser482Phefs*17	

(a) according to Polyphen2 (probably and possibly damaging), Sift (deleterious), Mutation Taster (deleterious), Grantham (considered as deleterious when ≥ 50) and GVGD (considered as deleterious when ≥ C25)

Table S4. Analysis of microsatellite markers for validation of *de novo PBX1* deletion in family 4 and paternity and maternity testing in the 5 families

Microsatellite markers	Position (Ensembl GrCh38)	nb alleles	% het	Family 1			Family 2			Family 3			Family 4			Family 5		
				Father	Mother	K175	Father	Mother	K179	Father	Mother	K186	Father	Mother	K181	Mother	K136	
D1S2675	ch1:162240203-162240364	8	72										140	158	140			Those 8 markers are refered to as A-H in Figure 1B
													160	160	158			
D1S2844	ch1:162979036-162979218	9	81										175	173	173			
													177	173	175			
D1S_PBX1_intron1	chr1:164562453-164562494	UK	UK										286	286	288			
													288	286	del			
D1S_PBX1_intron2-1	chr1:164651931-164651970	UK	UK										214	212	214			
													230	226	del			
D1S_PBX1_intron2-2	chr1:164707419-164707456	UK	UK										156	164	156			
													162	166	del			
D1S_PBX1_intron8	chr1:164834030-164834070	UK	UK										330	320	332			
													332	322	del			
D1S2762	ch1:166986900-166987137	8	81										228	240	240			
													242	244	242			
D1S196	ch1:167635063-167635195	5	73										271	269	269			
													273	271	271			
D1S433	ch1: 168398939-168399082	6	59	146	146	148							146	148	146			
				148	150	150							150	150	150			
D1S2643	ch1: 175553723-175553898	9	75	172	178	172	182	174	178	170	170	170	172	172	172	170	170	
				172	178	178	182	178	182	170	170	170	172	178	178	178	172	
D3S1270	ch3:1406588-1406749	9	75	165	165	165	165	165	165	165	165	165	165	163	165	153	153	
				165	173	173	169	169	165	173	165	165	165	165	165	167	167	
D3S2446	ch3: 81919331-81919574	UK	69	238	238	238	238	238	238	234	234	238	238	234	234	238	238	
				246	246	246	246	238	246	238	238	238	242	242	238	238	238	
D3S4554	ch3: 82542137-82542386	UK	65	248	248	248	256	248	248	252	248	248	248	248	248	248	256	
				248	252	252	256	248	256	260	256	252	260	256	256	260	260	
D4S3351	ch4: 158626043-158626231	UK	82	182	198	198	186	176	186	174	182	174	178	178	178	182	182	
				202	198	202	210	202	202	186	190	182	186	178	178	182	182	
D6S1572	ch6: 131016434-131016547	9	84	112	104	104	112	112	112	104	104	104	104	114	114	100	118	
				112	120	112	122	122	122	104	114	104	114	114	114	118	118	
D8S1820	ch8: 28140086-28140196	7	73	98	106	106	104	104	104	98	98	98	98	98	98	106	106	
				106	108	106	104	104	104	106	98	106	108	106	98	106	106	
D13S1268	ch13:66939348-66939481	9	80	122	118	118	118	120	136	120	130	120	118	134	134	120	120	
				136	140	136	136	140	140	120	136	136	140	136	140	142	120	
D14S997	ch14:62233775-62233986	8	76	210	204	204	214	204	212	202	202	202	212	202	202	206	202	
				212	214	210	216	212	216	212	210	212	214	212	214	216	206	
D15S1510	ch15: 80528302-80528551	UK	52	244	248	248	248	248	248	244	248	248	244	248	244	252	248	
				256	248	256	252	248	252	248	248	248	252	248	248	252	252	
D15S211	ch15:80900569-80900799	25	94				226	220	242	220	224	228						
							246	242	246	246	228	246						
D21S1903	ch21:44721130-44721407	14	83	245	255	245	255	249	257	255	245	245	241	245	245	241	241	
				257	261	261	257	257	257	257	257	257	253	245	253	249	259	
D21S1446	ch21: 46617673-46617893	UK	76										206	206	206	206	206	
													210	210	210	206	206	

Table S5. Burden analysis of rare variants in the unsolved CAKUT cases[a] (n=168) versus controls (n=426)					
		Madsen		Skat	
GENE	number of variants	PVALUE	STAT	PVALUE	STATRHO
Variant frequency < 0.1%, LOF + Missense damaging with polyphen 2 and Sift					
DCHS2	6	0.003261	34677	0.0037375	0.2
FZD3	2	0.02437	35358	0.037478	1
GRHL2	2	0.02437	35358	0.037478	1
HOXD13	4	0.037197	35228	0.067466	0.8
ANOS1[b]	3	0.037197	35228	0.042087	1
ECM1	4	0.03771	35229	0.064325	0.7
SULF1	4	0.03771	35229	0.064325	0.7
SPOCK2	4	0.038232	35230	0.065785	0.7
TBC1D1	3	ns	ns	0.037546	1
Variant frequency < 0.01%, LOF + Missense damaging with polyphen 2 and Sift					
ECM1	2	0.02437	35358	0.037478	1
FZD3	2	0.02437	35358	0.037478	1
GNB3	2	0.02437	35358	0.037478	1
GRHL2	2	0.02437	35358	0.037478	1
HOXD13	2	0.024371	35358	0.03938	1
DCHS2	3	0.037884	35230	0.039858	0.2
TBC1D1	3	ns	ns	0.037546	1

(a) cases with no mutation identified in *PBX1* and highly penetrant CAKUT genes *(HNF1B, PAX2, EYA1, ANOS1, GATA3, CHD7 or KIF14)*

(b) heterozygous variants in female cases

ns: non significant

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