Supplementary material

Diagnostic yield and benefits of whole-exome sequencing in CAKUT patients diagnosed in the first thousand days of life

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Supplementary Tables

Supplementary Table S1. Kidney and ureter phenotypes of 100 CAKUT patients diagnosed in the first 1,000 days of life and diagnostic yield in patients with a defined CAKUT phenotype

Phenotype	All patients	Diagnostic yield[a]	*p*-value[b]
Total CAKUT	**100% (100)**	**25% (25/100)**	-
Total bilateral CAKUT	**69% (69/100)**	**26.1% (18/69)**	1
Kidney dysplasia (bilateral)	24% (24/100)	33.3% (8/24)	0.45
Cystic kidney dysplasia (bilateral)	15% (15/100)	6.7% (1/15)	0.18
Kidney agenesis (unilateral) - and contralateral (cystic) kidney dysplasia - and contralateral kidney hypodysplasia - and contralateral ectopic kidney - and contralateral kidney dysplasia, hydronephrosis and obstructive megaureter - and contralateral kidney hypoplasia and hydronephrosis - and contralateral hydronephrosis	13% (13/100)	23.1% (3/13)	1
Crossed fused renal ectopia	5% (5/100)	20% (1/5)	1
Duplex kidney (bilateral)	4% (4/100)	50% (2/4)	0.28
Duplex kidney (unilateral) - and contralateral cystic kidney dysplasia - and bilateral ectopic ureter	2% (2/100)	50% (1/2)	0.45
Horseshoe kidney	1% (1/100)	0% (0/1)	1
Multicystic dysplastic kidney (unilateral) - and contralateral (cystic) kidney dysplasia - and contralateral kidney hypoplasia - and contralateral ureteropelvic junction stenosis, hydronephrosis	4% (4/100)	50% (2/4)	0.28
Kidney dysplasia (unilateral) - and contralateral hydronephrosis	1% (1/100)	0% (0/1)	1
Total unilateral CAKUT	**31% (31/100)**	**22.6% (7/31)**	1
Cystic kidney dysplasia (unilateral)	2% (2/100)	50% (1/2)	0.45
Multicystic dysplastic kidney (unilateral)	17% (17/100)	23.5% (4/17)	1
Kidney dysplasia (unilateral)	6% (6/100)	16.7% (1/6)	1
Kidney hypoplasia (unilateral)	1% (1/100)	0% (0/1)	1
Duplex kidney (unilateral)	3% (3/100)	33.3% (1/3)	1
Kidney agenesis (unilateral)	1% (1/100)	0% (0/1)	1
Primary obstructive megaureter (unilateral)	1% (1/100)	0% (0/1)	1

Patients additionally presenting with vesicoureteral reflux: 18/100

Patients receiving kidney replacement therapy before the age of 3 years: 21/100

[a]Solved cases carry a “Likely Pathogenic” or “Pathogenic” variant in an established CAKUT-associated gene (n=58)

[b]Comparison between the diagnostic yield in all CAKUT patients versus that in patients with a defined CAKUT phenotype using two-tailed Fisher’s exact test

Supplementary Table S2. Human genes (n=58) mutated in ≥3 CAKUT families according to [1] and updated

Gene (HGNC)	Protein (HGNC)	Inheri-tance	Reference
ACE	Angiotensin I converting enzyme	AR	[2, 3]
AGT	Angiotensinogen	AR	[2, 3]
AGTR1	Angiotensin II receptor type 1	AR	[2, 3]
ANOS1	Anosmin 1	XL	[4, 5]
BICC1	BicC family RNA binding protein 1	AD	[5, 6]
BNC2	Basonuclin 2	AD	[7]
BMP4	Bone morphogenetic protein 4	AD	[8, 9]
CDC5L	Cell division cycle 5 like	AD	[5, 10, 11]
CHRNA3	Cholinergic receptor nicotinic alpha 3 subunit	AR	[12]
CHD1L	Chromodomain helicase DNA binding protein 1 like	AD	[5, 11, 13, 14]
COL4A1	Collagen type IV alpha 1 chain	AD	[15]
CRKL	CRK like proto-oncogene, adaptor protein	AD	[16]
DACT1	Dishevelled binding antagonist of beta catenin 1	AD	[17]
DSTYK	Dual serine/threonine and tyrosine protein kinase	AD	[18, 19]
DYRK1A	Dual specificity tyrosine phosphorylation regulated kinase 1A	AD	[20]
EYA1	EYA transcriptional coactivator and phosphatase 1	AD	[5, 11, 21]
FAT4	FAT atypical cadherin 4	AR/AD	[14, 22]
FOXC1	Forkhead box C1	AD	[23]
FOXP1	Forkhead box P1	AD	[24]
FRAS1	Fraser extracellular matrix complex subunit 1	AR/AD	[25-27]
FREM1	FRAS1 related extracellular matrix 1	AR	[27, 28]
FREM2	FRAS1 related extracellular matrix 2	AR/AD	[26, 27, 29]
GATA3	GATA binding protein 3	AD	[5, 11, 30]
GDF6	Growth differentiation factor 6	AD	[31]
GLI3	GLI family zinc finger 3	AD	[14, 32, 33]
GREB1L	GREB1 like retinoic acid receptor coactivator	AD	[32, 34-36]
GRIP1	Glutamate receptor interacting protein 1	AR/AD	[14, 27]
HNF1B	HNF1 homeobox B	AD	[5, 37-40]
HPSE2	Heparanase 2 (inactive)	AR	[41, 42]
ITGA8	Integrin subunit alpha 8	AR	[27, 43]
KIF14	Kinesin family member 14	AR/AD	[5, 44]
LIFR	LIF receptor subunit alpha	AD	[45]
LRIG2	Leucine rich repeats and immunoglobulin like domains 2	AR	[46]
LRP4	LDL receptor related protein 4	AR/AD	[14, 47-49]
MUC1	Mucin 1, cell surface associated	AD	[50]
NADSYN1	NAD synthetase 1	AR	[51]
NEK8	NIMA related kinase 8	AR	[52-54]
PAX2	Paired box 2	AD	[5, 11, 14, 55, 56]
PBX1	PBX homeobox 1	AD	[5, 57, 58]
REN	Renin	AR	[2, 3]
RET	Ret proto-oncogene	AD	[5, 11, 59]
ROBO1	Roundabout guidance receptor 1	AR/AD	[5, 14, 36, 60]
ROBO2	Roundabout guidance receptor 2	AD	[11, 61-63]
SALL1	Spalt like transcription factor 1	AD	[5, 11, 64]
SIX2	SIX homeobox 2	AD	[8, 11]

Gene (HGNC)	Protein (HGNC)	Inheri-tance	Reference
SIX5	SIX homeobox 5	AD	[11, 32, 65]
SON	SON DNA and RNA binding protein	AD	[66]
SLIT2	Slit guidance ligand 2	AD	[36, 67]
SOX11	SRY-box transcription factor 11	AD	[68]
SOX17	SRY-box transcription factor 17	AD	[69]
TBC1D1	TBC1 domain family member 1	AD	[70]
TBX6	T-box transcription factor 6	AD	[71, 72]
TBX18	T-box transcription factor 18	AD	[5, 73]
TNXB	Tenascin XB	AD	[40, 62]
TRAP1	TNF receptor associated protein 1	AR	[74]
UMOD	Uromodulin	AD	[14, 54, 75]
UPK3A	Uroplakin 3A	AD	[14, 76, 77]
WNT4	Wnt family member 4	AR/AD	[19, 78, 79]

HGNC, HUGO Gene Nomenclature Committee; AR, autosomal recessive; AD, autosomal dominant; XL, X-linked.

Supplementary Table S3. Details of 27 heterozygous variants classified as “Likely Pathogenic” or “Pathogenic” detected in 25 CAKUT patients with kidney involvement diagnosed in the first thousand days of life

Patient ID	Gene	Chromosomal position[a]	Transcript ID	Nucleotide change, amino acid change	Reference SNP	Translation impact	Inheritance	ClinVar ID, HGMD ID	ACMG/AMP or ACMG/ClinGen criteria [80, 81]	ACMG classification
A014-01	*BMP4*	14:54416892	NM_001202.6	c.1085A>G p.(Asn362Ser)	rs546306238	Missense	Maternal	– –	PS4, PM1, PP3	LP
A001-01	*COL4A1*	13:110818603	NM_001845.6	c.3997G>A p.(Asp1333Asn)	rs141395813	Missense	ND	– CM1913741 (DM)	PS1, PM1, PS4, PP3	P
A001-01	*GREB1L*	18:19095415	NM_001142966.2	c.4939T>C p.(Ser1647Pro)	rs1201761633	Missense	ND	– –	PS4, PP2, PP3	LP
B036-01	*DACT1*	14:59113346	NM_016651.6	c.2005C>G p.(Pro669Ala)	–	Missense	Maternal	– –	PS3, PS4, PP3	LP
B027-01	*EYA1*	8:72184070	NM_000503.6	c.889C>T p.(Arg297*)	rs1131691667	Stop gain	ND	VCV000429912 CM001984 (DM)	PVS1, PS1, PS4	P
A017-01	*GATA3*	10:8115750	NM_001002295.2	c.1099C>T p.(Arg367*)	rs104894164	Stop gain	Maternal	VCV000016626.3 CM011940 (DM)	PVS1, PS1, PS4	P
F006-01	*GDF6*	8:97157413	NM_001001557.4	c.746C>A p.(Ala249Glu)	rs121909352	Missense	Maternal	VCV000008371.8 CM082790 (DM)	PS1, PS3, PM1, PM2, BP4	P
N079-01	*GDF6*	8:97157413	NM_001001557.4	c.746C>A p.(Ala249Glu)	rs121909352	Missense	Paternal	VCV000008371.8 CM082790 (DM)	PS1, PS3, PM1, PM2, BP4	P
C007-01	*HNF1B*	17:36091682	NM_000458.4	c.949G>A p.(Ala317Thr)	rs193922492	Missense	Paternal	VCV000036854.4 –	PS1_M, PS4, BP4	LP
A039-01	*HNF1B*	17:36091625	NM_000458.4	c.1006C>G p.(His336Asp)	rs138986885	Missense	Paternal	VCV000595653.11 CM067046 (DM)	PS1_M, PM2, BP4	LP
F005-01	*HNF1B*	17:36104875	NM_000458.4	c.1_1674del –	–	Gene deletion	ND	VCV000974554 –	2A	P
N006-01	*HNF1B*	17:36104632	NM_000458.4	c.244G>A p.(Asp82Asn)	rs140562402	Missense	Maternal	VCV000193101.11 CM1410695 (DM)	PS1, PM2, PP3	LP
N006-01	*SIX2*	2:45233463	NM_016932.5	c.722C>T p.(Pro241Leu)	rs147806994	Missense	Paternal	– CM086341 (DM)	PS1_M, PS3_M, PS4, BP4	LP
A002-01	*SIX2*	2:45233463	NM_016932.5	c.722C>T p.(Pro241Leu)	rs147806994	Missense	Paternal	– CM086341 (DM)	PS1_M, PS3_M, PS4, BP4	LP

A010-01	*SIX2*	2:45233463	NM_016932.5	c.722C>T p.(Pro241Leu)	rs147806994	Missense	Paternal	– CM086341 (DM)	PS1_M, PS3_M, PS4, BP4	LP
CEL004-01	*SIX2*	2:45233463	NM_016932.5	c.722C>T p.(Pro241Leu)	rs147806994	Missense	Maternal	– CM086341 (DM)	PS1_M, PS3_M, PS4, BP4	LP
C017-01	*LIFR*	5:38523603	NM_001127671.2	c.478_479delAG p.(Arg160fs*15)	rs1242667371	Frameshift	ND	VCV000656451.3 –	PVS1, PS3, PS4	P
A004-01	*LIFR*	5:38506022	NM_001127671.2	c.1273_1276delGTTA p.(Val425fs*2)	rs1114167358	Frameshift	De novo[b]	VCV000369648.1 CD175330 (DM)	PVS1, PS2, PS3, PS4	P
A011-01	*PAX2*	10:102509529	NM_003990.5	c.76delG p.(Val26fs*3)	rs75462234	Frameshift	De novo[b]	VCV000013801.1 CD992538 (DM)	PVS1, PS1, PS2, PS4	P
B061-01	*PAX2*	10:102509528	NM_003990.5	c.76dupG p.(Val26fs*28)	rs768607170	Frameshift	Maternal	VCV000156297 CI951965 (DM)	PVS1, PS1, PS2, PS4	P
F002-01	*ROBO1*	3:78766486	NM_002941.4	c.856C>T p.(Arg286*)	–	Stop gain	Maternal	– –	PVS1, PS4	P
A009-01	*SALL1*	16:51173374	NM_002968.2	c.2759C>G p.(Ser920*)	–	Stop gain	De novo[b]	– –	PVS1, PS2, PS4	P
C027-01	*SALL1*	16:51173332	NM_002968.2	c.2801delG p.(Ser934fs*32)	rs1597228490	Frameshift	De novo[b]	VCV000829881.1 –	PVS1, PS2, PS4	P
A007-01	*TBC1D1*	4:38016356	NM_015173.4	c.644_653delACCCGCCCCA p.(Asn215fs*93)	rs1427906397	Frameshift	De novo[b]	– CD161326 (DM)	PVS1, PS2, PS3, PS4	P
B047-01	*TBC1D1*	4:38051521	NM_015173.4	c.1910+2T>G –	–	3' Exon extension	Maternal	– –	PVS1, PS4	P
F004-01	*UMOD*	16:20357588	NM_003361.3	c.1042C>T p.(Gln348*)	rs199631490	Stop gain	Maternal	– –	PVS1, PS4	P
A022-01	*UMOD*	16:20352452	NM_003361.3	c.1538delA p.(Asn513fs*6)	–	Frameshift	Maternal	– –	PVS1, PS4	P

ACMG/AMP, American College of Medical Genetics and Genomics/Association for Molecular Pathology; ClinGen, Clinical Genome Resource; del, deletion; DM, disease mutation; dup, duplication; LP, likely pathogenic; M, moderate; ND, not determined; P, pathogenic.

[a]Reference genome build used: hg19/GRCh37

[b]Paternity and maternity confirmed

Supplementary Table S4. Genes affected by “Likely Pathogenic” or “Pathogenic” variants in CAKUT patients diagnosed in the first 1,000 days of life, main signaling pathways the encoded proteins play a role in, variants and phenotypes in patients compared to phenotypes of mutant/knockout mouse models, and gene expression in the murine developing kidney

Gene	**Pathway**	**Patients**			**Mouse models**			**Ref.**
		Patient ID, transcript: variant	**Kidney phenotype**	**Extrarenal phenotype**	**Kidney phenotype of mutant/knockout mouse**	**Extrarenal phenotype of mutant/knockout mouse**	**Gene expression in developing kidney**	
BMP4	GDNF/RET signaling	A014-01, NM_001202.6: c.1085A>G p.(Asn362Ser)	Kidney dysplasia (r+l)	None	(Hypo-) dysplastic kidney, hydronephrosis, hydroureter, double collecting system, ectopic ureterovesical junction	Craniofacial malformation, ocular abnormalities, heart defects, posterior truncation, polydactyly	Kidney and ureter primordia (confined to undifferentiated mesenchyme), starting at E10.5	[82-85]
COL4A1	FAK-Src signaling	A001-01, NM_001845.6: c.3997G>A p.(Asp1333Asn)	Dysplastic duplex kidney (r+l), ureteropelvic and ureterovesical junction obstruction (l), VUR (r+l)	None	Delayed glomerulogenesis, glomerular cysts, dilated glomerular capillaries, dilated Bowman’s spaces with retracted capillary tufts, podocyte disorganization, dilated proximal tubules, albuminuria and hematuria	Cerebral and ocular abnormalities, respiratory distress	Mesenchymal kidney cells at E12.5	[15, 86-90]
DACT1	WNT/β-catenin signaling	B036-01, NM_016651.6: c.2005C>G p.(Pro669Ala)	MCDK (l), dilated ureter ending in ureterocele (l)	None	Unilateral or bilateral kidney agenesis, kidney fusion at the midline, hydronephrosis	Neurological, gastrointestinal, genital, and skeletal anomalies	Mesenchyme of ureter from E11.5, capsular, cortical, and medullary kidney stroma from E12.5, reduced at E16.5, strongly diminished at E18.5	[17, 91, 92]

EYA1	GDNF/RET signaling	B027-01, NM_000503.6: c.889C>T p.(Arg297*)	Kidney agenesis (r), hypodysplasia with hydronephrosis (l)	Lateral branchial fistula	Unilateral kidney agenesis, kidney hypoplasia	Craniofacial and skeletal defects, ear abnormalities including hearing loss, absence of thymus and parathyroid glands	Nephrogenic cord and metanephric mesenchyme at E9.5, disappearing by E12.5	[93]
GATA3	GDNF/RET signaling	A017-01, NM_001002295.2: c.1099C>T p.(Arg367*)	Kidney dysplasia (r+l), VUR (r+l)	Intellectual disability, ear malformation, sensorineural deafness, planovalgus deformity, muscular hypotonia, elevated liver enzymes, hypoparathyroidism	Kidney agenesis (15%), duplex kidneys (33%), kidney aplasia (20%) and severe dysplasia (65%, including hydronephrosis and hydroureter)	Hearing loss, genital defects	Nephric duct starting at E10.5	[94, 95]
GDF6	BMP signaling	F006-01, NM_001001557.4: c.746C>A p.(Ala249Glu)	Crossed fused renal ectopia (l), megaureter (r+l), hydronephrosis (r+l), VUR (r+l)	Suspected microphthalmia, auricle dysplasia and atresia of the external auditory canal (l), vertebral segmentation defects including fusions, scoliosis, ventricular septal defects, patent foramen ovale, anal atresia, rectovestibular fistula	Not analyzed	Cranial, joint, ligament, tendon, cartilage defects	All compartments of the developing ureteric tree, including the ureteric tips and the ureter at E11.5 to E14.5	[31, 96-98]
		N079-01, NM_001001557.4: c.746C>A p.(Ala249Glu)	Cystic kidney dysplasia (l)	Paravertebral and retrovesical cysts				
GREB1L	Retinoic acid signaling	A001-01, NM_001142966.2: c.4939T>C p.(Ser1647Pro)	Dysplastic duplex kidney (r+l), ureteropelvic and ureterovesical junction obstruction (l), VUR (r+l)	None	Kidney agenesis in homozygous knockout mice, unilateral double ureter in heterozygous knockout mice	Exencephaly, cardiac morphogenesis defect, genital tract anomalies, small body size	Nephrogenic zone of kidney cortex and epithelial cells of renal tubules at E16	[35]

HNF1B	GDNF/RET, WNT/β-catenin, uromodulin signaling	N006-01, NM_000458.4: c.244G>A p.(Asp82Asn)	Duplex kidney (r+l), ureterocele (r+l), VUR (r+l)	None	Multicystic dysplastic kidney, bilateral renal cysts, hydronephrosis	Pancreatic dysfunction, genital tract abnormalities	Epithelial branches and ureter at E12.5	[99-102]
		C007-01, NM_000458.4: c.949G>A p.(Ala317Thr)	MCDK (r)	Hyperuricemia				
		A039-01, NM_000458.4: c.1006C>G p.(His336Asp)	Kidney hypoplasia (r+l)	Suspected congenital lacrimal duct stenosis, atypical abdominal hernia (r+l)				
		F005-01, NM_000458.4: c.1_1674del	Cystic kidney dysplasia (l), duplex kidney (r)	Loss of interlobular bile ducts, elevated liver enzymes, fructose / sorbitol intolerance, hypomagnesemia, hyperhidrosis				
LIFR	LIF signaling	C017-01, NM_001127671.2: c.478_479delAG p.(Arg160fs*15)	MCDK (l)	None	Kidney hypoplasia, microcystically dilated tubules, hydronephrosis, hydroureter, blind-ending ureter, ureter ectopia, narrow ureteric lumen due to muscular hypertrophy and a thickened urothelium	Reduced number of astrocytes and motor neurons in the brain stem and spinal cord, bone development abnormalities including severe osteopenia, high stores of liver glycogen, cryptorchidism, small body size and reduced weight, perinatal death of homozygous knockout mice	Mesenchymal compartment at E12.5-E18.5, thin tubules probably representing loops of Henle at E18.5, nerves around the urethra at E18.5, urothelium at E18.5	[45, 103-105]
		A004-01, NM_001127671.2: c.1273_1276 delGTTA p.(Val425fs*2)	Kidney agenesis (r), kidney dysplasia, hydronephrosis, obstructive megaureter (l)	Attention deficit disorder, prefascial testis ectopia				

PAX2	GDNF/RET signaling	A011-01, NM_003990.5: c.76delG p.(Val26fs*3)	Kidney dysplasia (r+l)	Myopia, hydrocele testis	Kidney agenesis, duplex kidney, dysplastic kidney, laterally displaced ureteral orifices, VUR in homozygous knockout mice, hypoplastic kidneys in heterozygous knockout mice	Missing midbrain-hindbrain region, bilateral optic nerve colobomas, abnormalities of ear development, lack of genital tract in homozygous knockout mice	Wolffian duct and mesonephric mesenchyme at E9.5	[106-109]
		B061-01, NM_003990.5: c.76dupG p.(Val26fs*28)	MCDK (r), renal dysplasia (l), VUR (l)	None				
ROBO1	SLIT2/ROBO1 signaling	F002-01, NM_002941.4: c.856C>T p.(Arg286*)	Kidney dysplasia (l)	Mild pulmonary stenosis, patent foramen ovale	(Cystic) multiplex kidney	Ventricular septal defects, overriding aorta, pericardial defects	Early metanephric mesenchyme, comma/ S-shaped body at E17.5	[60, 110-112]
SALL1	GDNF/RET signaling	A009-01, NM_002968.2: c.2759C>G p.(Ser920*)	Kidney dysplasia (r+l)	None	Kidney agenesis, kidney hypoplasia and (cystic) dysplasia	Hearing loss, anorectal defects, limb malformations	Metanephric mesenchyme surrounding the ureteric bud at E11.5	[113-116]
		C027-01, NM_002968.2: c.2801delG p.(Ser934fs*32)	Kidney dysplasia (r+l)	Ear tags				
SIX2	GDNF/RET signaling	N006-01, NM_016932.5: c.722C>T p.(Pro241Leu)	Duplex kidney (r+l), ureterocele (r+l), VUR (r+l)	None	Kidney hypoplasia, ectopic super-numerary renal vesicles	Craniofacial defects	Metanephric mesenchyme at E10.5	[117, 118]
		A002-01, NM_016932.5: c.722C>T p.(Pro241Leu)	Kidney dysplasia (r+l)	Mitral valve insufficiency, café-au-lait spots, hypogammaglobulinemia				
		A010-01, NM_016932.5: c.722C>T p.(Pro241Leu)	Cystic kidney dysplasia (r+l)	None				

SIX2	GDNF/RET signaling	CEL004-01, NM_016932.5: c.722C>T p.(Pro241Leu)	Duplex kidney, megaureter and ureterocele (l)	None	Kidney hypoplasia, ectopic super-numerary renal vesicles	Craniofacial defects	Metanephric mesenchyme at E10.5	[117, 118]
TBC1D1	Insulin signaling	A007-01, NM_015173.4: c.644_653 delACCCG-CCCCA p.(Asn215fs*93)	Kidney agenesis (r), hypodysplasia (l)	Insulin resistance/ prediabetes, obesity	Dilated kidney pelvis, nephrogenic rest, reduced Glut4 expression	Reduced body weight, decreased respiratory quotient, elevated resting metabolic rate, impaired glucose and insulin tolerance, increased lipid clearance, altered Glut4 expression in skeletal muscle	Largely ubiquitous expression throughout the urogenital system at E11.5-E18.5, high expression in medullary structures consistent with collecting ducts in E18.5	[70, 119, 120]
		B047-01, NM_015173.4: c.1910+2T>G	Kidney dysplasia (r+l)	None				
UMOD	Uromodulin signaling	F004-01, NM_003361.4: c.1042C>T p.(Gln348*)	MCDK (r)	Cryptorchidism, phimosis, hyperuricemia	Normal kidney structure, normal histology, salt and water wasting, reduced glomerular filtration, predisposition to urinary tract infection	Hyperuricemia, hypertension	Epithelial cells of the thick ascending limb of Henle's loop starting at E16.5	[121-125]
		A022-01, NM_003361.4: c.1538delA p.(Asn513fs*6)	MCDK (l), kidney hypoplasia, VUR (r)	None				

E, embryonic day; del, deletion; dup, duplication; l, left; MCDK, multicystic dysplastic kidney; r, right; VUR, vesicoureteral reflux

Supplementary Table S5. Rare heterozygous loss-of-function variants in the *LIFR* (NM_001127671.2) gene in CAKUT patients

Patient ID, gender	Chromosomal position[a]	Nucleotide change	Amino acid change	Variant effect	Reference SNP number	MAF[b]	Segregation	Kidney phenotype	Extrarenal phenotype	ACMG classification
C017-01, male	5:38523603-38523604	c.478_479 delAG	p.(Arg160fs*15)	Frameshift	rs1242667371	0.0	Not determined	MCDK (l)	None	P
A004-01, male	5:38506022-38506025	c.1273_1276 delGTTA	p.(Val425fs*2)	Frameshift	rs1114167358	0.0	*De novo*[c]	Kidney agenesis (r), kidney dysplasia, hydronephrosis, obstructive megaureter (l)	Attention deficit disorder, prefascial testis ectopia	P
Israel-01, female	5:38485942-38485946	c.2472_2476 delTATGT	p.(Ser824fs*41)	Frameshift	-	0.0	Paternal	MCDK (r)	Developmental delay, vitreous hemorrhage, ventricular septal defect	LP

[a]According to GRCh37/hg19

[b]According to Genome Aggregation Database (gnomAD v.2.1.1 controls; http://gnomad.broadinstitute.org/)

[c]Paternity and maternity confirmed

Supplementary Table S6. Rare heterozygous loss-of-function variants in the *TBC1D1* (NM_015173.4) gene in CAKUT patients

Patient ID, gender	Chromosomal position[a]	Nucleotide change	Amino acid change	Variant effect	Reference SNP number	MAF[b]	Segregation	Kidney phenotype	Extrarenal phenotype	ACMG classification
Spain-01	4:38016355-38016356	c.643_644 delAA	p.(Asn215fs*32)	Frameshift	-	0.0	Not determined	Kidney dysplasia (r+l)	Intrauterine growth retardation, postnatal failure to thrive, mild developmental delay, anomalous pulmonary venous connection	LP
A007-01, male	4:38016356-38016365	c.644_653 delACCCG CCCCA	p.(Asn215fs*93)	Frameshift	-	0.0	*De novo*[c]	Kidney agenesis (r), hypo-dysplasia (l)	Insulin resistance/ prediabetes, obesity	P
B047-01, male	4:38051521	c.1910+2T>G	-	Splice donor	-	0.0	Maternal	Kidney dysplasia (r+l)	None	P
Case 4 [126], female	4:38104775	c.2553delC	p.(Arg854fs*24)	Frameshift	-	0.0	Paternal	Pelvic kidney dysfunction (l)	Full uterine agenesis, anal atresia with vestibular fistula, ventricular septal defect, accessory auricle	P

[a]According to GRCh37/hg19

[b]According to Genome Aggregation Database (gnomAD v.2.1.1 controls; http://gnomad.broadinstitute.org/)

[c]Paternity and maternity confirmed

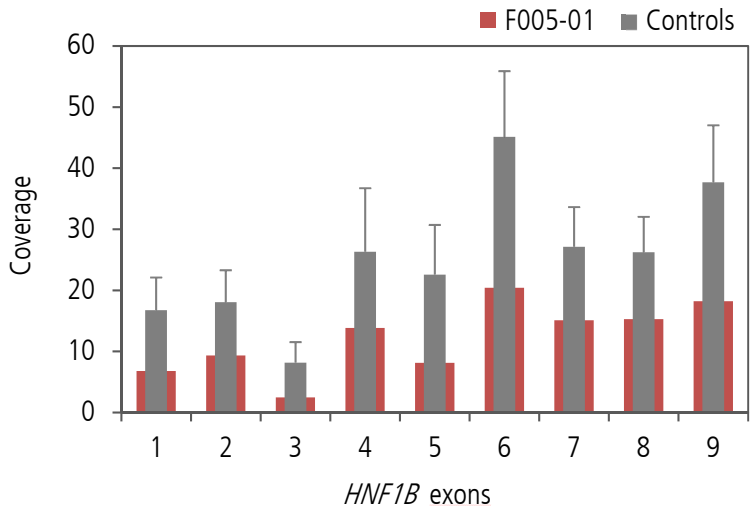
Supplementary Table S7. Rare heterozygous loss-of-function variants in the *UMOD* (NM_003361.4) gene in CAKUT patients

Patient ID, gender	Chromosomal position[a]	Nucleotide change	Amino acid change	Variant effect	Reference SNP number	MAF[b]	Segregation	Kidney phenotype	Extrarenal phenotype	ACMG classifi-cation
F004-01, male	16:20357588	c.1042C>T	p.(Gln348*)	Stop gain	rs199631490	0.00001828	Maternal	MCDK (r)	Cryptorchidism, phimosis, hyperuricemia, preterm birth	P
A022-01, female	16:20352452	c.1538delA	p.(Asn513fs*6)	Frameshift	-	0.0	Maternal	MCDK (l), kidney hypoplasia with VUR (r)	None	P
Case 3 [127], female	16:20348714	c.1639C>T	p.(Arg547*)	Stop gain	rs748318229	0.000009140	Not determined	Kidney agenesis (l), hypodysplasia (r)	Absent ureteric orifice (l), absent trigone, common urogenital sinus, patulous urethra with continuous leakage, hematocolpos and hematosalpinx (l) due to septate obstructed hemivagina, hyperuricemia	LP

[a]According to GRCh37/hg19

[b]According to Genome Aggregation Database (gnomAD v.2.1.1 controls, http://gnomad.broadinstitute.org/)

Supplementary Figures



Supplementary Figure S1. Coverage analysis of whole-exome sequencing reads showing the whole-gene deletion of *HNF1B* in patient F005-01. The number of reads was reduced for all exons of *HNF1B* in patient F005-01 (in red) compared with the mean number of reads in 25 control DNAs analyzed in parallel (in gray).

NM_001202.6(*BMP4*):c.1085A>G

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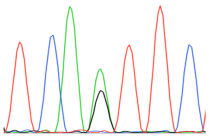	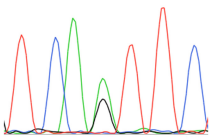	NA

NM_001845.6(*COL4A1*):c.3997G>A

A001-01, index (+/-)	A001-02, mother	A001-03, father
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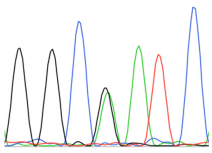	NA	NA

NM_001142966.2(*GREB1L*):c.4939T>C

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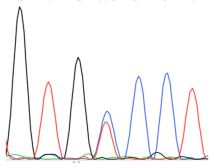	NA	NA

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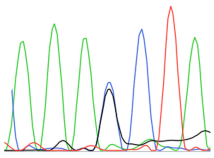	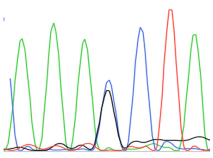	NA

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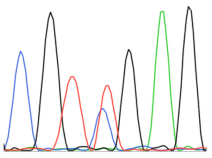	NA	NA

NM_001002295.2(*GATA3*):c.1099C>T

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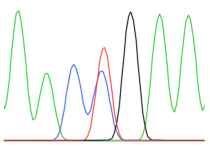	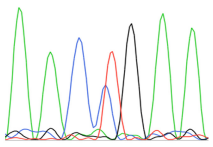	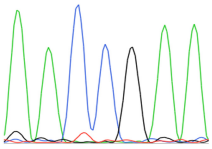

NM_001001557.4(*GDF6*):c.746C>A

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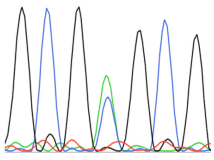	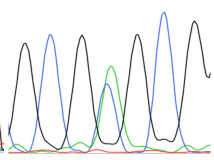	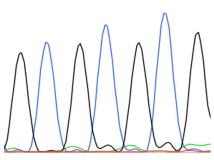

NM_001001557.4(*GDF6*):c.746C>A

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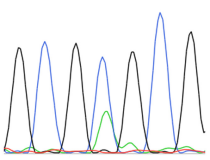	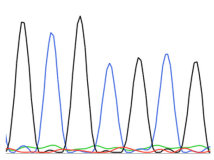	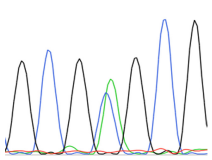

NM_015173.4(*TBC1D1*):c.644_653delACCCGCCCCA

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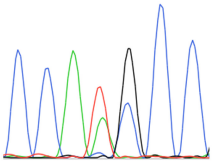	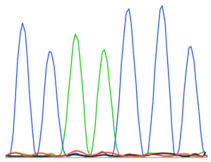	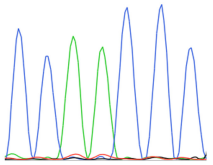

NM_015173.4(*TBC1D1*):c.1910+2T>G

B047-01, index (+/-)	B047-02, mother (+/-)	B047-03, father (+/+)
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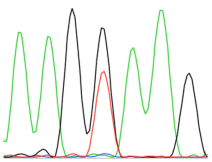	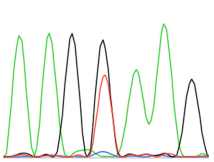	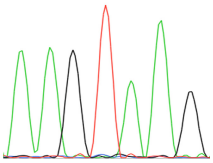

NM_001127671.2(*LIFR*):c.478_479delAG

C017-01, index (+/-)	C017-02, mother	C017-03, father
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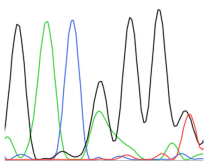	NA	NA

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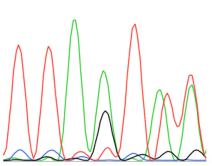	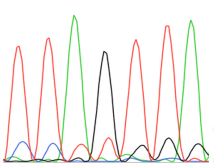	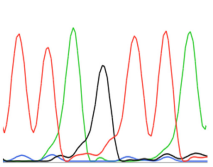

NM_003990.5(*PAX2*):c.76delG

A011-01, index (+/-)	A011-03, mother (+/+)	A011-02, father (+/+)
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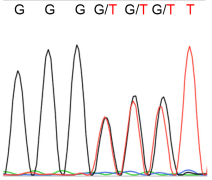	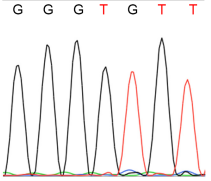	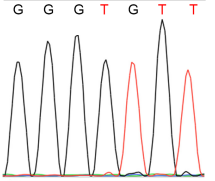

NM_003990.5(*PAX2*):c.76dupG

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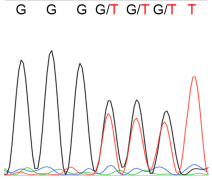	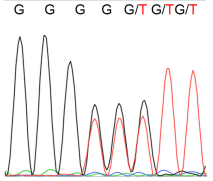	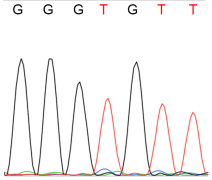

NM_002941.4(*ROBO1*):c.856C>T

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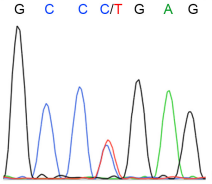	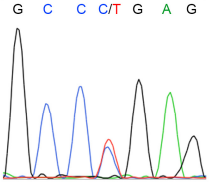	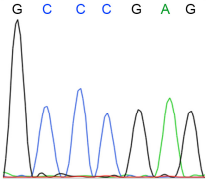

NM_002968.2(*SALL1*):c.2759C>G

A009-01, index (+/-)	A009-02, mother (+/+)	A009-03, father (+/+)
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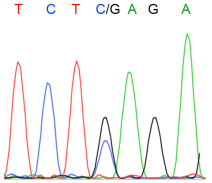
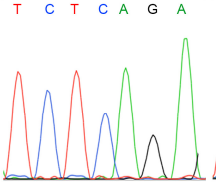
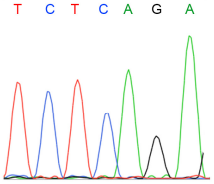
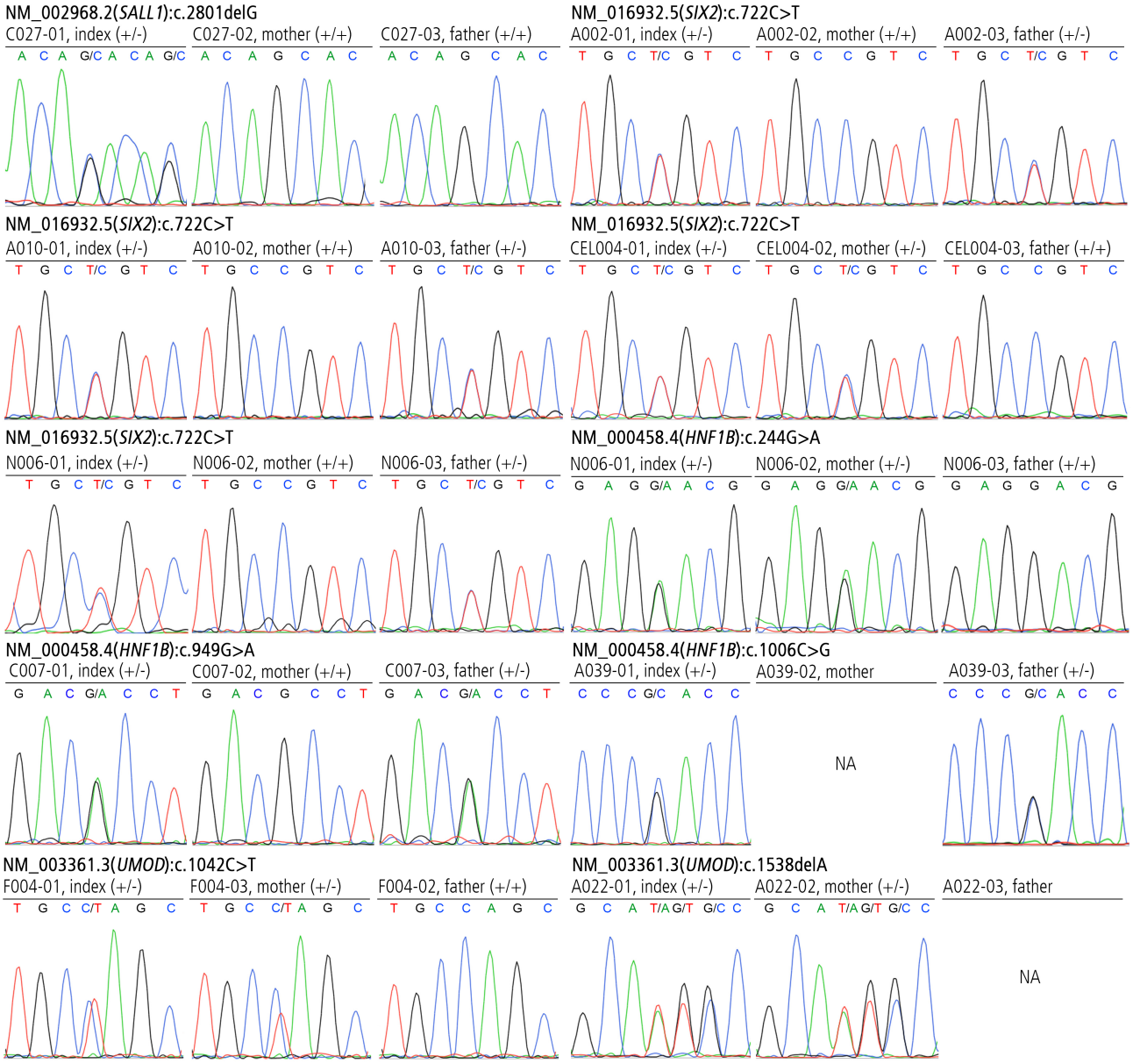
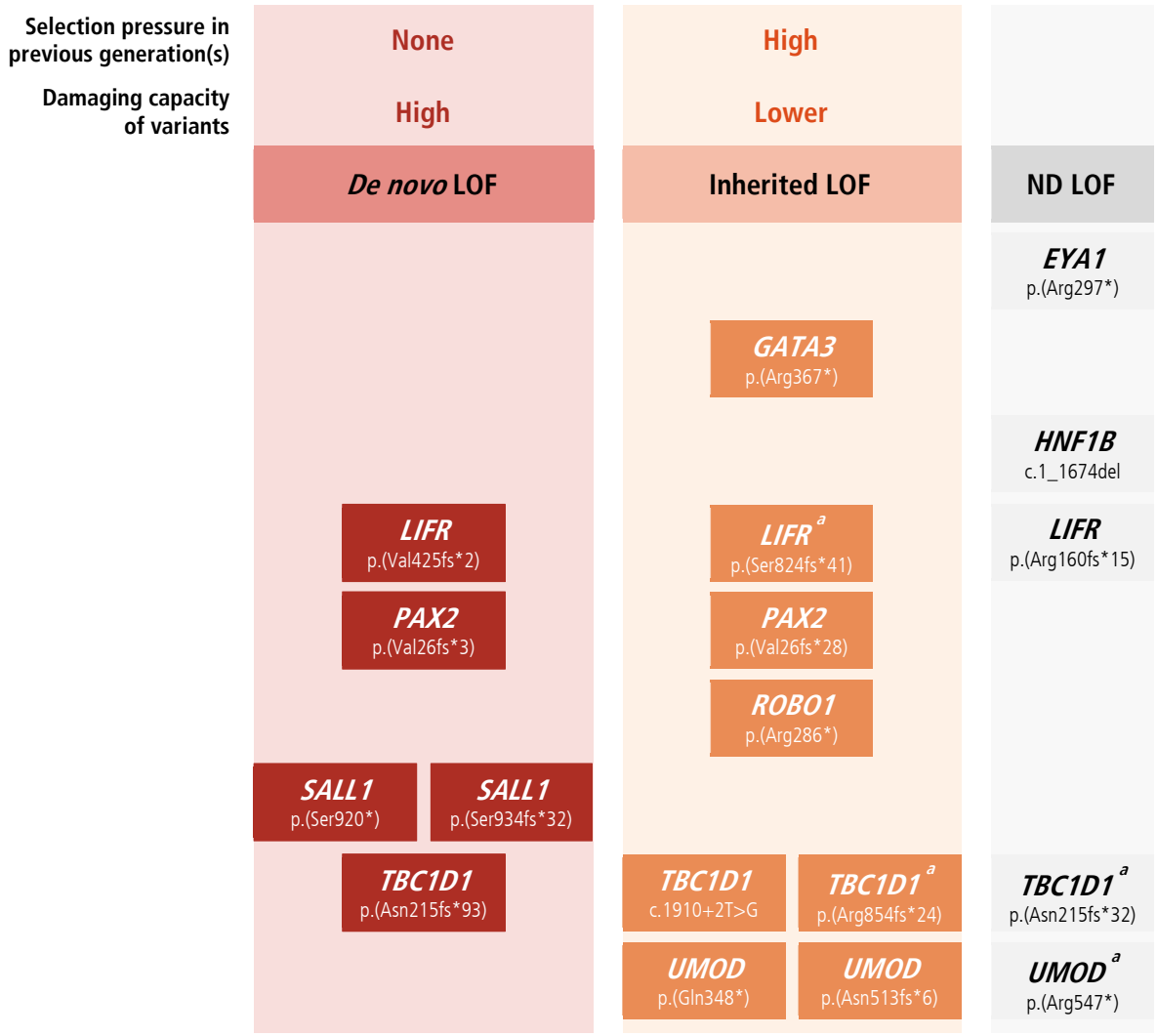
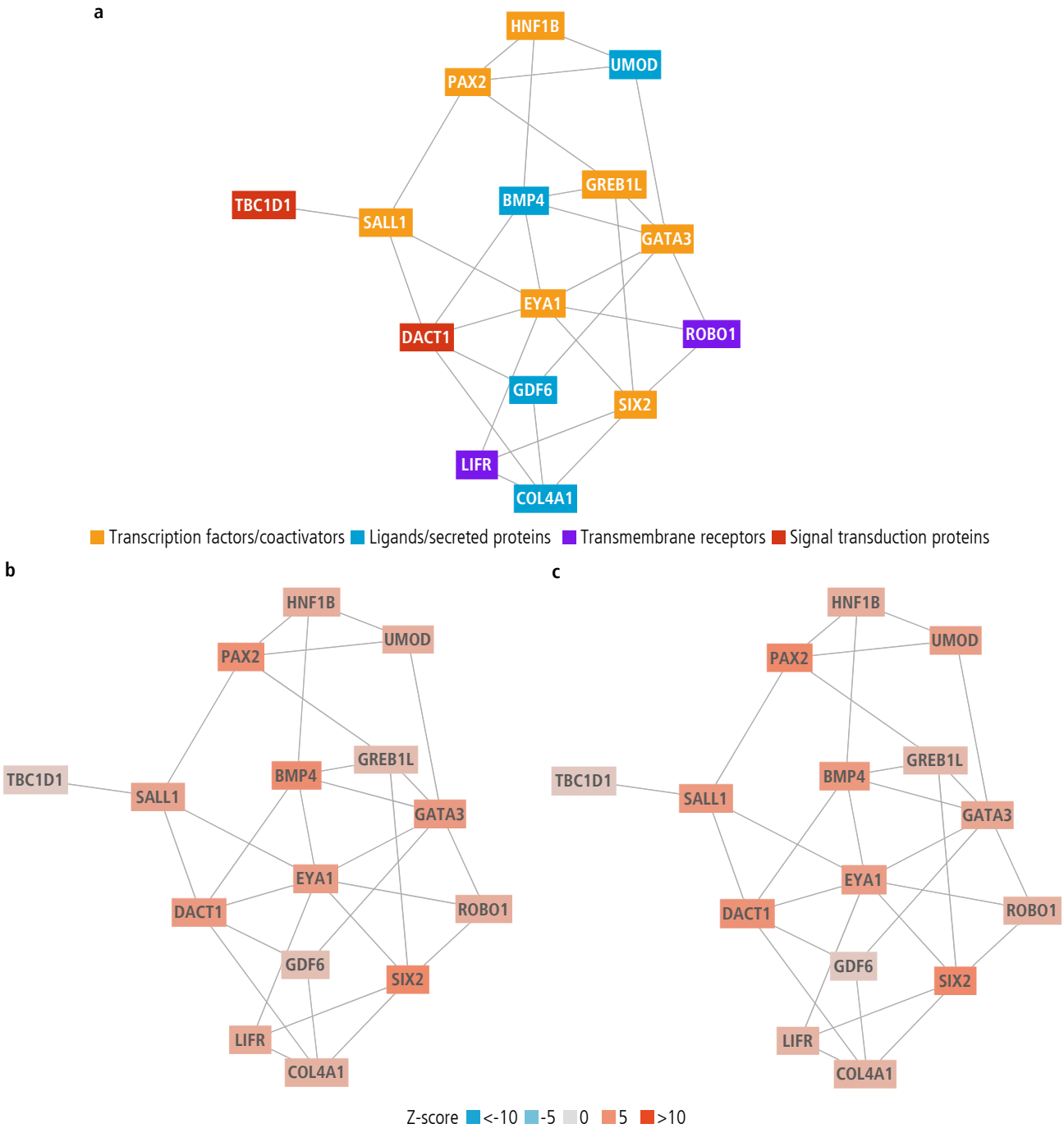
		



Supplementary Figure S2. Electropherograms of variants classified as “Likely Pathogenic” or “Pathogenic” and their segregation, as verified by targeted sequencing. NA, parental DNA was not available.



Supplementary Figure S3. Scheme of all loss-of-function variants identified in CAKUT patients here, and their presumed damaging capacity based on the fact whether they are inherited or *de novo* variants and have thus undergone selection pressure in previous generations or not. LOF, loss of function; ND, not determined. [a]Additional cases listed in Supplementary Tables S5-S7



Supplementary Figure S4. Visualization of an interaction network of the proteins encoded by the 15 genes found to be mutated in CAKUT patients diagnosed in the first 1,000 days of life. The analysis is based on human kidney-derived gene expression data and the tool "function enrichment" was used (kidney.genenetwork.nl; [128]). Nodes represent proteins and edges represent protein-protein interactions. (a) A color code is used to identify transcription factors/coactivators, ligands/secreted proteins, transmembrane receptors, or signal transduction proteins within the network. (b, c) According to "GO_P" pathway enrichment, this protein network is most likely involved in (b) 'ureteric bud development' (GO:0001657; $p=1.1x10^{-10}$) and (c) 'ureteric bud branching' (GO:0001658, $p=1.3x10^{-10}$). A Z-score above 0 indicated by shades of red predicts degree of involvement of the proteins; the higher the score, the more likely the involvement.

References

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