OMIM gene number	Gene symbol	OMIM syndrome name	Biomolecular pathway	Loss-of-function variant carriers in 60,706 individuals from ExAC database	pLI-score in ExAC database	CAKUT phenotypes	Phenotypic findings	Mode of inheritance
Transcription factors								
*601653	*EYA1*	Branchio-oto-renal syndrome	Protein phosphatase required for regulating genes encoding growth control and signaling molecules. Transcriptional co-activator of *SIX1.*	3	0.96	Syndromic RHD	Sensorineural hearing loss, preauricular pits, branchial cysts, microtia	Autosomal Dominant
*605515	*FOXP1*	Mental retardation with language impairment and with or without autistic features	Forkhead box transcription factors play important roles in the regulation of tissue- and cell type-specific gene transcription during both development and adulthood.	10	1.00	(Syndromic) RHD, VUR, duplication of the collecting system	Structural brain abnormalities, seizures, developmental delay, facial dysmorphisms, skeletal abnormalities	Autosomal Dominant
*131320	*GATA3*	Hypoparathyroidism, sensorineural deafness, and renal dysplasia	Regulator of T-cell development and plays an important role in endothelial cell biology.	2	0.88	RHD	Hypoparathyroidism, sensorineural deafness, genital malformations	Autosomal Dominant
*165240	*GLI3*	Pallister-Hall syndrome	C2H2-type zinc finger proteins subclass of transcription factors that mediate Sonic hedgehog signaling.	3	1.00	Syndromic RHD	Cardiac malformations, facial dysmorphisms, skeletal abnormalities	Autosomal Dominant

*189907	*HNF1B*	Renal cysts and diabetes syndrome	Member of the homeodomain-containing superfamily of transcription factors. Role in nephron and pancreas development.	4	1.00	Isolated RHD	Maturity onset diabetes in the young type 5, hyperuricemia, hypomagnesemia, genital malformations	Autosomal Dominant
*142994	*MNX1*	Currarino syndrome	Nuclear protein, which contains a homeobox domain and transcription factor	1	-	Syndromic RHD, renal ectopia, VUR	Caudal regression syndrome, anorectal malformations, developmental delay, skeletal abnormalities	Autosomal Dominant
*167409	*PAX2*	Papillorenal syndrome	Transcription factor factor of paired box domain family. *PAX2* is believed to be a target of transcriptional suppression by the tumor suppressor gene *WT1*.	16	0.12	Isolated RHD	Retinal and optic nerve coloboma	Autosomal Dominant
*176310	*PBX1*	Leukemia, acute pre-B-cell	PBX homeobox family of transcriptional factors. May be involved in the regulation of osteogenesis, and required for skeletal patterning and programming.	3	0.91	Syndromic RHD, VUR, obstructive uropathy, horseshoe kidney, renal ectopia	Deafness, developmental delay, skeletal abnormalities, facial dysmorphisms, 1q23.3-q24.1 deletion syndrome (cardiac defects, genital malformations, spina	Autosomal Dominant

							bifida), leukemia	
*604613	*TBX18*	Congenital anomalies of kidney and urinary tract	Transcription factor that plays a crucial role in embryonic development. The family is characterized by the presence of the DNA-binding T-box domain.	1	1.00	Isolated obstructive uropathy, VUR	-	Autosomal Dominant
*602218	*SALL1*	Townes-Brocks syndrome	Zinc finger transcriptional repressor that may be part of the NuRD histone deacetylase complex (HDAC).	2	0.99	Syndromic RHD, VUR, renal ectopia, posterior urethral valves	Thumb abnormalities, facial dysmorphisms, gastrointestinal malformations, genital malformations	Autosomal Dominant
*607343	*SALL4*	Duane-radial ray syndrome	This gene encodes a zinc finger transcription factor thought to play a role in the development of abducens motor neurons.	7	1.00	Syndromic renal ectopia, CAKUT	Radial abnormalities, facial dysmorphisms, sensorineural deafness, gastrointestinal malformations, genital malformations	Autosomal Dominant
*601205	*SIX1*	Branchio-oto-renal syndrome	Homeobox protein thought to be involved in limb development.	0	0.93	Syndromic RHD	Sensorineural hearing loss, preauricular pits, branchial cysts, microtia	Autosomal Dominant

*610928	*SOX17*	VUR	SOX (SRY-related HMG-box) family-member of transcription factors involved in the regulation of embryonic development and in the determination of the cell fate.	0	0.87	VUR	Corpus callosum hypoplasia(?), chronic constipation(?)	Autosomal Dominant
Chromatin binding proteins/DNA helicases								
#214800	*CHD7*	CHARGE syndrome	Protein that contains several helicase family domains.	5	1.00	RHD, renal ectopia, VUR	Cardiac malformations, developmental delay, choanal atresia, gastrointestinal malformations, skeletal abnormalities	Autosomal Dominant
*600140	*CREBBP*	Rubinstein-Taybi syndrome	Involved in the transcriptional coactivation of many different transcription factors. Critical role in embryonic development, growth control, and homeostasis by coupling chromatin remodeling to transcription factor recognition.	46	1.00	Syndromic RHD, VUR	Developmental delay, facial dysmorphisms, cardiac malformations, skeletal abnormalities	Autosomal Dominant
*300128	*KDM6A*	Kabuki-syndrome	The encoded protein of this gene contains catalyzes the	2	1.00	Syndromic VUR, RHD,	Developmental delay, facial dysmorphisms,	X-linked

			demethylation of tri-/dimethylated histone H3.			renal ectopia	cardiac malformations, feeding difficulties	Dominant
*602113	*KMT2D*	Kabuki-syndrome	Histone methyltransferase that methylates the Lys-4 position of histone H3.	21	1.00	Syndromic VUR, RHD, renal ectopia	Developmental delay, facial dysmorphisms, cardiac malformations, feeding difficulties	Autosomal Dominant
*608667	*NIPBL*	Cornelia de Lange syndrome	Encodes protein that facilitates enhancer-promotor communication and serves as chromosomal adherin with roles in chromatid cohesion, chromosomal condensation and DNA repair.	1	1.00	Syndromic RHD	Intrauterine growth retardation, long curly eyelashes, cardiac malformations, developmental delay	Autosomal Dominant
Signaling molecules/Growth factors								
*602007	*CRKL*	Atypical DiGeorge syndrome	Protein kinase which has been shown to activate the RAS and JUN kinase signaling pathways and transform fibroblasts in a RAS-dependent fashion.	1	0.16	RHD, VUR, obstructive uropathy	Developmental delay, ventricular septum defect, genital malformations	Autosomal Dominant
*612666	*DSTYK*	Spastic paraplegia	Protein kinase which is expressed in multiple tissues and presumed to function as a regulator of cell death.	39	0.15	Isolated RHD, ureteropelvic junction obstruction	Skin pigment abnormalities (recessive), seizures(?)	Autosomal Dominant

*605558	*FGF20*	Renal hypodysplasia/aplasia	Fibroblast growth factors possess broad mitogenic and cell survival activities, and are involved in a variety of biological processes including embryonic development, cell growth, morphogenesis, tissue repair, tumor growth and invasion.	1 (0 hom)	0.70	Isolated RHD (Bilateral)	Varus feet, pulmonary hypoplasia, skin abnormalities	Autosomal Recessive
*136350	*FGFR1*	Hypogonadotropic hypogonadism with or without anosmia	Member of the fibroblast growth factor receptor family. Signaling molecule that influences mitogenesis and differentiation.	12	0.99	RHD, obstructive uropathy	Hyposmia/anosmia, genital malformations, skeletal malformations, endocrine abnormalities	Autosomal dominant
*607830	*FRAS1*	Fraser syndrome (homozygous loss-of-function variants)	Extracellular matrix protein with function in the regulation of epidermal-basement membrane adhesion and organogenesis during development.	145 (0 hom)	0.00	RHD, VUR, duplication of the collecting system, posterior urethral valves(?)	Facial dysmorphisms, developmental delay, genital malformations	Autosomal Recessive (hypomorphic alleles)
*608944	*FREM1*	Bifid nose with or without anorectal and renal anomalies (Fraser-associated)	Basement membrane protein that plays a role in craniofacial and renal development.	89 (1 hom)	-	RHD, VUR, duplication of the collecting system, posterior urethral	Bifid nose, developmental delay, gastrointestinal malformations, genital	Autosomal Recessive (hypomorphic alleles)

						valves(?)	malformations	
*608945	*FREM2*	Fraser syndrome (homozygous loss-of-function variants)	Integral membrane protein localized to the basement membrane that plays a role in epidermal-dermal interactions.	63 (0 hom)	0.00	RHD, VUR, duplication of the collecting system, posterior urethral valves(?)	Facial dysmorphisms, developmental delay, genital malformations	Autosomal Recessive (hypomorphic alleles)
*605710	*GDNF*	Hirschsprung disease	Member of transforming growth factor-beta superfamily of proteins. Encodes a neurotrophic factor that promotes survival and differentiation and regulates apoptosis. Ligand for the product of *RET*.	8	0.70	Isolated RHD	Absent enteric ganglia, pheochromocytoma, central hypoventilation syndrome	Autosomal Dominant
*300037	*GPC3*	Simpson-Golabi-Behmel syndrome	Bind to and inhibit the dipeptidyl peptidase activity of CD26, inducing apoptosis in certain cell types.	0 (0 hemi)	0.99	Syndromic RHD, cysts, VUR	Facial dysmorphisms, developmental delay, cardiac malformations, genital malformations, skeletal abnormalities	X-linked Recessive
*613469	*HPSE2*	Urofacial syndrome	Endoglycosidase that degrades heparin sulfate proteoglycans on the	44 (0 hom)	0.00	Bladder dysfunction,	Abnormal facial expression upon	Autosomal Recessive

			extracellular matrix and cell surface. Involved in biological processes such as remodeling of the extracellular matrix and angiogenesis.			VUR	smiling and crying	
+601290	*JAG1*	Alagille syndrome	Human jagged 1 is the ligand for the receptor notch 1.	1	1.00	RHD, cysts	Facial dysmorphisms, cardiac malformations, cholestatic liver disease, skeletal abnormalities	Autosomal Dominant
*300836	*KAL1*	Hypogonadotropic hypogonadism with or without anosmia (Kallmann syndrome)	Similar in sequence to proteins that function in neural cell adhesion and axonal migration. May have anti-protease activity.	4 (2 hemi)	0.94	RHD, obstructive uropathy	Hyposmia/anosmia, genital malformations, skeletal malformations, endocrine abnormalities	X-linked Recessive
*608869	*LRIG2*	Urofacial syndrome	Transmembrane protein that promotes epidermal growth factor signaling and increased proliferation.	65 (0 hom)	0.00	Bladder dysfunction, VUR	Abnormal facial expression upon smiling and crying	Autosomal Recessive
*600275	*NOTCH2*	Alagille syndrome	Notch family members play a role in a variety of developmental processes by controlling cell fate decisions. Regulates interactions	7	1.00	RHD, cysts	Facial dysmorphisms, cardiac malformations, cholestatic liver	Autosomal Dominant

			between physically adjacent cells.				disease, skeletal abnormalities	
*603961	*SEMA3A*	Hypogonadotropic hypogonadism with or without anosmia	Secreted protein that stimulates the outgrowth of apical dendrites. Plays role in normal neuronal pattern development.	6	0.99	RHD, obstructive uropathy	Hyposmia/anosmia, genital malformations, skeletal malformations, endocrine abnormalities	Autosomal dominant
*191830	*RET*	Hirschsprung disease	Member of the cadherin superfamily, cell-surface tyrosine kinase receptor that is implicated in cell growth and differentiation.	2	1.00	Syndromic RHD	Absent enteric ganglia, multiple endocrine neoplasia, central hypoventilation syndrome	Autosomal Dominant
*602431	*ROBO2*	VUR	Transmembrane receptor for the slit homolog 2 protein that functions in axon guidance and cell migration.	6	1.00	Isolated VUR(?), RHD, obstructive uropathy	-	Autosomal Dominant
*603746	*SLIT2*	-	Encodes a secreted glycoprotein that is a ligand for the ROBO receptor family; potential role in cell migration.	8	1.00	Isolated RHD, cysts	-	Autosomal Dominant

*610132	*VANGL1*	Neural tube defects	Involved in mediating intestinal trefoil factor during wound healing in the intestinal mucosa.	6	0.53	Syndromic RHD, renal ectopia	Caudal regression syndrome	Autosomal Dominant
*603490	*WNT4*	Mullerian aplasia and hyperandrogenism	Signaling protein implicated in several developmental processes, including regulation of cell fate and patterning during embryogenesis.	10	0.15	Isolated RHD, renal ectopia	Genital malformations, endocrine abnormalities	Autosomal Dominant
Renin-angiotensin system								
+106180	*ACE*	Renal tubular dysgenesis	Enzyme involved in catalyzing the conversion of angiotensin I into angiotensin II.	127 (0 hom)	0.00	Renal tubular dysgenesis	Pulmonary hypoplasia, facial dysmorphisms	Autosomal Recessive
+106150	*AGT*	Renal tubular dysgenesis	Pre-angiotensinogen or angiotensinogen precursor, cleaved by renin in response to lowered blood pressure.	23 (0 hom)	0.00	Renal tubular dysgenesis	Pulmonary hypoplasia, facial dysmorphisms	Autosomal Recessive
*106165	*AGTR1*	Renal tubular dysgenesis	This gene encodes the angiotensin II type 1 receptor that mediates the major cardiovascular effects of	16 (0 hom)	0.01	Renal tubular dysgenesis	Pulmonary hypoplasia, facial dysmorphisms	Autosomal Recessive

			angiotensin II.					
*179820	*REN*	Renal tubular dysgenesis	Aspartyl protease that cleaves angiotensinogen to form angiotensin I.	27 (0 hom)	0.01	Renal tubular dysgenesis	Pulmonary hypoplasia, facial dysmorphisms	Autosomal Recessive
G-proteins								
*118494	*CHRM3*	Prune Belly syndrome	Muscarinic cholinergic receptors that binds acetylcholine leading to adenylate cyclase inhibition, phosphoinositide degeneration, and potassium channel mediation.	0	0.94	Bilateral megaureters, RHD	Abdominal wall abnormalities, bilateral cryptorchidism	Autosomal Recessive
*609850	*TBC1D1*	-	Member of TBC protein family presumed to have a role in regulating cell growth and differentiation.	54	0.00	RHD, obstructive uropathy, cysts, VUR	Insulin resistance	Autosomal Dominant
*606523	*SRGAP1*	-	GTPase activator, working with the GTPase CDC42 to negatively regulate neuronal migration. Interacts with ROBO1.	16	0.99	RHD, duplication of the collecting system, horseshoe kidney	Cleft palate, developmental delay(?)	Autosomal Dominant

Other/unknown								
*602858	*DHCR7*	Smith-Lemli-Opitz syndrome	Enzyme that alters the chemical structure of sterols and catalyzes the conversion of 7-dehydrocholesterol to cholesterol.	520 (0 hom)	0.00	Syndromic RHD, cysts, VUR	Low cholesterol, facial dysmorphisms, developmental delay, cardiac malformations, genital malformations, skeletal abnormalities	Autosomal Recessive
-pending	*GREB1L*	-	Role in hoxb1and shha signaling in zebrafish, co-factor in retinoid acid and steroid signaling.	-	-	RHD	-	Autosomal dominant

*602490	*NRIP1*	-	Nuclear protein that interacts with hormone-dependent activation of nuclear receptors.	2	0.99	RHD, VUR, ectopic kidney	-	Autosomal Dominant
*606219	*TRAP1*	-	Heat shock protein 90 family member and mitochondrial chaperone protein. The encoded protein has ATPase activity and interacts with tumor necrosis factor type I.	94 (0 hom)	0.00	Syndromic RHD, VUR	Vertebral anomalies, anorectal malformations, cardiovascular disease, tracheoesophageal fistula, esophageal atresia, renal anomalies and limb defects (VACTERL)	Autosomal Recessive

Supplemental Table 1. Monogenic forms of CAKUT with depleted loss of function variants in population controls.

Overview of single-gene causes of isolated and syndromic forms of CAKUT. The presented genes have a loss-of-function variant frequency of <1:1,000 in the Exome Aggregation Consortium database(150) (URL: http://exac.broadinstitute.org) for autosomal dominant traits, or, in case of autosomal recessive/X-linked CAKUT, homozygous loss of function variants are depleted. The pLI-score is a probability score that a gene is intolerant to a loss of function mutation (i.e. higher score is less tolerant). Biomolecular pathway description is based on the NCBI gene repository (https://www.ncbi.nlm.nih.gov/gene). Gene number, syndrome names and phenotypic findings were extracted from the Online Mendelian Inheritance in Man (OMIM) database (https://www.omim.org). (?) = evidence inconclusive; CHARGE = coloboma of the eye, heart defects, atresia of the nasal choanae, retardation of growth and/or development, genital and/or urinary abnormalities, and ear abnormalities and deafness; ExAC = Exome Aggregation Consortium; pLI = probability of being loss-of-function in tolerant; RHD = renal hypodysplasia; VUR = vesicoureteral reflux