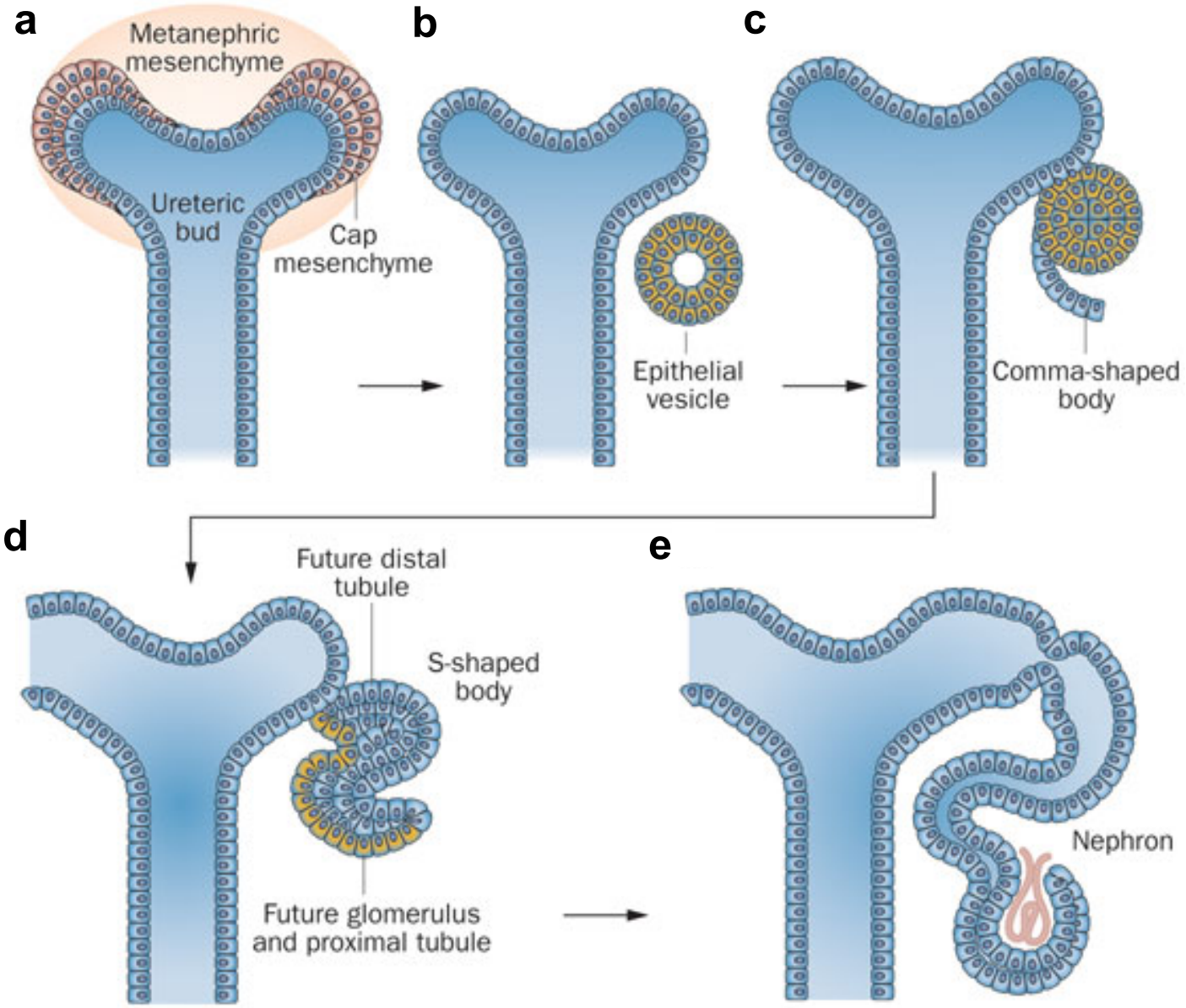
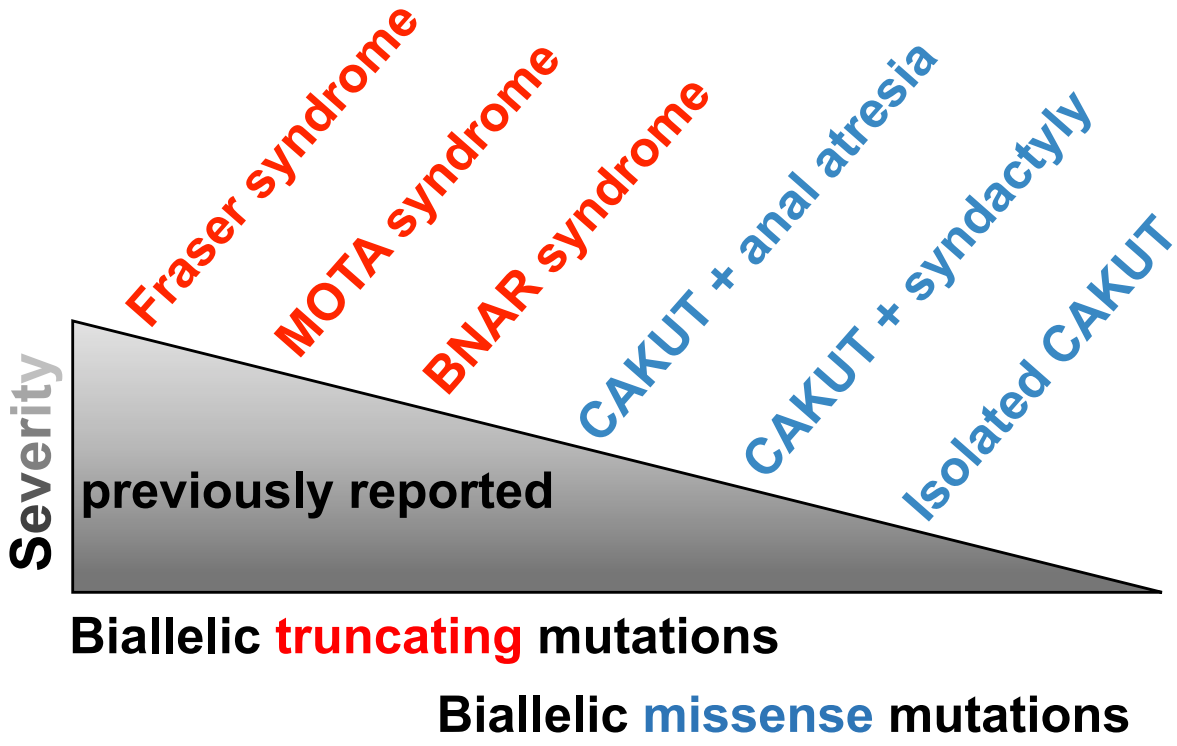


Supplementary Figure 1. Stages of nephron development.

a) Metanephric mesenchyme in closest proximity to the ureteric bud condenses around the ureteric bud-tips and forms the cap mesenchyme.
b) The cap mesenchyme subsequently gives rise to the most primitive nephron progenitor structure, the epithelial vesicle. During the maturation process, the epithelial vesicle sequentially undergoes distinct developmental stages, i.e.
c) the comma-shaped body,
d) the S-shaped body, and
e) the mature nephron.

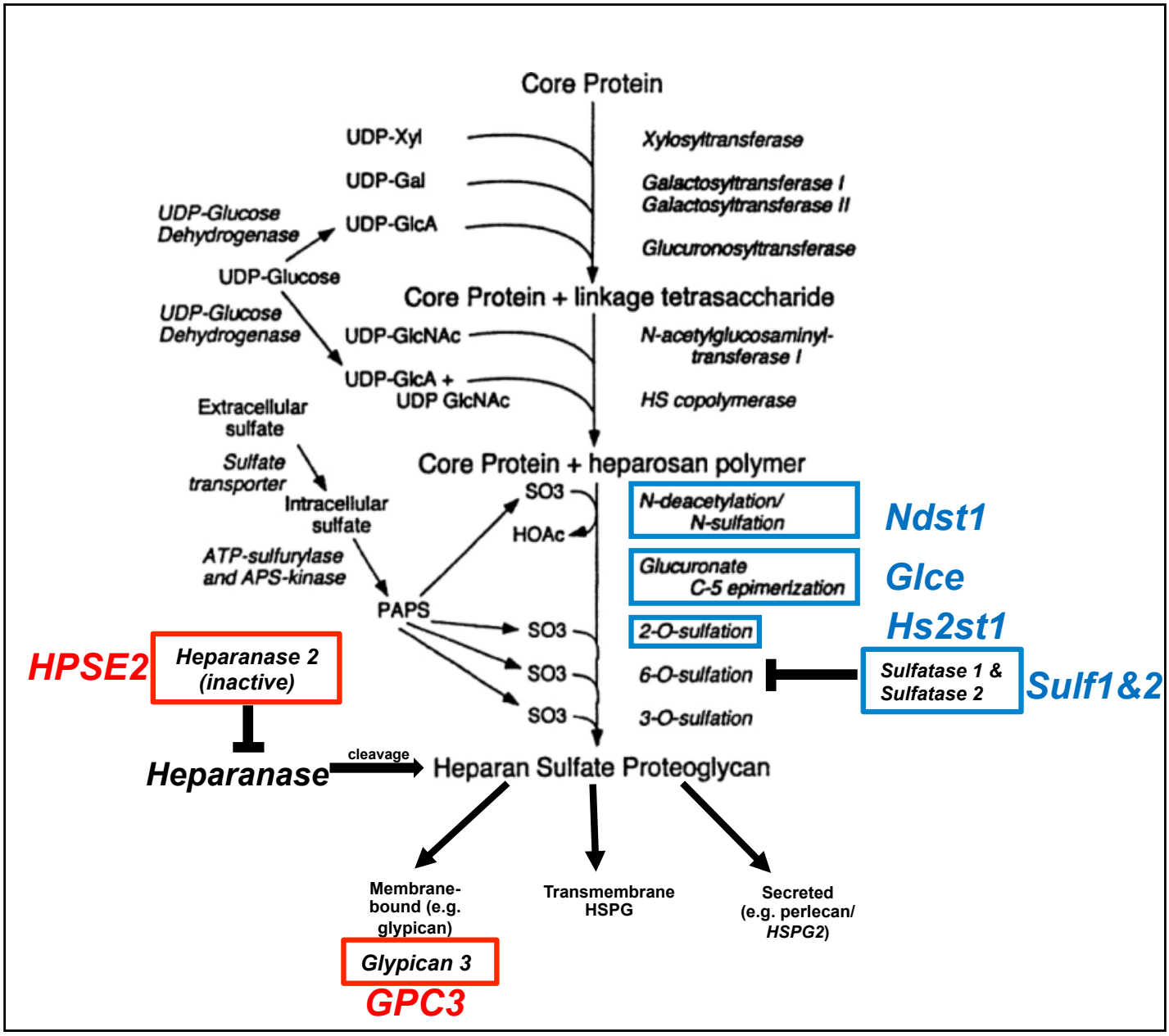
(From Kamath, Spinner & Rosenblum, Nat Rev Neph, 2013).



Supplementary Figure 2. Phenotypic variability of mutations in genes encoding the Fraser-complex.

Biallelic truncating mutations in genes encoding members of the Fraser-Complex (***FRAS1, FREM1, FREM2)*** and the associated protein ***GRIP1*** are known monogenic causes of the severe, syndromic CAKUT phenotypes of Fraser syndrome (***FRAS1, FREM2, GRIP1***) and of MOTA/BNAR syndrome (Manitoba-oculo-tricho-anal/bifid nose with or without anorectal and renal anomalies) (***FREM1***).

Studies by Kohl et al. (Kohl *JASN* 25:1917-22, 2014), however revealed that also a significant proportion (13/590; ~2.2%) of individuals with predominantly isolated CAKUT phenotypes carry recessive mutations in these known Fraser- and MOTA/BNAR syndrome genes. Mutations identified in patients with isolated CAKUT were found to be milder ("hypomorphic") than mutations published to be causative of the respective syndromic phenotype thus indicating an "allelism" for the broad phenotypic spectrum of the ***FRAS1***, ***FREM2***, ***GRIP1*** and ***FREM1*** genes.
This hypothesis will have to further be tested by the generation of additional genetic and functional data in the future.



Supplementary Figure 3. Overview of enzymes involved in synthesis and breakdown of heparan-sulfate proteoglycan (HSPG) chains.

The synthesis of HSPG requires a multiplicity of different enzymatic reactions. The genes encoding enzymes in the HSPG pathway ***Ndst1***, ***Glce***, ***Hs2st1***, ***Sulf1*** & ***Sulf2, HPSE2*** as well as one HSPG subtype ***GPC3*** have previously been implicated to cause syndromic CAKUT phenotypes, if mutated in mice (blue). ***HPSE2*** and ***GPC3*** are also known to cause CAKUT in humans, if mutated (red) (see also **Supplementary Table 1**). The role of ECM proteins in renal morphogenesis and the pathogenesis of CAKUT is related to their importance for structural integrity and/or regulation of the intricate cross-talk between the structures of the developing kidney. (modified from Lander, Selleck, *J Cell Biol* 148:227, 2000).

Supplementary Table 1: 183 Monogenic causes of murine CAKUT.

183 genes that, if mutated, cause CAKUT in mice were retrieved from the MGI database (http://www.informatics.jax.org/) by searching for the following terms: “abnormal mesonephric mesenchyme”, “abnormal mesonephric mesenchyme morphology”, “abnormal metanephric mesenchyme”, “abnormal metanephric mesenchyme morphology”, “abnormal metanephric ureteric bud development”, “abnormal ureter development”, “abnormal ureter morphology”, “abnormal ureteric bud elongation”, “abnormal ureteric bud invasion”, “abnormal ureterovesical junction”, “abnormal urinary system development”, “absent kidney”, “absent metanephric mesenchyme”, “absent metanephros”, “absent ureter”, “dilated ureter”, “double kidney pelvis”, “double kidney pelvis”, “double ureter”, “duplex kidney”, “ectopic ureter”, “ectopic ureteric bud”, “hydroureter”, “impaired branching involved in ureteric bud morphogenesis”, “pelvic kidney”, “renal hypoplasia”, “short ureter”, “single kidney”, “small metanephros”, “ureter hypoplasia”, “abnormal nephrogenic mesenchyme morphogenesis”, “ureteropelvic junction obstruction”. Mouse CAKUT genes are listed here in parallel with the corresponding human phenotype that was extracted from the OMIM database (www.omim.org). Human phenotypes representing CAKUT are underlined (source: clinical synopsis table, OMIM, www.omim.org).

Gene	Protein	PubMed ID MGI Ref. ID	Human Phenotype (contains CAKUT)	Human phenotype OMIM #
Ace	Angiotensin I converting enzyme	8642790	Renal tubular dysgenesis	267430
Acvr2b	Activin A Receptor Type 2B	9242489	Heterotaxy, visceral, 4, autosomal	613751
Adamts1	ADAM Metallopeptidase With Thrombospondin Type 1 Motif 1	10811842	-	-
Agt	Angiotensinogen	8675666	Renal tubular dysgenesis	267430
Agtr1a	Angiotensin II receptor, type 1a	10024874	Renal tubular dysgenesis	267430
Agtr1b	Angiotensin II receptor, type 1b	10024874	Renal tubular dysgenesis	267430
Agtr2	Angiotensin II Receptor Type 2	10024874	-	-
Aldh1a2	Aldehyde Dehydrogenase 1 Family Member A2	20040494	-	-
Amer1	APC Membrane Recruitment Protein 1	21571217	Osteopathia striata with cranial sclerosis	300373

Anp32b	Acidic Nuclear Phosphoprotein 32 Family Member B	21636789	-	-
Aprt	Adenine Phosphoribosyltransferase	8864750	Adenine phosphoribosyl-transferase deficiency	614723
Aqp2	Aquaporin 2	3184310	Diabetes insipidus, nephrogenic	125800
Arhgap1	Rho GTPase Activating Protein 1	17227869	-	-
Arhgap35	Rho GTPase Activating Protein 35	26859289	-	-
Arid5b	AT-Rich Interaction Domain 5B	17143286	-	-
Arl3	ADP Ribosylation Factor Like GTPase 3	16565502	-	-
Atmin	ATM Interactor	24852369	-	-
Atp7a	ATPase Copper Transporting Alpha	11534785	Menkes disease; Occipital horn syndrome; Spinal muscular atrophy, distal, X-linked 3	309400; 304150; 300489
Axin1	Axin 1	17246824 13340237	Hepatocellular carcinoma, somatic	114550
Bag6	BCL2 Associated Athanogene 6	16287848	-	-
Bcl2	BCL2, Apoptosis Regulator	8623928	Leukemia/ lymphoma, B-cell, 2	n/a
Bmp4	Bone Morphogenetic Protein 4	10749566	Microphthalmia, syndromic 6	607932
Bmp5	Bone Morphogenetic Protein 5	5692092	-	-
Bmp7	Bone Morphogenetic Protein 7	7590254	-	-
Bmper	BMP Binding Endothelial Regulator	17035289	Diaphano-spondylo-dysostosis	608022
Cc2d2a	Coiled-Coil And C2 Domain Containing 2A	J:175213	COACH syndrome; Joubert syndrome 9; Meckel syndrome 6	216360; 612285; 612284

Cdc42	Cell Division Cycle 42	23555292	Takenouchi-Kosaki syndrome	616737
Cdh4	Cadherin 4	11839813	-	-
Cdh6	Cadherin 6	10864459	-	-
Chrm3	Cholinergic Receptor Muscarinic 3	10944224	Prune belly syndrome	100100
Cntrl	Centriolin	J:175213	-	-
Crb3	Crumbs 3, Cell Polarity Complex Component	26631503	-	-
Crim1	Cysteine Rich Transmembrane BMP Regulator 1	22511315	-	-
Ctdnep1	CTD Nuclear Envelope Phosphatase 1	23360989	-	-
Ctnnb1	Catenin Beta 1	20454682	Colorectal cancer, somatic; Hepatocellular carcinoma, somatic; Medullo-blastoma, somatic; Mental retardation, autosomal dominant 19; Ovarian cancer, somatic; Pilomatricoma, somatic	114500; 114550; 155255; 615075; 167000; 132600
Ctnnbip1	Catenin Beta Interacting Protein 1	17803964	-	-
Cxcr4	C-X-C Motif Chemokine Receptor 4	J:175213	WHIM syndrome	193670
Cyp26a1	Cytochrome P450 Family 26 Subfamily A Member 1	11157778	-	-
Dact1	Dishevelled Binding Antagonist Of Beta Catenin 1	20145239	-	-
Dchs1	Dachsous Cadherin-Related 1	21303848	Mitral valve prolapse 2; Van Maldergem syndrome 1	607829; 601390
Dhcr7	7-Dehydrocholesterol Reductase	11230174	Smith-Lemli-Opitz syndrome	270400

Dlg1	Discs Large MAGUK Scaffold Protein 1	17172448	-	-
Dlg5	Discs Large MAGUK Scaffold Protein 5	17765678	{Inflammatory bowel disease 20}	612288
Dnah11	Dynein Axonemal Heavy Chain 11	J:175213	Ciliary dyskinesia, primary, 7, with or without situs inversus	611884
Dnah5	Dynein Axonemal Heavy Chain 5	J:175213	Ciliary dyskinesia, primary, 3, with or without situs inversus	608644
Dym	Dymeclin	18852472	Dyggve-Melchior-Clausen disease; Smith-McCort dysplasia	223800; 607326
Dync2h1	Dynein Cytoplasmic 2 Heavy Chain 1	J:175213	Short-rib thoracic dysplasia 3 with or without polydactyly	613091
Efnb2	Ephrin B2	15223334	-	-
Emx2	Empty Spiracles Homeobox 2	9165114	Schizencephaly	269160
Esrrg	Estrogen Related Receptor Gamma	21138943	-	-
Etl4/Etn2	Early transposon element insertion site 2	23436999	Epilepsy, familial temporal lobe, 4	611631
Etv4	ETS variant 4	19898483	-	-
Etv5	ETS variant 5	19898483	-	-
Exoc5	Exocyst complex component 5	26046524	-	-
Eya1	EYA Transcriptional Coactivator And Phosphatase 1	10471511	Branchiooto-renal syndrome 1, with or without cataracts; Branchiootic syndrome 1; Anterior segment anomalies with or without cataract; Otofaciocervical syndrome	113650; 602588; 602588; 166780
Fat4	FAT Atypical Cadherin 4	21303848	Van Maldergem syndrome 2; Hennekam lymph-angiectasia-lymphedema syndrome 2	615546; 616006

Fgf10	Fibroblast Growth Factor 10	11062007	Aplasia of lacrimal and salivary glands; LADD syndrome	180920; 149730
Fgf7	Fibroblast Growth Factor 7	9876183	-	-
Fgf8	Fibroblast Growth Factor 8	16049111	Hypo-gonadotropic hypogonadism 6 with or without anosmia	612702
Fgfr2	Fibroblast Growth Factor Receptor 2	15843416	Antley-Bixler syndrome; Apert syndrome; Beare-Stevenson cutis gyrata syndrome; Bent bone dysplasia syndrome; Craniofacial-skeletal-dermatologic dysplasia; Crouzon syndrome; Gastric cancer, somatic; Jackson-Weiss syndrome; LADD syndrome; Pfeiffer syndrome; Saethre-Chotzen syndrome; Scaphocephaly, maxillary retrusion, and mental retardation	207410; 101200; 123790; 614592; 101600; 123500; 613659; 123150; 149730; 101600; 101400; 609579
Fgfrl1	Fibroblast Growth Factor Receptor-Like 1	19715689	-	-
Fmn1	Formin 1	7517224	-	-
Foxc1	Forkhead Box C1	5500588	Anterior segment dysgenesis 3, multiple subtypes; Axenfeld-Rieger syndrome, type 3	601631; 602482
Foxd1	Forkhead Box D1	8666231	-	-
Foxd2	Forkhead Box D2	10648626	-	-
Foxg1	Forkhead Box G1	16109771	Rett syndrome, congenital variant	613454

Fras1	Fraser Extracellular Matrix Complex Subunit 1	12766769	Fraser syndrome	219000
Frem1	FRAS1 Related Extracellular Matrix 1	12766769	Bifid nose with or without anorectal and renal anomalies; Manitoba oculotrichoanal syndrome; Trigonocephaly 2	608980; 248450; 614485
Frem2	FRAS1 Related Extracellular Matrix Protein 2	12766769	Fraser syndrome	219000
Fstl1	Follistatin Like 1	22485132	-	-
Fzd4	Frizzled Class Receptor 4	21343368	Exudative vitreoretinopathy 1; Retinopathy of prematurity	133780; 133780
Fzd8	Frizzled Class Receptor 8	21343368	-	-
Gata2	GATA Binding Protein 2	18233958	Emberger syndrome; Immunodeficiency 21	614038; 614172
Gata3	GATA Binding Protein 3	16319112	Hypopara-thyroidism, sensorineural deafness, and renal dysplasia	146255
Gdf11	Growth Differentiation Factor 11	12729564	-	-
Gdnf	Glial Cell Derived Neurotrophic Factor	11422733	Central hypoventilation syndrome	209880
Gfra1	GDNF Family Receptor Alpha 1	23542432	-	-
Glce	Glucuronic Acid Epimerase	12788935	-	-
Gli3	GLI Family Zinc Finger 3	11978771	Greig cephalopoly-syndactyly syndrome; Pallister-Hall syndrome; Polydactyly, postaxial, types A1 and B; Polydactyly,	175700; 146510; 174200; 174700

			preaxial, type IV	
Gpc3	Glypican 3	10402475	Simpson-Golabi-Behmel syndrome, type 1; Wilms tumor, somatic	312870; 194070
Grem1	Gremlin 1, DAN Family BMP Antagonist	15201225	-	-
Grip1	Glutamate Receptor Interacting Protein 1	10974668	Fraser syndrome	219000
Hnf1b	HNF1 Homeobox B	23362348	Diabetes mellitus, noninsulin-dependent; Renal cysts and diabetes syndrome	125853; 137920
Hoxa11	Homeobox A11	7596412	Radioulnar synostosis with amegakaryo-cytic thrombocyto-penia 1	605432
Hoxd11	Homeobox D11	12050119	-	-
Hoxa13	Homeobox A13	12783783	Guttmacher syndrome; Hand-foot-uterus syndrome	176305; 140000
Hoxc10	Homeobox C10	19623272	-	-
Hoxc11	Homeobox C11	12050119	-	-
Hpse2	Heparanase 2	25510506	Urofacial syndrome 1	236730
Hs2st1	Heparan Sulfate 2-O-Sulfotransferase 1	9637690	-	-
Hsd17b2	Hydroxysteroid 17-Beta Dehydrogenase 2	18048640	-	-
Hspa4l	Heat Shock Protein Family A (Hsp70) Member 4 Like	16923965	-	-
Htr3a	5-Hydroxytryptamine Receptor 3A	15201326	-	-

Id2	Inhibitor Of DNA Binding 2, HLH Protein	15569159	-	-
Ilk	Integrin Linked Kinase	19829382	-	-
Itga3	Integrin Subunit Alpha 3	10433923	Interstitial lung disease, nephrotic syndrome, and epidermolysis bullosa, congenital	614748
Itga6	Integrin Subunit Alpha 6	10433923	Epidermolysis bullosa, junctional, with pyloric stenosis	226730
Itga8	Integrin Subunit Alpha 8	9054500 17537792	Renal hypodysplasia/ aplasia 1	191830
Itgb1	Integrin Subunit Beta 1	19439520	-	-
Kif26b	Kinesin Family Member 26B	20439720	-	-
Lama5	Laminin Subunit Alpha 5	10625553	-	-
Lamc1	Laminin Subunit Gamma 1	12015298	-	-
Lgr4	Leucine Rich Repeat Containing G Protein-Coupled Receptor 4	21523854 22738954	{Bone mineral density, low, susceptibility to}	615311
Lhx1	Luteinizing Hormone/Choriogona do-tropin Receptor	16216236	-	-
Lin7c	Lin-7 Homolog C, Crumbs Cell Polarity Complex Component	17923534	-	-
Lrp4	LDL Receptor Related Protein 4	20454682	Sclerosteosis 2; Cenani-Lenz syndactyly syndrome; ?Myasthenic syndrome, congenital, 17	614305; 212780; 616304
Lzts2	Leucine Zipper Tumor Suppressor 2	21949185	-	-
Megf8	Multiple EGF Like Domains 8	18043505	Carpenter syndrome 2	614976
Mks1	Meckel Syndrome, Type 1	21045211	Meckel syndrome 1	249000

Mmp14	Matrix Metallopeptidase 14	20727881	?Winchester syndrome	277950
Mmp17	Matrix Metallopeptidase 17	21347258	-	-
Mycn	V-Myc Avian Myelocytomatosis Viral Oncogene Neuroblastoma Derived Homolog	1459449	Feingold syndrome 1	164280
Ndst1	N-Deacetylase And N-Sulfotransferase 1		Mental retardation, autosomal recessive 46	616116
Nf1	Neurofibromin 1	7926784	Neurofibromatosis, type 1	162200
Nfia	Nuclear Factor I A	17530927	-	-
Nmnat2	Nicotinamide Nucleotide Adenylyltransferase 2	23082226	-	-
Nog	Noggin	18028901	Brachydactyly, type B2; Multiple synostoses syndrome 1; Stapes ankylosis with broad thumb and toes; Symphalangism, proximal, 1A; Tarsal-carpal coalition syndrome	611377; 186500; 184460; 185800; 186570
Notch2	Notch 2	20299358	Alagille syndrome 2; Hajdu-Cheney syndrome	610205; 102500
Npnt	Nephronectin	17537792	-	-
Osr1	Odd-Skipped Related Transciption Factor 1	16790474	-	-
Parva	Parvin Alpha	19829382	-	-
Pax2	Paired Box 2	8575306	Papillorenal syndrome; Glomerulo-sclerosis, focal segmental, 7	120330; 616002
Pax8	Paired Box 8	12435636	Hypothyroidism, congenital, due to thyroid dysgenesis or hypoplasia	218700

Pbx1	PBX Homeobox 1	12591246	Leukemia, acute pre-B-cell	176310
Pcnt	Pericentrin (kendrin)	25220058	Microcephalic osteodysplastic primordial dwarfism, type II	210720
Pcsk5	Proprotein Convertase Subtilisin/Kexin Type 5	18519639	-	-
Pdgfra	Platelet Derived Growth Factor Receptor Alpha	19217431	Gastrointestinal stromal tumor, somatic; Hyper-eosinophilic syndrome, idiopathic, resistant to imatinib	606764; 607685
Pds5a	PDS5 Cohesin Associated Factor A	19412548	-	-
Plxnb1	Plexin B1	18799546	-	-
Plxnb2	Plexin B2	21035938	-	-
Plxnd1	Plexin D1	J:175213	-	-
Ppp3r1	Protein Phosphatase 3 Regulatory Subunit B, Alpha	15057312	-	-
Prickle1	Prickle Planar Cell Polarity Protein 1	25190059	Epilepsy, progressive myoclonic 1B	612437
Ptch1	Patched 1	22792366	Basal cell carcinoma, somatic; Basal cell nevus syndrome; Holopros-encephaly 7	605462; 109400; 610828

Pten	Phosphatase And Tensin Homolog	17540362	Bannayan-Riley-Ruvalcaba syndrome; Cowden syndrome 1; Endometrial carcinoma, somatic; Lhermitte-Duclos syndrome; Macrocephaly/autism syndrome; Malignant melanoma, somatic; Squamous cell carcinoma, head and neck, somatic; VATER association with macrocephaly and ventriculo-megaly	153480; 158350; 608089; 158350; 605309; 155600; 275355; 276950
Ptprf	Protein Tyrosine Phosphatase, Receptor Type F	19273906	?Breasts and/or nipples, aplasia or hypoplasia of, 2	616001
Pygo1	Pygopus Family PHD Finger 1	17425782	-	-
Pygo2	Pygopus Family PHD Finger 2	17425782	-	-
Rara	Retinoic Acid Receptor Alpha	9376317	Leukemia, acute promyelocytic	612376
Rdh10	Retinol Dehydrogenase 10 (All-Trans)	21930923 17473173	-	-
Rere	Arginine-Glutamic Acid Dipeptide Repeats	23451234	Neurodevelopmental disorder with or without anomalies of the brain, eye, or heart	616975
Ret	Ret Proto-Oncogene	16452504	Central hypoventilation syndrome, congenital; Medullary thyroid carcinoma; Multiple endocrine neoplasia IIA; Multiple endocrine neoplasia IIB; Pheochromo-	209880; 155240; 171400; 162300; 171300

			cytoma	
Robo1	Roundabout Guidance Receptor 1	J:175213	-	-
Robo2	Roundabout Guidance Receptor 2	17357069	Vesicoureteral reflux 2	610878
Rspo2	R-Spondin 2	17904116 12782276	-	-
Sall1	Spalt Like Transcription Factor 1	11688560	Townes-Brocks syndrome; Townes-Brocks branchio-otorenal-like syndrome	107480
Sall4	Spalt Like Transcription Factor 4	17216607	Duane-radial ray syndrome; IVIC syndrome	607323; 147750
Sc5d	Sterol-C5-Desaturase	J:175213	Lathosterolosis	607330
Scarb2	Scavenger Receptor Class B Member 2	12620969	Epilepsy, progressive myoclonic 4, with or without renal failure	254900
Sema3a	Semaphorin 3A	18249526	{Hypogonado-tropic hypogonadism 16 with or without anosmia}	614897
Sestd1	SEC14 And Spectrin Domain Containing 1	23696638	-	-
Shh	Sonic Hedgehog	12399320	Holopros-encephaly 3; Microphthalmia with coloboma 5; Schizencephaly; Single median maxillary central incisor	142945; 611638; 269160; 147250
Six1	SIX Homeobox 1	14695375	Branchiootic syndrome 3; Deafness, autosomal	608389; 605192

			dominant 23	
Six2	SIX Homeobox 2	17036046	-	-
Slit2	Slit Guidance Ligand 2	15130495	-	-
Slit3	Slit Guidance Ligand 3	14550534	-	-
Sox4	SRY-Box 4	16109771	-	-
Sox9	SRY-Box 9	20881014	Acampomelic campomelic dysplasia; Campomelic dysplasia; Campomelic dysplasia with autosomal sex reversal	114290
Spry1	Sprouty RTK Signaling Antagonist 1	15691764	-	-
Sulf1	Sulfatase 1/ Sulfatase 2	17593974	-	-
Sulf2	Sulfatase 1/ Sulfatase 2	17593974	-	-
Tbc1d32	TBC1 Domain Family Member 32	J:175213	-	-
Tbx18	T-Box 18	24016759	Congenital anomalies of kidney and urinary tract 2	143400
Tbx6	T-Box 6	4073528	Spondylocostal dysostosis 5	122600
Tcf21	Transcription Factor 21	10572052	-	-
Tfcp2l1	Transcription Factor CP2-Like 1	17079272	-	-
Tgfb2	Transforming Growth Factor Beta 2	9217007	Loeys-Dietz syndrome 4	614816

Trp53	Transformation related protein 53	11780111	Adrenal cortical carcinoma; Breast cancer; Choroid plexus papilloma; Colorectal cancer; Hepatocellular carcinoma; Li-Fraumeni syndrome; Nasopharyngeal carcinoma; Osteosarcoma; Pancreatic cancer	202300; 114480; 260500; 114500; 114550; 151623; 607107; 259500; 260350
Trps1	Transcriptional Repressor GATA Binding 1	19820125	Trichorhino-phalangeal syndrome, type I; Trichorhino-phalangeal syndrome, type III	190350; 190351
Tshz3	Teashirt Zinc Finger Homeobox 3	18776146	-	-
Tyr	Tyrosinase	J:179802	-	-
Upk3a	Uroplakin 3A	11085999	-	-
Wasl	WAS/WASL Interacting Protein Family Member 1	23555292	-	-
Wdpcp	WD Repeat Containing Planar Cell Polarity Effector	24302887	?Congenital heart defects, hamartomas of tongue, and polysyndactyly	217085
Wnt11	Wnt Family Member 11	12783789	-	-
Wnt4	Wnt Family Member 4	7990960	Mullerian aplasia and hyperandro-genism; ?SERKAL syndrome	158330; 611812

Wnt5a	Wnt Family Member 5A	J:175213	Robinow syndrome, autosomal dominant 1	180700
Wnt7b	Wnt Family Member 7B	19060336	-	-
Wnt9b	Wnt Family Member 9B	16054034	-	-
Wt1	Wilms Tumor 1	18040647	Denys-Drash syndrome; Frasier syndrome; Meacham syndrome; Mesothelioma, somatic; Nephrotic syndrome, type 4; Wilms tumor, type 1	194080; 136680; 608978; 156240; 256370; 194070
Xpl	X-linked polydactyly	7391545	Orofaciodigital syndrome I	311200
Yap1	Yes Associated Protein 1	23555292	Coloboma, ocular; Coloboma, ocular, with or without hearing impairment, cleft lip/palate, and/or mental retardation	120433
Zbtb14	Zinc Finger And BTB Domain Containing 14	J:175213	-	-

Supplementary Table 2: Human monogenic CAKUT genes with reported involvement in GDNF-RET signaling.

List of human CAKUT genes with known (direct or indirect) involvement in GDNF-RET signaling (upstream or downstream of RET).

Please note that genes in parenthesis have not been explicitly mentioned in the references provided themselves, but are part of pathways that otherwise have been demonstrated to be involved.

Gene	Protein	Reference
Autosomal dominant		
BMP4	Bone morphogenic protein 4	Woolf and Davies JASN 24:19 2013; Short and Smyth Nat Rev Nephr 12:754 2016; Schedl Nat Rev Genet 8:791 2007; Davis Pediatr Nephrol 29:597 2014
EYA1	Eyes absent homolog 1	Short and Smyth Nat Rev Nephr 12:754 2016; Schedl, *Nat Rev Genet* 2007; Davis Pediatr Nephrol 29:597 2014
GATA3	GATA binding protein 3	Costantini Dev Biol 1:693 2012; Davis Pediatr Nephrol 29:597 2014
HNF1B	HNF homeobox B	Costantini Dev Biol 1:693 2012
(NRIP1)	Nuclear Receptor Interacting Protein 1	Costantini Dev Biol 1:693 2012; Davis Pediatr Nephrol 29:597 2014
PAX2	Paired box 2	Short and Smyth Nat Rev Nephr 12:754 2016; Schedl Nat Rev Genet 8:791 2007; Costantini Dev Biol 1:693 2012; Davis Pediatr Nephrol 29:597 2014
RET	Proto-oncogene tyrosine-protein kinase receptor Ret	Woolf and Davies JASN 24:19 2013; Short and Smyth Nat Rev Nephr 12:754 2016; Schedl Nat Rev Genet 8:791 2007; Costantini Dev Biol 1:693 2012; Davis Pediatr Nephrol 29:597 2014
ROBO2	Roundabout, axon guidance receptor, homolog 2 (Drosophila)	Short and Smyth Nat Rev Nephr 12:754 2016; Schedl Nat Rev Genet 8:791 2007; Davis Pediatr Nephrol 29:597 2014
SALL1	Sal-like protein 1 (also known as spalt-like transcription factor 1)	Short and Smith Nature Reviews, 2016; Schedl, Nat Rev Genet, 2007; Davis Pediatr Nephrol 29:597 2014
SIX1	SIX homeobox 1	Costantini Dev Biol 1:693 2012; Davis Pediatr Nephrol 29:597 2014
SIX2	SIX homeobox 2	Short and Smith, Nature Reviews, 2016
SLIT2	Slit homolog 2	Short and Smyth Nat Rev Nephr 12:754 2016; Schedl Nat Rev Genet 8:791 2007; Davis Pediatr Nephrol 29:597 2014
(SRGAP1)	SLIT-ROBO Rho GTPase activating protein 1	Short and Smyth Nat Rev Nephr 12:754 2016; Schedl Nat Rev Genet 8:791 2007; Davis Pediatr Nephrol 29:597 2014

Autosomal recessive		
(ACE)	Angiotensin-converting enzyme	Woolf and Davies JASN 24:19 2013; Davis Pediatr Nephrol 29:597 2014
(AGT)	Angiotensinogen	Woolf and Davies JASN 24:19 2013; Davis Pediatr Nephrol 29:597 2014
AGTR1	Angiotensin II receptor, type 1	Davis Pediatr Nephrol 29:597 2014
FRAS1	Extracellular matrix protein FRAS1	Short and Smyth Nat Rev Nephr 12:754 2016
FREM1	FRAS1 related extracellular matrix protein 1	Short and Smyth Nat Rev Nephr 12:754 2016
FREM2	FRAS1 related extracellular matrix protein 2	Short and Smyth Nat Rev Nephr 12:754 2016
(GRIP1)	Glutamate receptor interacting protein 1	Short and Smyth Nat Rev Nephr 12:754 2016
ITGA8	Integrin α8	Short and Smyth Nat Rev Nephr 12:754 2016; Schedl Nat Rev Genet 8:791 2007; Davis Pediatr Nephrol 29:597 2014
(REN)	Renin	Woolf and Davies JASN 24:19 2013; Davis Pediatr Nephrol 29:597 2014

Supplementary Table 3: **Extracellular matrix components with a role in the development of the kidneys and urinary tract.** Note that all murine and human phenotypes are recessive (autosomal or X-linked). Genes are divided into three groups: Fraser-complex related (light blue), Integrins/Laminins (light green), and HSPG-related (light orange) (see also **Suppl. Fig. 3**).

	Gene symbol	Protein	Phenotype Mice	Phenotype Human
Fraser-complex related	***FRAS1***	Fraser extracellular matrix complex subunit 1	Mutant mice exhibit significant amount of embryonic lethality due to hemorrhaging of embryonic blisters. Survival is variable on genetic background. Further phenotypes include severe renal developmental defects and syndactyly. (McGregor Nat Genet 34:203 2003)	Fraser Syndrome (OMIM 219000); isolated CAKUT (McGregor Nat Genet 34:203 2003; van Haelst Am J Med Genet A 146A:2252 2008; Kohl JASN 25:1917 2014)
	FREM1	Fras1 related extracellular matrix protein 1	Homozygous mice have subepidermal blistering, cryptophthalmos, syndactyly, and renal agenesis. (Kiyozumi Proc Natl Acad Sci USA 103:11981 2006)	Bifid nose with or without anorectal and renal anomalies (BNAR, OMIM 608980); Manitoba oculotrichoanal syndrome (MOTA, OMIM 248450); isolated CAKUT (Alazami Am J Hum Genet 85:414 2009; Slavotinek J Med Genet 48:375 2011; Kohl JASN 25:1917 2014)
	FREM2	Fras1 related extracellular matrix protein 2	Homozygous mice display a significant amount of embryonic lethality due to hemorrhagic embryonic blisters. Renal developmental defects and syndactyly are common. Phenotypes of homozygous mutants are indistinguishable from those of Fras1 homozygous mutants. (Jadeja Nat Genet 37:520 2005)	Fraser Syndrome (OMIM 219000); isolated CAKUT (Jadeja Nat Genet 37:520 2005; Kohl JASN 25:1917 2014)
	GRIP1	Glutamate receptor interacting protein 1	Homozygous mice show increased embryonic lethality, blistering skin lesions and CAKUT. (Swiergiel Dev Dyn 219:21 2000)	Fraser Syndrome (OMIM 219000); isolated CAKUT (Vogel J Med Genet 49:303 2012; Schanze Am J Med Genet A 164A:837 2014; Kohl JASN 25:1917 2014)
	ITGA8	Integrin alpha 8	Homozygous mice die on the second day after birth. Survivors have reduced kidney size and abnormal steriocilia in the inner ear. (Muller Cell 88:6031997; Linton Development 134:2501 2007)	Isolated CAKUT (Humbert Am J Hum Genet 94:288 2014)

	NPNT	Nephronectin	Homozygous mice exhibit kidney agenesis or hypoplasia attributed to a delay in the invasion of the metanephric mesenchyme by the ureteric bud at an early stage of kidney development. (Linton Development 134:2501 2007)	-
Integrins, Laminins	***ITGβ1***	Integrin beta 1	Homozygous null mice die at or soon after implantation. Tissue-specific knockouts exhibit symptoms including skin blisters, brain and heart defects, as well as CAKUT phenotypes. (Wu Am J Physiol Renal Physiol 297:F210 2009)	-
	LAMA5	Laminin alpha 5	Homozygous null mice exhibit symptoms including exencephaly, syndactyly, CAKUT, and lethality in late gestation. (Miner Dev Biol 217:278 2000; Lo, MGI Ref ID J:175213)	nothing reported in OMIM, HGMD: Focal segmental glomerulosclerosis (Chatterjee Plos One 8:e76360 2013)
	LAMC1	Laminin gamma 1	Homozygous null mice display a syndromic phenotype including features from the CAKUT spectrum. (Willem Development 129:2711 2002)	nothing reported in OMIM, HGMD: Dandy-Walker malformation (Darbro Hum Mutat 34:1075 2013)

Supplementary Table 3 (contd.)

	Gene symbol	Protein	Phenotype Mice	Phenotype Human
HSPG metabolism	***Glce***	Glucuronyl C5-epimerase	Homozygous mice display severe developmental defects including renal agenesis, lung abnormalities, and skeletal malformations. (Li J Biol Chem. 278:28363 2003)	-
	Gpc3	Glypican 3	The gene trap mouse model exibits neonatal lethality, embryonic overgrowth and kidney cysts. The Gpc3 null mouse exhibits enhanced UB branching. (Cano-Gauci J Cell Biol 146:255 1999)	Simpson-Golabi-Behmel Syndrome, Type 1 (OMIM 312870) (Veugelers Hum Mol Genet 9:1321 2000; Baujat Am J Med Genet C 137C:4 2005; Sakazume Am J Med Genet A 150B:151 2007; Kehrer Prenat Diagn 36:961 2016; Cotterau Am J Med Genet C 164A:282 2013)
	Hpse2	Heparanase 2	Homozygous mice exhibit symptoms including distended urinary bladder, abnormal voiding behavior, renal dysfunction urinary bladder fibrosis, and lethality within one month of age. (Guo Hum Mol Genet 24:1991 2015)	Urofacial Syndrome 1 (OMIM 236730) (Pang Am J Hum Genet 86:957 2010; Stuart JASN 26:797 2015)
	Hs2st1	Heparan sulfate 2-O-sulfotransferase 1	Homozygous mice exhibit bilateral renal agenesis, bone defects, eye development abnormalities and cataracts. (Bullock Genes Dev 15:1894 1998)	-
	Ndst1	N-deacetylase/N-sulfotransferase (heparan glucosaminyl) 1	Homozygous mice die late in gestation or neonatally. They exhibit a mutisystemic phenotype including hydronephrosis and kidney cysts, respiratory distress and failure. (Fan FEBS 467:7 2000; Lo, MGI ID J:175213)	Mental retardation (OMIM 616116) (Reuter Am J Med Genet 164A:2753 2014; Najmabadi Nature 478:57 2011)

	Sulf1+Sulf2	Sulfatase 1 + Sulfatase 2	Mice deficient in both genes exhibited highly penetrant neonatal lethality associated with multiple developmental defects including skeletal and renal abnormalities (CAKUT spectrum). (Holst Plos One 2:e575 2007)	-

Supplementary Table 4: Proteins that are related to BMP signaling and play a role in the development of the kidneys and the urinary tract. Corresponding genes/proteins are subcategorized in three groups: Regulators of BMP signaling (light red), BMP ligands (light blue), and BMP receptor(s) (light orange).

	Gene symbol	Protein	Phenotype Mice	Reference Mice MGI ID	Phenotype Human (contains CAKUT) OMIM#
Regulators of BMP signalling	***BMPER*** *(Cross-veinless 2)*	**BMP-binding endothelial regulator**	Renal hypoplasia	Ikeya *Development* 133:4463 2006; **MGI 1920480**	Diaphanospondylodysostosis #608022
	CTDNEP1 *(Dullard)*	**CTD Nuclear Envelope Phosphatase**	Failure of postnatal nephron maintenance, renal hypoplasia.	Sakaguchi *Nat Commun* 4:1398 2013; **MGI 1914431**	-
	CRIM1	**Cysteine rich transmembrane BMP regulator 1**	Perinatal lethality, syndactyly, and eye and kidney abnormalities.	Chiu *Genesis* 50:711 2012, Wilkinson *Kidney Internat* 76:1161 2009; **MGI 1354756**	-
	FST	**Follistatin**	Renal dysgenesis (**this phenotype not reported in MGI**)	Matzuk *Nature* 374:360 1995; **MGI 95586**	-
	GPC3	**Glypican 3**	Renal medullary cystic dysplasia	Cano-Gauci *J Cell Biol* 146:255 1999; **MGI 104903**	Simpson-Golabi-Behmel syndrome, type 1, # 312870
	GREM1	**Gremlin1**	Bilateral agenesis of kidneys and ureter	Michos *Development* 131:3401 2004; **MGI 1344337**	isolated human CAKUT (Kohl *JASN* 25:1917 2014)

Supplementary Table 4 (contd.)

	Gene symbol	Gene name	Phenotype Mice	Reference Mice MGI ID	Phenotype Human (contains CAKUT) OMIM#
BMP ligands	***BMP2***	**Bone Morphogenic Protein 2**	Homozygotes lethal between E7 and E10.5; Heterozygotes: increased proliferation and branching of ureteric bud **(this phenotpe not reported in MGI)**	Zhang and Bradley *Development* 122:2977 1996; Hartwig *Mech Dev* 122:928 2005; Singh *Sex Dev* 2:134 2008; **MGI 88177**	Brachydactyly, type A2; #112600
	BMP4	**Bone Morphogenic Protein 4**	Homozygotes lethal between E6.5 and E9.5; Heterozygotes: renal abnormalities from within the CAKUT spectrum	Miyazaki *J Clin Invest* 105:863 2000; **MGI 88180**	isolated human CAKUT (Weber *JASN* 19:891 2008); syndromic microphthalmia 6 #607932; Orofacial cleft 1, #600625
	BMP5	**Bone Morphogenic Protein 5**	Hydronephrosis	Kingsley *Cell* 71:399 1992; King *Dev Biol* 166:112 1994; **MGI 88181**	-
	BMP7	**Bone Morphogenic Protein 7**	Renal dysgenesis and hydroureter, arrested development	Dudley *Genes Dev* 9:2795 1995; Luo *Genes Dev* 9:2808 1995; **MGI 103302**	-
BMP receptor(s)	***BMPR1A***	**Bone Morpho-genetic Protein Receptor Type 1A**	Medullary hypoplasia and cortical cysts in conditional knockout mutants in ureteric epithelium; Renal aplasia/dysgenesis or medullary dysplasia in mutants overexpressing Bmpr1a throughout ureteric epithelium **(this phenotype not reported in MGI)**	Hartwig *J Am Soc Nephrol* 19:117 2008; Hu *Development* 130:2753 2003; **MGI 1338938**	Polyposis syndrome #174900; #610069; #174900