REVIEW

A Primer on Congenital Anomalies of the Kidneys and Urinary Tracts (CAKUT)

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Abstract

Congenital anomalies of the kidneys and urinary tracts (CAKUT) are disorders caused by defects in the development of the kidneys and their outflow tracts. The formation of the kidneys begins at week 3 and nephrogenesis continues until week 36, therefore, the kidneys and outflow tracts are susceptible to environmental risk factors that perturb development throughout gestation. Many genes have been implicated in kidney and outflow tract development, and mutations have been identified in patients with CAKUT. In severe cases of CAKUT, when the kidneys do not form, the fetus will not survive. However, in less severe cases, the baby can survive with combined kidney and outflow tract defects or they may only be identified in adulthood. In this review, we will cover the clinical presentation of CAKUT, its epidemiology, and its long-term outcomes. We will then discuss risk factors for CAKUT, including genetic and environmental contributions. Although severe CAKUT is rare, low nephron number is a much more common disorder with its effect on kidney function increasingly apparent as a person ages. Low nephron number appears to arise by the same mechanisms as CAKUT, but it differs in terms of the magnitude of the insult and the timing of when it occurs during gestation. By understanding the causes of CAKUT and low nephron number, we can begin to identify preventive treatments and establish clinical guidelines for how these patients should be followed.

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Introduction and Epidemiology of Congenital Anomalies of the Kidneys and Urinary Tracts

Congenital anomalies of the kidneys and urinary tracts (CAKUT) are embryonic disorders that arise during development and result in a spectrum of defects in the kidneys and outflow tracts which include the ureters, the bladder, and the urethra. The prevalence is estimated at 4–60 per 10,000 births, depending on the registry, with variation due to differences in sample size, method of diagnosis, and ethnic differences between studies (1). In 2018, there were approximately 4 million live births in the United States, suggesting that 400–6000 infants were born with some form of CAKUT. These children are surviving due to improvements in the management of CKD, corrective urologic surgery, dialysis, and transplantation. For children with severe CAKUT that require dialysis and transplantation as infants, there are significant comorbidities that have an effect on the ability of these children to lead independent lives as adults. Individuals with mild forms of CAKUT, such as reduced nephron endowment at birth, are likely much more common than appreciated and may only be identified in adulthood. However, thus far, there has been no way to identify them in a systematic way due to the absence of noninvasive methods to assess nephron number.

Clinical Presentation and Diagnosis of Congenital Anomalies of the Kidneys and Urinary Tracts

Developmental abnormalities of the kidneys and urinary tracts were originally described by Dr. E. Potter who examined necropsies from fetuses and babies to understand normal and abnormal development (Figure 1) (2). Congenital kidney malformations are defined macroscopically by changes in kidney size, shape, position, or number, or microscopically by a reduced number of nephrons and/or abnormal histology (Table 1). The spatial and temporal events that give rise to CAKUT are critical for the phenotypes that arise. An absent or malformed kidney is a severe defect occurring early in gestation (Figure 1), whereas defects that occur later are generally less severe. Later defects include obstruction, vesicoureteric reflux (VUR), or posterior urethral valves, in which kidneys form but the outflow tract is abnormal.

Most cases of CAKUT are diagnosed from antenatal ultrasound imaging, which examines the kidneys, the outflow tracts, and—most importantly—the amniotic fluid volume. After the 18th week of gestation, amniotic fluid is primarily composed of urine produced by the fetal kidneys (3). Antenatal ultrasounds correctly diagnose CAKUT in 60%–85% of infants, especially if imaging is performed in the third trimester (4–6). The remaining cases of CAKUT are mostly diagnosed after an infant or child presents with a urinary tract infection prompting ultrasound and/or other imaging studies to examine the kidneys and outflow tracts. Individuals born with one or two kidneys, but low nephron number, may not exhibit any signs or symptoms until adolescence or adulthood when early onset hypertension and/or CKD may be diagnosed.

Malformed kidneys that are small by length measurements on ultrasound are classified as hypoplastic

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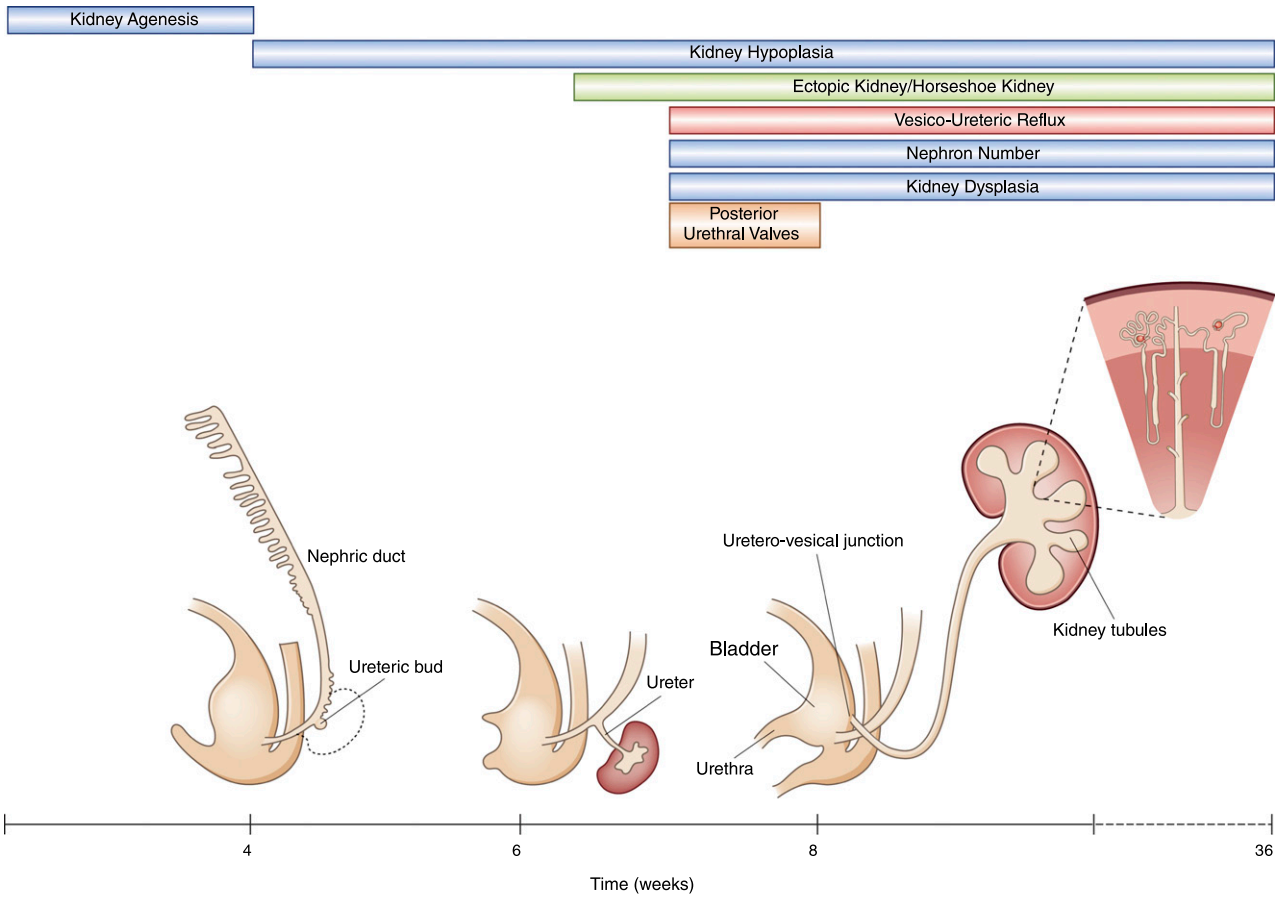

Figure 1. | CAKUT defects can occur throughout fetal development, with more severe defects emerging earlier in development. Major developmental events in the formation of the kidneys and urinary tract including ureteric bud formation, ureter extension and kidney formation, bladder formation, kidney tubule branching and nephrogenesis (shown as an inset at 8 weeks), and ureterovesical junction formation. CAKUT defects are shown within the time window in which they are most likely to occur. Our timeline is based on findings from Potter (58) and Vize *et al.* (59).

kidneys; whereas those that are small, hyperechoic, and with/without cysts are described as dysplastic kidneys. Although renal hypoplasia/dysplasia refers to the histologic appearance of the kidney, this type of CAKUT is rarely diagnosed by kidney biopsy partly because the small kidney size and/or the coexistence of a dilated ureter may increase complications from the biopsy. In summary, ultrasound and other imaging studies including voiding cystourethrograms and nuclear medicine scans are the predominant investigations used to identify the location and morphology of the kidneys and to determine if there are dilated or obstructed outflow tracts (Figure 2). Once CAKUT is identified by imaging, this prompts an assessment of kidney function with a serum creatinine test to reveal the magnitude of the nephron deficit, which can be due to abnormal development combined with kidney infection, and/or increased intrarenal pressure from outflow tract obstruction.

Long-Term Outcomes

The long-term outcome of CAKUT suggests that affected children are more likely to need RRT during adulthood than childhood. This was demonstrated in a study of 212,930 patients followed over a 20-year period, in which approximately 2% of the entire cohort had CAKUT (7). The authors demonstrated that, up until the age of 45 years, most individuals who needed RRT had a diagnosis of CAKUT. This was also revealed by the median age for commencement of RRT, which was 31 years in the CAKUT cohort versus 61 years in the non-CAKUT cohort. Another study suggested that 25% of children born with bilateral CAKUT will develop ESKD during the first two decades of life (8). Syndromic forms of CAKUT due to mutations that affect other organs along with the kidneys and outflow tracts may result in comorbidities. For example, mutations in the transcription factor *HNF1β* may cause both CAKUT and diabetes, resulting in two conditions that cause a decrease in nephron number: one from an impairment in nephrogenesis and the other from diabetic injury resulting in nephron loss.

Although there is some information on the long-term outcome of severe CAKUT, little is known about milder forms that manifest as a deficit in nephron number at birth. Because low birth weight and prematurity are both associated with low nephron number, they have been used as

Table 1. Categories of CAKUT disorders

Type of Anomaly	CAKUT Disorder	Definition
Kidney number	Renal agenesis	Unilateral or bilateral, kidney and outflow system fail to form
Kidney size and morphology	Renal hypoplasia	Unilateral or bilateral, kidney shape is normal, but smaller in size and reduced number of nephrons
	Renal dysplasia	Unilateral or bilateral, kidney shape and tissue differentiation is abnormal, reduced number of nephrons
	Multicystic dysplastic kidney	Multiple cysts within a dysplastic kidney giving it an abnormal shape
Kidney position	Horseshoe kidney	Kidneys are fused posteriorly forming a horseshoe shape
	Ectopic/pelvic kidney	Kidney in an abnormal location, typically pelvic
Outflow abnormalities	Ureteropelvic junction obstruction	Unilateral or bilateral, junction between kidney and ureter is obstructed, preventing drainage of urine from pelvis of the kidney
	Vesicoureteric reflux	Unilateral or bilateral, junction between ureter and bladder is defective, resulting in urine backflow from bladder
	Duplex collecting system	Unilateral or bilateral, duplication of ureter and kidney pelvis, can be accompanied with duplicated kidneys; outflow system may reflux or exhibit obstruction
	Megaureter	Unilateral or bilateral, distension of ureter resulting in defects in impaired urine flow
	Posterior urethral valves	Membrane that forms in urethra preventing emptying of bladder, limited to males

Definitions have been adapted from Potter's *Normal and Abnormal Development of the Kidney* (58). CAKUT, congenital anomalies of the kidneys and urinary tracts.

surrogates of nephron number. The Helsinki study (9) followed approximately 20,000 people born between 1924 and 1944 until death or age 86 years and established that low birth weight was a risk factor for CKD in males, whereas prematurity (birth before 34 weeks of gestation) was a risk factor for CKD in females. In another study from Sweden, Crump *et al.* (10) demonstrated that preterm birth, defined as <37 weeks, and extreme preterm birth, defined as <28 weeks, were strongly associated with an increased risk of CKD in childhood and up to midadulthood, which was the oldest age group examined. Keller *et al.* (11) demonstrated that low nephron number is a risk factor for hypertension in middle-aged adults compared with age-, sex-, and race-matched controls without hypertension. Although this study did not clarify the etiology of the low nephron number, the authors proposed a mechanism by which low nephron number at birth could be a risk factor for adult-onset hypertension (11). Another example of CAKUT manifesting as low nephron number is suggested by the association of mutations in *PAX2*, a transcription factor critical for kidney development, and adult-onset FSGS. Barua *et al.* (12) described families diagnosed with FSGS anywhere from 7 to 68 years of age due to dominantly inherited mutations in *PAX2*. One patient had a kidney biopsy sample that exhibited glomerulomegaly, which can occur secondary to low nephron endowment at birth. Some of the affected individuals had imaging studies that revealed other CAKUT phenotypes including small kidneys and hydronephrosis (12).

Genetic Risk Factors for Congenital Anomalies of the Kidneys and Urinary Tracts

Although there is strong evidence for a monogenic origin of CAKUT (13), genetic mutations account for, at most, 20% of cases. Several studies have looked at familial cases of CAKUT using linkage analysis. After identifying a linked genomic locus, genes within the locus are sequenced, leading to the discovery of "candidate" genes associated with CAKUT (14). Although hundreds of candidate genes have been identified from animal models, familial linkage analysis, and candidate gene sequencing, mutations in *PAX2* and *HNF1β*—which encode transcription factors—are most commonly associated with dominantly inherited CAKUT and account for 5%–15% of cases in some studies (14). There is a wide spectrum of disorders associated with *PAX2* and *HNF1β* mutations (15–17). However, in an analysis of 208 candidate genes in patients with CAKUT, only three of 453 patients harbored *PAX2* mutations and only one patient had a mutation in *HNF1β* (18). This highlights the ongoing need for identification of new candidate genes. Other genes include *SIX1* (19), *SIX5* (20), *SALL1* (21), *EYA1* (22), *GATA3* (23), *FRAS1*, and *FREM2* (24) (Table 2). Many of the genes are associated with syndromes that include extrarenal defects in addition to CAKUT.

The genetic characterization of CAKUT has been challenging for a number of reasons. Many of the mutations identified are unique to a single patient and their affected family members and cannot be replicated in other cohorts. Sporadic severe cases of CAKUT are especially hard to classify because these infants may not survive to reproductive age to establish if the genotype segregates with the phenotype in offspring of the affected individual (25,26). The mutations also often manifest with variable expressivity and/or incomplete penetrance which can limit the success of functional validation of the mutation in model organisms or in relevant cell lines. Finally, the mode of inheritance of CAKUT varies: autosomal dominant, autosomal recessive, and X-linked inheritance have been identified (27).

Recently, investigators have used whole-exome sequencing in large cohorts to identify genes that are associated

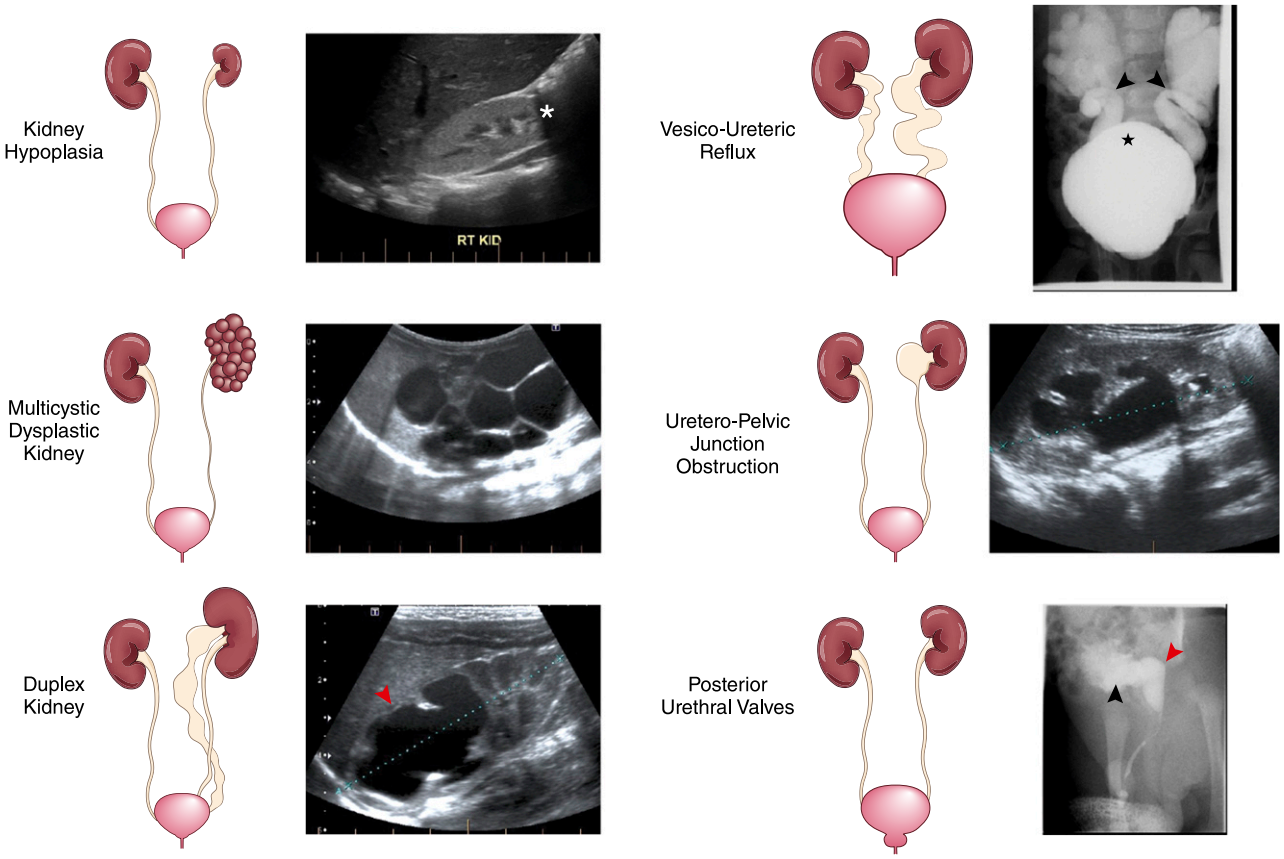

Figure 2. | CAKUT defects can be identified through radiological findings. Kidney hypoplasia: a small malformed kidney depicted in the cartoon corresponding to the adjacent ultrasound of a small hyperechoic kidney, indicated by an asterisk (*). Multicystic dysplastic kidney: a kidney with dysplastic tissue and multiple cysts. Dark fluid-filled sacs representing cysts are seen throughout the kidney on ultrasound. Duplex kidney: duplex kidney shows two ureters on the left with a dilated ureter attached to the upper pole. The ultrasound shows dilation of the upper pole indicated by a red arrowhead. Vesicoureteric reflux: reflux is shown with dilated ureters entering the kidneys. The adjacent image shows a voiding cystourethrogram which is performed by injecting a radio-opaque agent into the bladder. An enlarged bladder (star) is shown with dilated tortuous ureters (black arrow heads) refluxing urine to the kidneys. Ureteropelvic junction obstruction: obstruction at the connection between the ureter and kidney, causing hydronephrosis in the kidney seen on ultrasound. Posterior urethral valve: congenital obstruction of urethra results in abnormal bladder. Adjacent voiding cystourethrogram shows a distended irregular bladder (black arrows) and dilated prostatic urethra.

with CAKUT (27,28). These large-scale, unbiased approaches need to be continued and combined with high-throughput functional validation of sequence variants to understand the genomic landscape of CAKUT.

The Shift from Small to Large Genetic Changes

Despite the identification of hundreds of candidate genes, CAKUT cannot be attributed to a monogenic cause in >80% of cases. This suggests contributions from other genetic, epigenetic, and environmental factors. Copy number variants (CNVs) are deletions or duplications of chromosomal regions that result in a change in gene dosage, and they have been examined in patients with CAKUT. CNVs are significantly enriched in both syndromic and nonsyndromic forms of CAKUT (29,30). Verbitsky *et al.* (29) reported 45 CNVs in 37 distinct loci that were associated with CAKUT, further demonstrating its genetic complexity. Six loci were "hotspots" for CNVs: 1q21, 4p16.1-p16.3, 16p11.2, 16p13.11, 17q12, and 22q11.2. Surprisingly, despite a large number of cases (2824), only one patient had a large CNV deletion encompassing *PAX2*. A total of 26 patients exhibited large CNVs at 17q12, which encompasses *HNF1β* (29). Although these studies are impressive in their sample size and findings, CNVs account for only 4% of cases of CAKUT, again supporting the contribution of other genetic and environmental factors. Although small (single or dinucleotide) exonic deletions are easy to model in animals, large deletions (encompassing many genes and/or duplications) are far more challenging, thus validating the causality of gene dosage remains difficult.

Identifying New Genes and Validating Screens: the Use of Animal Models

The mouse is a good model to complement human variant studies because of its similar kidney physiology, structure, and development, as well as its genetic similarity to humans. Mouse models have recapitulated many CAKUT phenotypes including kidney agenesis/hypoplasia, VUR (31), and obstruction. Mouse models have also provided evidence that mild CAKUT, manifesting as low nephron number,

Table 2. Genetic risk factors for CAKUT

Type of Mutation	Genetic Factor	Gene Function/Consequence of Mutation	Associated Defects in Humans
Single gene polymorphism	*HNF1β*	Transcription factor, autosomal dominant	Multicystic renal dysplasia, renal hypoplasia, renal cysts, and diabetic syndrome (17)
	PAX2	Transcription factor, autosomal dominant	Renal hypoplasia, VUR, renal coloboma, FSGS (15)
	SIX1	Transcription factor, autosomal dominant	Renal hypodysplasia, VUR, branchio-oto-renal syndrome (19)
	SIX5	Transcription factor, autosomal dominant	Renal hypodysplasia, VUR, branchio-oto-renal syndrome (20)
	EYA1	Trascriptional coactivator, autosomal dominant	Renal hypoplasia, branchio-oto-renal syndrome (22)
	SALL1	Transcription factor, autosomal dominant	Townes–Brocks syndrome, renal hypodysplasia (21)
	GATA3	Transcription factor, autosomal dominant	Renal dysplasia, hypoparathyroidism-deafness-renal dysplasia syndrome (23)
	FREM2	Integral membrane protein, autosomal recessive	Renal agenesis, Fraser syndrome (24)
	FRAS1	Extracellular matrix protein, autosomal recessive	Renal agenesis, Fraser syndrome (24)
Copy number variants (29)	1q21	Deletion or duplication of region	Renal hypoplasia/dysplasia/cysts, PUV, UPJO, VUR
	4p16.1-16.3	Deletion or duplication of region	Renal hypoplasia/dysplasia/cysts
	16p11.2	Deletion or duplication of region	Renal hypoplasia/dysplasia/cysts, PUV, UPJO, duplex collecting system, VUR
	16p13.11	Deletion or duplication of region	Renal hypoplasia/dysplasia/cysts, UPJO, duplex collecting system
	17q12	Deletion or duplication of region, contains HNF1β	Renal hypoplasia/dysplasia/cysts, PUV, UPJO, duplex collecting system
	22q11.2	Deletion or duplication of region	DiGeorge syndrome, renal hypoplasia/dysplasia/cysts, UPJO, PUV, dual collecting system, VUR

CAKUT, congenital anomalies of the kidneys and urinary tracts; VUR, vesicoureteric reflux; PUV, posterior urethral valve; UPJO, ureteropelvic junction obstruction.

results in adult-onset CKD and hypertension (32,33). Historically, mouse models of CAKUT have been mostly used to phenocopy loss-of-function mutations or nonsense mutations in which no protein is made. However, it is increasingly apparent that many of the mutations identified in human studies of CAKUT are missense mutations in which an abnormal full-length protein is produced, and these also need to be functionally validated to demonstrate causality. In the mouse, this can be done by inserting the mutation in the mouse genome using clustered regularly interspaced short palindromic repeats (CRISPR) gene editing to prove that a mutation is causal for CAKUT.

Zebrafish are another common model used to understand CAKUT. Zebrafish develop a pronephros and do not form the adult kidney seen in humans. Nonetheless, evaluation of the zebrafish pronephros has been useful to functionally validate potential CAKUT-causing candidates. Large genetic screens have been performed in zebrafish in which mutations have been induced using chemical mutagenesis and offspring have been surveyed to determine if any have defects in kidney development (34,35). These screens are effective in that they are high throughput, the phenotypes are easy to discern, and they can be done in a relatively short time frame. Finally, zebrafish are also a practical model for high-throughput drug screens that could be used to assess treatments for CAKUT (36).

The use of cell fate mapping and single cell RNA sequencing in animal models are standard techniques in developmental biology. By determining how stem cells within the kidneys and outflow tracts differentiate, organize, and respond to environmental cues, new insight about when and how CAKUT phenotypes arise can be garnered (37).

Environmental Factors and Congenital Anomalies of the Kidneys and Urinary Tracts

About 50% of pregnancies are unplanned; therefore, many women may not realize they are pregnant, resulting in fetal exposure to teratogens and environmental toxicants. Although most organs are formed between weeks 4 and 8 of gestation, nephron formation continues until the 36th week. This longer period of exposure to the environment has complicated epidemiology studies that have attempted to identify risk factors for CAKUT (Table 3).

Maternal malnutrition and uteroplacental insufficiency are associated with low birth weight and premature delivery. In a small study of babies who died within 2 weeks of birth, babies born with a low birth weight of <2.5 kg were found to have significantly fewer nephrons compared with babies with a birth weight >2.5 kg (38). Similarly, extreme prematurity (birth weight <1000 g) has been shown to correlate with low nephron number in autopsy studies (39).

From animal and human studies, maternal diabetes is a risk factor for CAKUT (40). Excessive alcohol consumption is a risk factor for fetal alcohol syndrome, which can include CAKUT. It is hypothesized that excessive maternal alcohol

Table 3. Environmental risk factors for CAKUT

Environmental Factors	CAKUT Phenotypes
Maternal diet	
Folic acid use (47)	Duplex collecting system, VUR, PUV
Low folate (46)	UPJO, renal agenesis, renal cysts
Vitamin A deficiency (43,44)	VUR, renal hypoplasia, renal dysplasia
Maternal conditions	
Maternal obesity (48)	Duplex collecting system, VUR
Maternal diabetes (40)	Wide range of CAKUT phenotypes including kidney abnormalities and outflow tract
Maternal malnutrition (38)	Low nephron number, low birth weight
Maternal substance use	
Maternal cocaine (45)	Horseshoe kidney, renal hypoplasia, renal dysplasia, duplex collecting system, VUR
Maternal alcohol (41)	Fetal alcohol syndrome, renal hypoplasia, kidney insufficiency
Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers (47)	Acute kidney injury, renal hypoplasia
In vitro fertilization (48)	UPJO, duplex collecting system, PUV, VUR

CAKUT, congenital anomalies of the kidneys and urinary tracts; VUR, vesicoureteric reflux; PUV, posterior urethral valve; UPJO, ureteropelvic junction obstruction.

consumption may result in fetal vitamin-A deficiency and low nephron number through competition between ethanol and retinol for metabolism *via* the alcohol dehydrogenase pathway (41,42). Vitamin A and its signaling pathway are a fundamental morphogenetic pathway needed for human organogenesis. Indeed, maternal vitamin-A deficiency and excess also result in CAKUT in humans and in animal models (43,44). Maternal use of cocaine is another risk factor, with one study reporting a 14% incidence of CAKUT in fetuses exposed to cocaine (45).

Although a lack of maternal folate by diet or use of antifolate medications are known risk factors for neural tube defects, they are also risk factors for CAKUT (46). Folate is a micronutrient that is needed for DNA synthesis and methylation during embryogenesis, which controls gene expression. DNA methylation and histone modifications are fundamental mechanisms that result in chromatin being "open" or "closed," which dictates whether a gene is expressed or not. Other medications that are linked to CAKUT include maternal intake of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers, especially if taken during the second and third trimesters of pregnancy (47).

Knowledge on the environmental factors that result in CAKUT is limited because only a few registries report on CAKUT. The AGORA database in The Netherlands used questionnaires administered to parents of infants with CAKUT and established that maternal obesity, maternal diabetes, artificial insemination, *in vitro* fertilization, and the use of folate supplements were all risk factors for CAKUT. The mechanism for how these factors result in CAKUT is unknown, especially for folate, which in some studies appears to decrease the risk of CAKUT. Although the use of questionnaire data may be limited by recall bias, the information is vital to generate hypotheses on possible mechanisms (48).

Epigenetic Changes: How the Environment Affects Gene Expression

The environment can have a significant effect on the expression of genes implicated in CAKUT. Changes in gene activity or expression that are not caused by changes in the DNA sequence of a gene are known as epigenetic changes and include processes like DNA methylation or histone modification. Because the epigenetic landscape is often tissue specific and dynamically remodeled due to environmental factors, the assessment of the epigenome needs to occur when CAKUT arises during embryogenesis and within the affected embryonic tissue. These factors have made it difficult to directly assess the role of the epigenome in CAKUT. Recent studies have shown the importance of DNA methyltransferases in regulating the timing of gene expression during nephrogenesis: mouse models that lack the methyltransferase, DNMT1, have severe kidney abnormalities (49,50). As the use of assisted reproductive technologies (ART) procedures becomes more common, its effect on epigenetic regulation of embryonic development needs to be examined. It has been shown that ART procedures cause a high level of chromosomal abnormalities including aneuploidies, chromosomal breaks, rearrangements which can lead to CNVs, and epigenetic changes (51). Furthermore, due to the timing of ART, which is performed during major epigenetic remodeling in the early embryo, inappropriate gene silencing or activation could result in CAKUT or other defects.

Nephron Endowment and Congenital Anomalies of the Kidneys and Urinary Tracts in the Future

From animal and human studies, low nephron endowment at birth is a manifestation of CAKUT. To understand the prevalence of low nephron number, there is a need for methods to capture this phenotype in real time and not only from postmortem studies (52). Indirect approximations of nephron number have incorporated birth weight and estimates of nephron loss with age, but these formulas have not been validated in large populations with diverse ethnicities (53). From evaluations of adult kidney donors, there are methods to estimate nephron number using glomerular counts from kidney biopsies coupled with

computed-tomography scan imaging to estimate the cortical compartment size (54). This could be applied to capture low nephron endowment in CAKUT but is significantly limited by the need for a kidney biopsy. Other technologies are emerging that use magnetic resonance imaging coupled with a cationic tracer, like ferritin, to enrich accumulation in the negatively charged glomerular basement membrane to permit quantification of glomeruli (55).

How Can We Advance the Understanding of Congenital Anomalies of the Kidneys and Urinary Tracts?

Much remains to be uncovered about the genetic and environmental regulators of kidney and outflow tract development. In the future, model systems and in particular kidney organoids, in which cells are induced and grown to resemble an organ, will continue to be essential to validate genetic and environmental contributors to CAKUT. Recent papers by Taguchi and Nishinakamura (56) and Takasato *et al.* (57) have shown that kidney organoids can recapitulate fetal kidney development and nephrogenesis. Using induced pluripotent stem cells and CRISPR/Cas9 gene editing, kidney organoids can be generated that express the same genetic variants found in patients. Organoids also provide an accessible model that can be used to manipulate environmental stressors such as temperature, oxygen levels, nutrient supply, and teratogens to assess kidney development and/or effects on the epigenome. Organoids are still limited by the lack of a connection to a vascular system and defects of the outflow tracts cannot be modeled without the creation of a urinary filtrate. As organoids become more complex, drug screening to modify stem cell fate decisions (survival, differentiation, apoptosis) could be performed to enhance the survival of nephrogenic stem cells.

In summary, there is a need to perform long-term prospective studies of all patients with CAKUT that is coupled with comprehensive genomic characterization, functional validation of sequence variants, and an in-depth assessment of the *in utero* environment. This will significantly improve knowledge about the pathogenesis of CAKUT. The use of animal models and organoids are also essential to understand the mechanisms of how CAKUT arises to identify prevention and treatment options. To understand low nephron number or mild CAKUT, new technologies that are emerging need to be improved and standardized for clinical use so we can identify this phenotype and determine the magnitude of who is affected during childhood and adulthood.

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