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Single-Gene Causes of Congenital Anomalies of the Kidney and Urinary Tract (CAKUT) in Humans

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Abstract

Congenital anomalies of the kidney and urinary tract (CAKUT) cover a wide range of structural malformations that result from defects in the morphogenesis of the kidney and/or urinary tract. These anomalies account for about 40–50% of children with chronic kidney disease worldwide. Knowledge from genetically modified mouse models suggests that single gene mutations in renal developmental genes may lead to CAKUT in humans. However, until recently only a handful of CAKUT-causing genes were reported, most of them in familial syndromic cases. Recent findings suggest that CAKUT may arise from mutations in a multitude of different single gene causes. We focus here on single gene causes of CAKUT and their developmental origin. Currently more than 20 monogenic CAKUT-causing genes have been identified. High-throughput sequencing techniques make it likely that additional CAKUT-causing genes will be identified in the near future.

Keywords

Congenital Anomalies of the Kidney and Urinary Tract; CAKUT; genetic kidney disease; monogenic disease

Introduction

Congenital anomalies of the kidney and urinary tract (CAKUT) comprise a wide range of structural malformations that result from defects in the morphogenesis of the kidney and/or the urinary tract. These anomalies include among others: renal agenesis, renal hypodysplasia, multicystic dysplastic kidney, hydronephrosis, ureteropelvic junction obstruction, megaureter, ureter duplex, vesicoureteral reflux and posterior urethral valves [1]. CAKUT account for about 40–50% of children with chronic kidney disease [2]. The condition may appear as an isolated feature or as part of a systemic condition that

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encompasses extra-renal manifestations [3–5]. The notion that CAKUT may be caused by single gene mutations ("monogenic CAKUT") is suggested by three findings: (1) CAKUT may appear with familial aggregation [6]; (2) monogenic mouse models exhibit CAKUT phenotypes; (3) human multi-organ monogenic syndromes may include CAKUT phenotypes. Recently this notion was corroborated by the discovery of more than 20 single-gene causes for CAKUT in humans [7–11]. Until then only a handful of CAKUT-causing genes had been documented, most of which were identified among familial syndromic cases, including *HNF1B* (Renal Cysts and Diabetes Syndrome) [4], *PAX2* (Renal Coloboma Syndrome) [3], and *EYA1* (branchio-oto-renal syndrome) [5]. Recent findings suggest that CAKUT may be caused by a multitude of different disease-causing genes (Table 1), each gene representing a monogenic recessive or dominant cause of CAKUT [3–5, 12–36]. Given this broad genetic locus heterogeneity and the rapidly evolving sequencing technology, it is likely that many novel genes will be identified in the near future.

We focus here on single-gene causes of CAKUT and their developmental mechanisms. We mainly discus disease-causing genes related to isolated CAKUT or syndromic forms of CAKUT in which the renal phenotype predominates. Single-gene causes of human congenital urinary bladder diseases are beyond the scope of this review and have been recently reviewed [37].

CAKUT are due to disordered genetic control of kidney development

The pathology of CAKUT is based on the disturbance of normal nephrogenesis, and can be due to genetic abnormalities in renal developmental genes that direct this process [1, 38–41]. In order to understand the genetic basis of human CAKUT it is essential to consider how the normal kidney develops (Figure 1). Kidney development can be divided into the following developmental stages: ureteric bud induction, mesenchymal-to-epithelial transition (MET), renal branching morphogenesis, and nephron patterning and elongation (which include proximal and distal tubule morphogenesis and glomerulogenesis) [1, 38–41]. The underlying molecular control of these developmental stages is governed by a large number of genes and signaling pathways that orchestrate this complex process. Perturbation in each of these steps, as supported by mouse models, can lead to the clinical phenotype of CAKUT. Insights into the related molecular control mechanisms has led to a paradigm shift away from classic anatomic theories to contemporary cell biological and genetic views of the etiology of CAKUT [42].

For many years mouse models have been a key tool in our understanding of the molecular basis of kidney development with numerous mouse models re-capitulating human disease phenotypes. For instance, in mice the following monogenic causes of CAKUT have been described for the following process: (1) *Ret* and *Gdnf* for ureteric bud induction [43] (2) *Wnt4* for mesenchymal-to-epithelial transition (MET) [44] and (3) *Agtr2* (*Angiotensin receptor 2)* for branching morphogenesis [45]. Figure 1 outlines key steps during normal kidney development and their corresponding CAKUT-causing genes in mice and humans.

Classical studies [46] have also highlighted the importance of the position of the ureteric budding in the development of CAKUT and lead to the "budding hypothesis". According to

this hypothesis the precise position at which the ureteric bud grows out from the mesonephric duct is critical for subsequent normal kidney and urinary tract development. This hypothesis was generated following the anatomical analysis of duplex kidneys which showed that a more severe hypoplasia and dysplasia were closely correlated with mal-displacement of the ureteral orifice. This hypothesis, in part, is supported by the fact that many “early development” genes, involved in the ureteric budding stage, actually lead to CAKUT. In the following sections we will discuss the most important single gene causes of CAKUT in humans in relation to their corresponding function during kidney development.

Human CAKUT-causing genes involved in ureteric bud induction

The products of most genes that if mutated cause CAKUT in humans are involved in the control of the early morphogenesis stages of the kidney i.e. induction of the metanephric mesenchyme by the ureteric bud and mesenchymal-to-epithelial transition. Ureteric budding is promoted by GDNF signaling via its receptor RET. In humans, mutations in *RET* were initially recognized to cause multiple endocrine neoplasia (MEN) syndrome [47] and Hirschsprung disease [48]. *RET* mutations were subsequently reported to cause CAKUT in fetuses with bilateral renal hypodysplasia/agenesis [18, 49]. In addition the role of RET as CAKUT causing gene is suggested by the finding that many patients with Hirschprung disease have silent urinary tract defects [50]. Still, data regarding the frequency of *RET* as a CAKUT-causing gene are conflicting [18, 49]. Mutation analysis of *GDNF* has been performed in patients with CAKUT. However, no evidence supporting its causative role has been established so far [30, 51]. The GDNF-RET signaling pathway is regulated by multiple circuits. Given the central role of the GDNF-RET signaling pathway in ureteric budding it was likely that mutations in genes that regulate this pathway may result in CAKUT. Indeed, these regulatory mechanisms include transcription factors such as *PAX2*, *EYA1*, and *SALL1*, all of which have been initially recognized to be mutated in small pedigrees with multiple affected individuals with CAKUT and syndrome-specific extra-renal manifestations. Mutations in *PAX2* were first identified in patients with Renal Coloboma Syndrome which comprises renal hypodysplasia, optic nerve abnormalities and deafness [3]. To date, more than 55 disease causing mutations of *PAX2* have been reported worldwide [17]. Importantly, *PAX2* mutations were shown to also lead to isolated CAKUT without optic nerve or hearing abnormalities or with subtle features. In addition, *PAX2*-mutations were shown to lead to variable renal phenotypes across the spectrum of CAKUT, including renal hypodysplasia, vesicoureteral reflux renal cysts and multcystic dysplastic kidneys as the most common ones [17]. Mutations in *EYA1* lead to Branchio-Oto-Renal (BOR) syndrome which is characterized by hearing loss, structural defects of the ear, branchial fistula or cyst and CAKUT, ranging from mild renal hypoplasia to agenesis [5]. Interestingly, mutations in *SIX1* and *SIX5* have also been identified in patients with EYA1-negative BOR syndrome, and probably represent a more rare underlying etiology [22, 23]. Mutations in *SALL1* lead to Townes-Brocks Syndrome (TBS), which is characterized by kidney, anal, ear and thumb abnormalities [21]. An isolated CAKUT phenotype was reported in one patient with a *SALL1* mutation [52]. Unpublished data from our lab further support an isolated CAKUT phenotype.

BMP4 is expressed in the mesenchymal cells that surround the Wolffian duct and inhibits GDNF-RET-signaling [38]. Missense mutations in *BMP4* were identified in five CAKUT patients [12]. Subsequent functional analysis, using overexpression assays in zebrafish suggested that these mutations affect BMP4 protein function [53].

Human CAKUT-causing genes involved in mesenchymal-to-epithelial transition

Once the ureteric bud invades the metanephrogenic mesenchyme it induces condensation of the metanephrogenic mesenchymal cells around the ureteric bud tips. This step begins the polarization of the mesenchyme to generate the epithelial cells of the nephron in a process named mesenchymal-to-epithelial transition (MET) [38, 39]. WNT proteins, i.e. WNT9b and WNT4 that act within the WNT signaling pathway play a critical role in this process [38, 39]. Furthermore, recent evidence generated from mouse models supports that the WNT-pathway partially is regulated by SIX2 [54]. Interestingly, mutations in *WNT4* or *SIX2* have been identified in pediatric patients with CAKUT [12, 30]. Other important key players in MET are the fibroblast growth factor (FGF) ligands Fgf8 and Fgf9 (Figure 1) [38, 39]. In addition, in a recent report, on three affected fetuses with bilateral renal agenesis from a consanguineous family, an autosomal recessive loss of function mutation gene was identified in the *FGF20* [36].

Human CAKUT-causing genes involved in branching morphogenesis

Renal branching morphogenesis follows the primary ureteric bud outgrowth. The ureteric bud subsequently undergoes serial branching to generate approximately 15 generations of branches. During this time new nephrons are induced at the tip of each branching bud (Figure 1). Several factors have been shown to modulate the UB branching morphogenesis [39]. One of the factors that govern this process is Angiotensin 2. Angiotensin 2 activates both the angiotensin receptor type 1 and 2 on the ureteric bud to stimulate branching. In addition it is required for elongation of the collecting duct [39]. Accordingly, mutations in the genes encoding several components of the renin–angiotensin system: *AGT* (angiotensinogen), *REN* (renin), *ACE* (angiotensin-converting enzyme), and *AGTR1* (angiotensin II receptor type 1) have been linked to the distinct severe phenotype of CAKUT in humans of renal tubular dysgenesis [34] (Table 1). This rare fetal autosomal recessive disorder is characterized by early onset of persistent anuria leading to oligohydramnios and the Potter sequence, secondary to the absence or incomplete differentiation of the proximal tubules. Inactivation of different components of the RAS has been performed in mice. While *Agtr2* [45] and *Agt* [55] null mice have CAKUT, this phenotype was not recapitulated in *Ace* and *Ren* null mice. These findings illustrate the possible discrepancies between mouse models and human diseases whereas the former exhibit an earlier developmental insult (branching morphogenesis) as compared to the later insult (developmental abnormality of the proximal tubules due to impaired tubular growth and differentiation).

Human CAKUT-causing genes involved in nephron patterning and elongation

Whereas a large amount of research has focused on the initial stages of kidney formation, much less is known about the genetic programs that drive segmentation of the nephron [41]. Indeed, the only possible human CAKUT-causing gene that can be designated under this category is *UMOD*. The *Uromodulin* (*UMOD*) gene encodes the Tamm-Horsfall protein, which is the most abundant urinary protein in humans [56]. *UMOD* mutations cause a large variety of different kidney syndromes: (1) medullary cystic kidney disease type 2 (MCKD2), (2) familial juvenile hyperuricemic nephropathy (FJHN), and (3) glomerulocystic kidney disease (GCKD) [33]. All of these disorders are inherited in an autosomal dominant mode and may have a CAKUT phenotype. Nevertheless, in a previous study published by our group, no *UMOD* mutations were identified among 96 patients with isolated CAKUT, implying that it may represent a very rare etiology for this condition [57].

Human CAKUT-causing genes yet-unassigned to a specific developmental stage

The developmental role of some human CAKUT-causing genes is still poorly understood. In this respect we will discuss two important genes, *HNF1B* and *DSTYK*. Hepatocyte nuclear factor 1B (HNF1B) is a homeodomain-containing transcription factor. HNF1B is essential factor for embryogenesis of the kidney, pancreas, and liver, and is expressed in the Wolffian duct from a very early developmental stage of the kidney [58]. Mutations in *HNF1B have* originally been recognized as the cause of the Renal Cysts and Diabetes Syndrome (RCDS) [4]. Subsequently, *HNF1B*-mutations and deletions were reported among individuals with isolated CAKUT encompassing different renal malformations across its spectrum, such as renal hypodysplasia, multicystic dysplastic kidney, cystic kidney disease, single kidney, and oligomeganephronia [52, 59]. *HNF1B* mutations have also been recognized to result in genital tract abnormalities, elevated liver function tests, hyperuricemia [60] and hypomagnesaemia [61]. Interestingly, several recent publications showed that contiguous gene deletion in the 17q12 region (which includes the *HNF1B* transcription factor) has resulted in the clinical combination of autism/schizophrenia and CAKUT [62, 63].

With regard to pathomechanism, a link was identified between *HNF1B* mutations and autosomal recessive polycystic kidney disease (ARPKD), which is caused by mutations in *PKHD1* (polycystic kidney and hepatic disease 1). In mice, it has been shown that Hnf1b binds specifically to the *Pkhd1* promoter and stimulates gene transcription. Since Hnf1b directly regulates the transcription of *Pkhd1*, mutations in *HNF1B* can inhibit *PKHD1* gene expression and therefore may contribute to the formation of renal cysts in humans with RCDS [64].

Currently, *HNF1B* and *PAX2* are considered to be the most frequent CAKUT-causing genes. Still, they are responsible for not more than 5–15% of cases depending on the examined cohort [52, 65, 66].

In a recent study involving 7 affected family members with CAKUT, disease causing mutations were detected in the gene *DSTYK* [32]. Additional *DSTYK* mutations were detected in 7 out of 311 (2.3%) unrelated patients with CAKUT. The study demonstrated that DSTYK is a positive regulator of ERK phosphorylation downstream of FGF-receptor activation during kidney development [32].

Finally, another aspect of CAKUT that should be taken into consideration with regard to gene discovery is copy number variations (CNVs). Several lines of evidence support their role in CAKUT [67]. This concept has been highlighted recently in a study involving 522 patients with CAKUT in which 72 distinct known or novel copy-number variations in 87 (16.6%) patients were identified, suggesting that kidney malformations can, in part, result from pathogenic genomic imbalances [68].

Conclusions and future directions

CAKUT are a genetically heterogeneous group of disorders that are caused by mutations in genes involved in the embryogenesis of the kidneys. The malformation phenotypes due to the altered proteins vary from normally appearing kidneys with intact kidney function (i.e., incomplete penetrance) to severe hypodysplasia and end stage kidney disease. In clinical practice the evaluation of patients with CAKUT, in addition to standard care, should include: (1) meticulous evaluation for extra-renal syndrome-specific signs and symptoms (see Table 1); (2) thorough family evaluation for the presence of CAKUT in other family members; (3) referral to genetic counseling. Currently, the most common CAKUT-causing genes are *HNF1B* and *PAX2*. Other cases, which often present sporadically, are probably a result of many rare diseases causing genes.

Novel gene discovery for CAKUT is hampered by a high degree of sporadic cases, genetic heterogeneity, lack of genotype-phenotype correlation and phenotypic heterogeneity. For example single gene causes of primary VUR are still elusive despite the fact that multiple disease loci were published [69]. Although primary VUR is one of the most commonly detected CAKUT presentations, its phenotypic case ascertainment is challenging. The fact that improved prenatal ultrasound examinations have resulted in the recognition that often VUR is accompanied by concomitant other congenital kidney and urinary tract abnormalities can provide one explanation for that. However, the advent and progress in sequencing and bioinformatics technologies should ensure that additional CAKUT-causing genes will be described in the near future. This may lead to more relevant etiologic categorization of disease entities than can be provided by ultrasound imaging or histopathology alone. Such assignments may have prognostic implications for patients with CAKUT.

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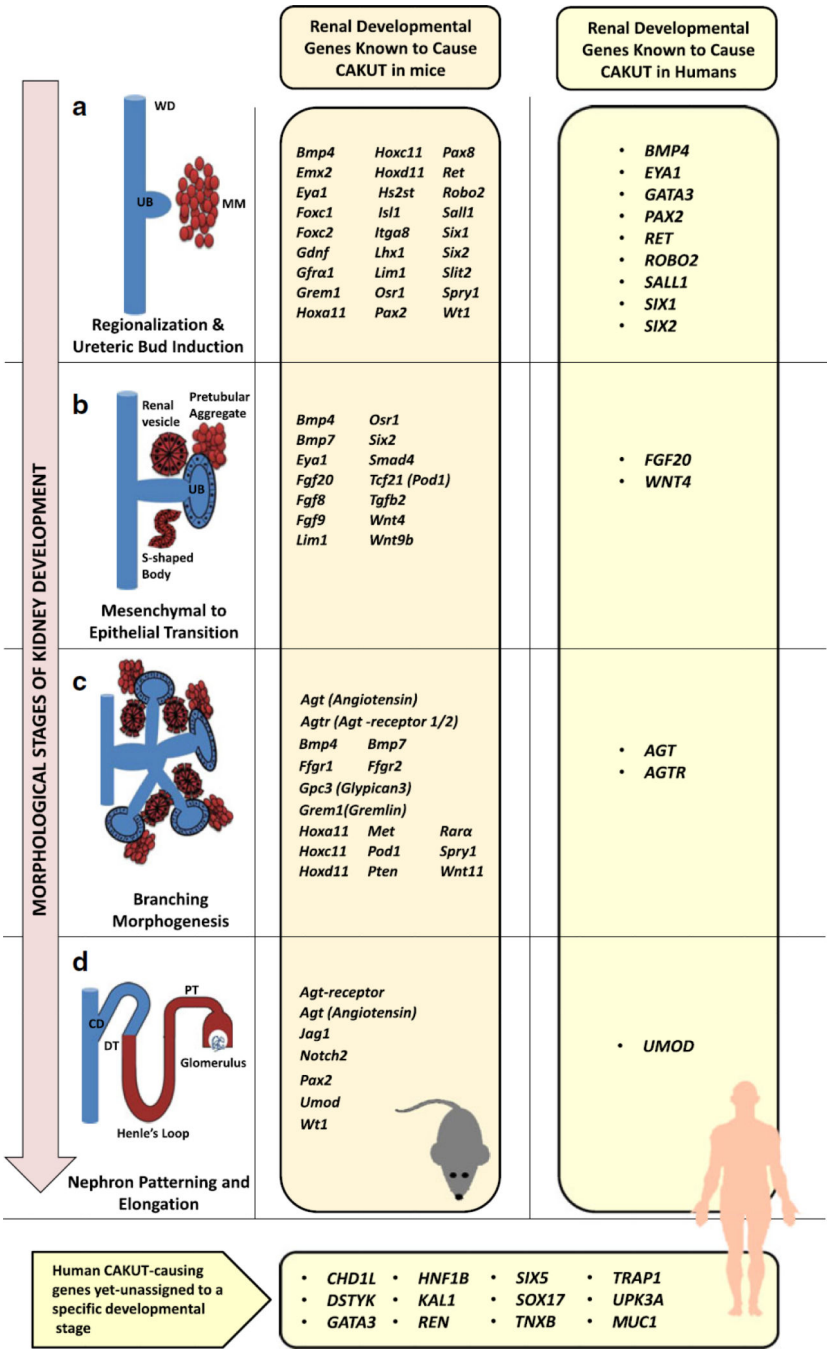

Figure 1. Mechanisms of kidney development and corresponding CAKUT-causing genes in mice and humans

Steps of nephrogenesis (*left column*, a to d) and the corresponding CAKUT-causing genes in mice (*orange column*) and human (*right yellow column*). The kidney is formed via reciprocal induction between the ureteric bud (UB) and the metanephric mesenchyme (MM) (**a**). The UB invades the MM cells, which in turn condense around the tip of the branching UB (pre-tubular aggregate). Polarized renal vesicles subsequently develop in mesenchyme-to-epithelial transition (MET) (**b**). The cells sequentially form comma-shaped and S-shaped

bodies and finally give rise to the mature nephron segments (distal and proximal tubule, loop of Henle, and glomerulus) (**d**). At the same time, the uretric bud branches in a highly reproducible manner and nephrons are induced at each ureteric bud tip (**c**). These branches eventually form the collecting system, including collecting ducts, renal pelvis, ureter and bladder trigone.

WD Wolffian duct; *UB* ureteric bud; *MM* matanephrogenic mesenchyme; *CD* collecting duct; *DT* distal tubule; *PT* proximal tubule.

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Table 1

Single gene causes of human isolated CAKUT and syndromes with a predominant CAKUT phenotype

Gene Symbol	Renal Phenotype	Extra-Renal Phenotype	Human Disease [OMIM#]	Mouse Model Het / Hom[d]		Ref
A. DOMINANT CAKUT						
BMP4	Renal hypodysplasia	Cleft lip, microophthalmia	Microphthalmia, syndromic 6 [*607932] Orofacial cleft 11 [*600625]	CAKUT	EL	[12]
EYA1	Multicystic dysplastic kidney, renal aplasia	Deafness, ear malformations, branchial cysts	Anterior segment anomalies with or without cataract 113650 Branchiootic syndrome 1 [*602588] Branchiootorenal syndrome 1, with or without cataracts [*113650] Otofaciocervical syndrome [*166780]	CAKUT	CAKUT	[5]
GATA3	Renal dysplasia	Hypoparathyroidism, heart defects, immune deficiency, deafness	Hypoparathyroidism, sensorineural deafness, and renal dysplasia [*146255]	None	EL	[13, 14]
HNF1B	Renal hypodysplasia, single kidney, horseshoe kidney	Diabetes mellitus (MODY5) Hyperuricemia, Hypomagnesaemia, elevated LFT	Diabetes mellitus, noninsulin-dependent [*125853] Renal cysts and diabetes syndrome [*137920]	None	EL	[4]
KAL1[a]	Renal agenesis	Micropenis, bilateral cryptorchidism, anosmia	Hypogonadotropic hypogonadism 1 with or without anosmia (Kallmann syndrome 1) [*308700]	N/A		[16]
PAX2	Vesicoureteral reflux, renal hypoplasia	Optic nerve colobomas, hearing loss	Papillorenal syndrome [*120330] Renal hypoplasia, isolated [*191830]	CAKUT	CAKUT	[3, 17]
RET	Renal agenesis	See OMIM# in the next column	Central hypoventilation syndrome, congenital [*209880] Medullary thyroid carcinoma [*155240] Multiple endocrine neoplasia IIA [*171400] Multiple endocrine neoplasia IIB [*162300] Pheochromocytoma [*171300] Renal agenesis [*191830]	None	PL, CAKUT	[18, 19]
ROBO2	VUR, ureterovesical junction defects	None	Vesicoureteral reflux 2 [*610878]	None	PL, CAKUT	[20]
SALL1	Renal hypodysplasia, renal agenesis	Limb, ear, anal abnormalities	Townes-Brocks syndrome [*107480]	CAKUT	CAKUT	[21]
SIX1	Renal hypodysplasia, VUR	Deafness, ear defects, branchial cysts	Brachiootic syndrome 3 [*608389] Deafness, autosomal dominant 23 [*605192]	None	CAKUT	[70]
SIX2	Renal hypodysplasia	None	-	None	PL, CAKUT	[12, 27]
SIX5	Renal hypodysplasia, VUR	Deafness, ear defects, branchial cysts	Branchiootorenal syndrome 2 [*610896]	None	None	[23]
SOX17	VUR, UPJO	None	Vesicoureteral reflux 3 [*613674]	None	EL	[24]
TNXB	VUR	Joint hypermobility	Ehlers-Danlos syndrome, autosomal dominant, hypermobility type [*130020] Ehlers-Danlos syndrome, autosomal recessive, due to tenascin × deficiency [*606408]	None	None	[25]

Gene Symbol	Renal Phenotype	Extra-Renal Phenotype	Human Disease [OMIM#]	Mouse Model Het / Hom[d]		Ref
UPK3A	Renal adysplasia	Subtle facial and limb defects	Renal adysplasia [*191830]	None	CAKUT	[26]
WNT4[2]	Renal hypodysplasia	Female-to-male sex reversal, adrenal dysplasia, lung dysplasia (SERKAL)	Mullerian aplasia and hyperandrogenism [*158330] SERKAL syndrome [*611812]	None	PL, CAKUT	[28–30]
CHD1L	Renal hypodysplasia, VUR, UPJO	None	-	N/A		[31]
DSTYK	Renal hypodysplasia, UPJO	Epilepsy in 2 out of 7 affected	-	N/A		[32]
MUC1	Medullary cystic kidney disease type 1	-	MCKD1– Medullary cystic kidney disease type1 [#174000]	N/A		[74]
UMOD	Medullary cystic kidney disease type 2	Hyperuricemia	MCKD2– Medullary cystic kidney disease type2 [#603860] HNFJ2 -Hyperuricemic nephropathy, familial juvenile 2 [#6130925],[#613092]	none	CAKUT[c]	[33]
B. RECESSIVE CAKUT						
ACE	Absence or incomplete differentiation of proximal tubules	Pulmonary hypoplasia (Potter sequence), skull abnormalities	Renal tubular dysgenesis (RTD) [*267430]	None	CAKUT?	[34, 35,71]
AGT	Similar to *ACE*	Similar to *ACE*	Renal tubular dysgenesis (RTD) [*267430]	None	CAKUT	[34, 35]
AGTR1	Similar to *ACE*	Similar to *ACE*	Renal tubular dysgenesis (RTD) [*267430]	None	CAKUT	[34, 35]
REN	Similar to *ACE*	Similar to *ACE*	Renal tubular dysgenesis [*267430]	None	PL, CAKUT?	[34, 35]
FGF20	Bilateral renal agenesis	None	-	None	CAKUT	[36]
TRAP1	VUR, renal agenesis	VACTERL association	-	N/A		[72]
FRAS1	Renal agenesis	Cryptophthalmos, nose ear and larynx malformations. Mental retardation and syndactyly manifest occasionally.	Fraser Syndrome [*219000]	None	CAKUT	[73][e]
FREM2	Renal agenesis	Cryptophthalmos, nose ear and larynx malformations. Mental retardation and syndactyly manifest occasionally.	Fraser Syndrome [*219000]	None	CAKUT	[74][e]

[a] X-linked recessive

[b] Mode of inheritance can be autosomal dominant or autosomal recessive

[c] Mice lacking uromodulin did not show any clinical or histological feature of MCKD, however transgenic mice that express the C147W mutant *uromodulin*, corresponding to reported human mutation

C148W, recapitulate most of the uromodulin-associated kidney diseases. *ACE* angiotensin-converting enzyme; *AD* autosomal dominant; *AR* autosomal recessive; *EL* embryonic lethal; *Het* Heterozygous; *Hom* Homozygous; *LFT* liver function tests; *MCDK* multicystic dysplastic kidney; *MODY 5* maturity onset diabetes of the young type 5; *MOI* mode of inheritance; *N/A* not available; *OMIM* online Mendelian inheritance inman; *PL* postnatal lethal; *Ref* Reference; *SERKAL* sex reversal, kidneys, adrenals, and lungs dysgenesis; *UPJO* ureteropelvic junction obstruction; *VACTERL* vertebra, anal, cardiac, trachea-esophageal, renal and limb anomalies; *VUR* vesicoureteral reflux

[d] The mouse model column in the table refers to the mouse model of each corresponding gene irrespective of whether it has CAKUT phenotype

[e] Hypomorphic recessive mutations have also been shown to cause isolated CAKUT (Kohl, unpublished)