CKJ REVIEW

Developmental pathology of congenital kidney and urinary tract anomalies

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ABSTRACT

Congenital anomalies of the kidneys or lower urinary tract (CAKUT) are the most common causes of renal failure in children and account for 25% of end-stage renal disease in adults. The spectrum of anomalies includes renal agenesis; hypoplasia; dysplasia; supernumerary, ectopic or fused kidneys; duplication; ureteropelvic junction obstruction; primary megaureter or ureterovesical junction obstruction; vesicoureteral reflux; ureterocele; and posterior urethral valves. CAKUT originates from developmental defects and can occur in isolation or as part of other syndromes. In recent decades, along with better understanding of the pathological features of the human congenital urinary tract defects, researchers using animal models have provided valuable insights into the pathogenesis of these diseases. However, the genetic causes and etiology of many CAKUT cases remain unknown, presenting challenges in finding effective treatment. Here we provide an overview of the critical steps of normal development of the urinary system, followed by a description of the pathological features of major types of CAKUT with respect to developmental mechanisms of their etiology.

Keywords: CAKUT, congenital, development, genetics, kidney, urinary tract

INTRODUCTION

The functioning unit of the kidney that produces urine is called the nephron. For the purpose of this article, the proximal nephron comprises the glomerulus, proximal tubules, loop of Henle and distal tubules. The distal nephron harbors the collecting system, mainly consisting of the collecting ducts. The filtrate, namely urine, from the kidney is passed to the lower urinary tract (ureter, bladder and urethra) for expulsion. Development of the urinary system is a highly complex process that depends on precise spatiotemporally regulated events and requires the integration of a variety of progenitor cell populations of different embryonic origins [1–3]. These events culminate in precise anatomical connections between the proximal and distal nephrons in the kidney (upper tract) and the upper and lower urinary tract. Most clinically relevant congenital anomalies of the kidneys or lower urinary tract (CAKUT) originate from the disruption of regulatory circuitry and the progenitor cells involved in these processes, especially in the morphogenesis of the urinary conduit or the functional aspects of the pyeloureteral peristaltic machinery. The power of genetics and molecular biology in model organisms has greatly advanced our knowledge that is directly relevant to CAKUT in humans [4–9]. In this review we will provide an overview of the major steps in nephrogenesis and the development of the lower urinary tract. We will then describe the pathological features of major types of CAKUT and discuss the developmental pathology leading to CAKUT, based on the evidence from human patients and animal disease models, especially murine models.

NORMAL DEVELOPMENT OF THE KIDNEYS AND THE URINARY TRACT

Development of the urinary system occurs in several stages in mammals, culminating in a kidney and a ureter from each half of the body, which are connected to the bladder. For simplicity and to correlate the pathogenesis of CAKUT with specific developmental processes, we categorize the development of the kidney and the urinary tract into the following stages [10, 11].

## Preureteric bud induction and Wolffian duct morphogenesis

Most components of the urinary system are derived from the intermediate mesoderm [12] that give rise to the nephrogenic cords at about 3 weeks of gestation (wg) in humans and about embryonic day 8 (E8) in mice. The nephrogenic cord produces three sets of nephric structures: pronephros, mesonephros and metanephros (Figure 1). Pronephros is the cranial most transient structure that emerges at about 3 wg in humans and regresses by 4 wg (E9.5 in mice). Mesonephros development coincides with pronephros regression and caudal extension of the nephrogenic cord that metamorphoses into the mesonephric duct (Wolffian duct) and is surrounded by mesonephric mesenchyme. In mammals, the mesonephros is transient but functional. In humans, the mesonephric tubules are linearly arranged along the Wolffian duct and are directly connected to it (Figure 2). The Wolffian duct joins the cloaca (future bladder), initiating the connection between the upper and lower urinary tracts. In humans, the mesonephros regresses by 16 wg in a caudal-to-cranial manner (by E11.5 in mice) except in males, where the cranial most mesonephric tubules become the epididymis and efferent ductules and the Wolffian duct becomes the vas deferens. The precise regression of the mesonephroi is critical for normal kidney development, and this process is regulated by signals in the Wolffian duct [13].

Ureteric bud induction

Metanephroi (definitive kidney) begin to form at 4.5 wg (and become functional at ~10 wg) in humans and E10.5 in mice. Metanephric development starts with the outgrowth of epithelial cells called the ureteric bud (UB) from the caudal Wolffian duct. The UB invasion of the metanephric mesenchyme (MM), in response to inductive signals from the MM, induces MM cells to aggregate around the UB tip. This leads to branching of the tip to form a T–shaped structure. The MM cells coalesce around the branched tips to form the cap mesenchyme here after referred to as nephron progenitors. The UB tip cells are the precursors of the collecting ducts. This entire process is called UB induction and indispensable for kidney formation. Thereafter the UB undergoes repetitive branching to form the elaborate collecting duct system through branching morphogenesis.

Branching morphogenesis

Branching morphogenesis requires reciprocal interactions among the UB, MM, stromal cells and endothelial cells. UB tips proliferate and branch to give rise to new UBs. The first few branches give rise to the major and minor calyces in humans, into which the collecting ducts from the respective papillae drain. All major calyces drain into the pelvis, finally leading into the ureter. Branching problems can cause decreased kidney mass (hypoplasia) and defective structures (dysplasia). Nephrogenesis begins when mesenchyme cells coalesce near the junction of the UB stalk and the UB
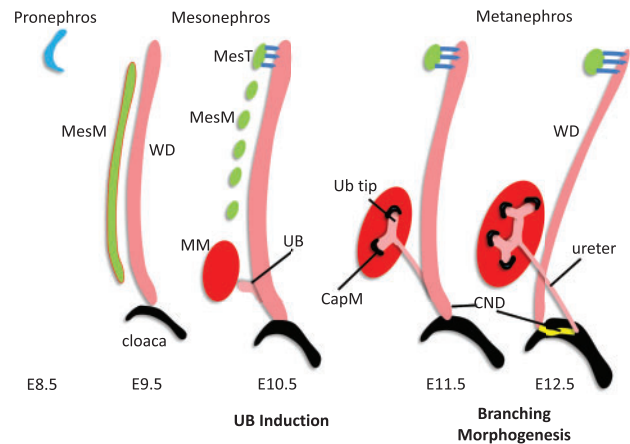

FIGURE 1: Illustration shows events in mammalian kidney development using mouse stages as an example. Pronephros, the first stage, begins at about embryonic day 8 (E8) from intermediate cells. Mesonephros includes mesonephric mesenchyme (MesM) and an epithelial tube called the Wolffian duct (WD). By E10.5, the Wolffian duct has inserted into the cloaca, MesM is degenerating and a bulge on the distal aspect of the WD develops into the UB that grows toward the MM. The portion of the Wolffian duct distal to the UB is called the common nephric duct (CND). At E11.5, the UB invades the MM, causing certain cells in the MM to coalesce around the UB tips. These are called cap mesenchyme cells (CaPM). Interactions between CaPM and UB and other cells in the MM initiate recursive branching called branching morphogenesis. At E12.5, the ureter remodeling process starts to insert into the primitive bladder (UGS) and separate from the Wolffian duct through a process of CND apoptosis (yellow).
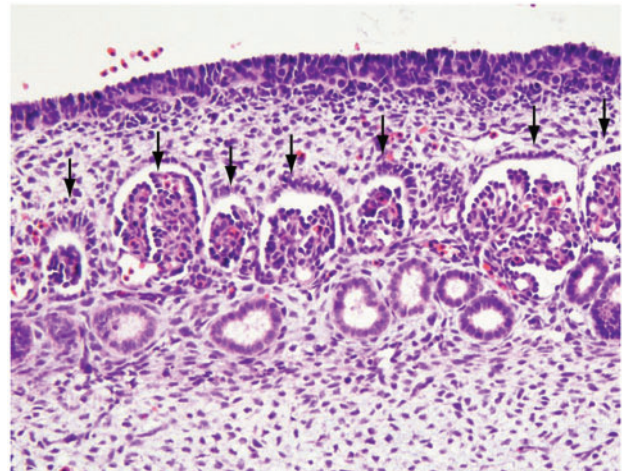
FIGURE 2: Hematoxylin and eosin–stained section from a human fetus during the mesonephros stage. Note the linearly arranged primitive glomeruli (arrows).

tips and transition into pretubular aggregates. These cells undergo a series of morphogenetic stages to form the proximal nephron, consisting of the glomerulus, the proximal tubules, descending and ascending loops of Henle, distal tubules and connecting tubules. The endothelial progenitors invade the cleft at the distal aspect of the S-shaped body along with the stromal cells to become the glomerular capillaries and mesangium, respectively [14–16]. Since the kidney grows in a centrifugal manner, the oldest glomeruli are toward the cortico-medullary junction and the newest ones toward the periphery. Nephrogenesis completes before birth in humans, but persists in early postnatal days in rodents. At the end, the human kidney has multiple lobes, each comprising the cortex, medulla and papillae that drain into minor and major
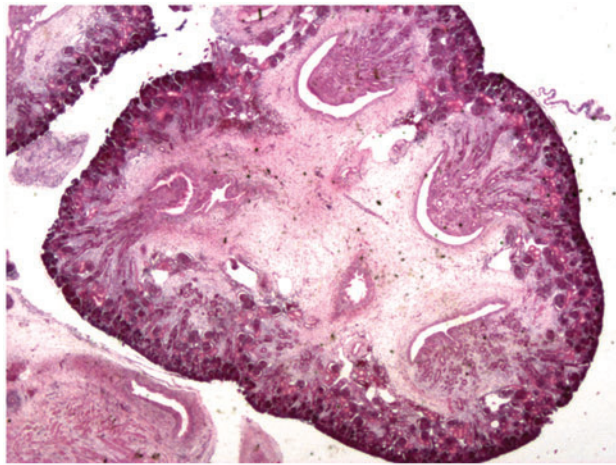
FIGURE 3: Hematoxylin and eosin–stained section of human perinatal kidney at low power shows organization into lobules (appear as bumps) with outer cortex (darker colored outer layer), medulla and papillae that drain into calyces (crescent-shaped white spaces).

calyces (Figure 3); mice have a single papilla that drains into the pelvis. The peristaltic activity to propulse urine through the ureter is initiated from pacemaker cells in the tips of the papillae.

Ascent and rotation

Concurrent to nephrogenesis, kidneys also undergo repositioning through ascent and rotation. The kidneys grow posteriorly (towards the back) during initial development. As development progresses, they rotate anteromedially such that each hilum points medially. Meanwhile, there is apparent ascent due to disproportionate growth of the caudal regions of the embryo such that the final position of the kidneys is retroperitoneal in the abdomen by ~9 wg. The blood supply to the developing kidney is initially via the caudal segments of the descending aorta or its iliac branches. As the kidneys ascend, the blood supply is derived from more cranial branches of the aorta while the caudal vascular connections degenerate. The failure of regression of transient blood vessels or sprouting of additional vessels to ensure adequate perfusion of the kidney may account for the variability seen in vascular supply to the kidney and accessory renal arteries. In some cases, failure of regression of transient vessels may compress the ureters, leading to hydronephrosis. Ascent and rotation defects can also result in fusion or ectopic kidneys.

Ureter maturation and bladder–urethra development

The initial stalk of the UB remains outside the MM, matures into a ureter, elongates and connects to the bladder [10, 17, 18]. Common nephric duct is the part of the Wolffian duct distal to the point where the ureter is initially attached to the Wolffian duct (Figure 1). The initial Wolffian duct–cloaca contact occurs before UB induction. After UB induction, the ureter separates from the Wolffian duct through a process of ureteral remodeling and maturation that leads to insertion of ureter into the bladder, the formation of a single lumen and separation of the Wolffian duct from the ureter. The Wolffian duct inserts in the urethra in males and degenerates in females. Ureteral smooth muscle differentiation within the ureteral mesenchyme commences at E14.5 in mice, following the establishment of a connection between the Wolffian duct and bladder epithelium,

with the appearance of the first wave of α smooth muscle actin–positive cells [19]. In humans, ureteral muscularization and development of elastic fibers start at 12 wg [20–23]. Bladder epithelium originates from the cloaca, a hindgut derivative with an endodermal origin, in contrast to the mesodermal origin of the kidney and the ureter epithelium from the Wolffian duct. Male urethra develops as the urogenital sinus extends to the surface of the genital tubercle.

PATHOLOGICAL AND CLINICAL FEATURES OF CONGENITAL KIDNEY AND LOWER URINARY TRACT DEFECTS

CAKUT is a term used broadly to describe developmental defects in the urinary system that can occur in isolation, in combination or as part of other syndromes. CAKUT comprises a wide spectrum of congenital defects in the urinary system, ranging from renal agenesis and hypoplasia, structural duplication and mispositioning to defects in the ureter and bladder. Genetic, epigenetic and environmental factors can all cause these abnormalities. The biology of CAKUT is further complicated by the fact that affected family members may exhibit different types of CAKUT [7, 8, 24–29]. We will discuss the clinicopathological features of the most common types of CAKUT in relation to underlying developmental defects and provide a summary of candidate genes, underlying CAKUT and the likely developmental mechanisms contributing to the CAKUT phenotype (Tables 1–3).

Duplication and supernumerary kidneys

In supernumerary kidneys, multiple UBs emerge separately and grow into the MM [162, 163]. Partial duplication, often clinically insignificant, can result from UB stalk bifurcation before invading the MM or prior to initial branching of the primary UB stalk in the MM. In complete duplication, two UBs emerge from the WD, resulting in two complete sets of kidneys and ureters that may insert into the bladder separately (Figure 4). These kidneys may appear fused due to their development in the same MM. In >95% of such cases, the lower ureter will enter the bladder at its normal location but tunnels through it abnormally, leading to reflux [164]. The upper ureter inserts more distally, closer to the reproductive tract or in the urethra and frequently results in an ureterocele. The ureterocele often drains the upper kidney or the upper pole of a duplex kidney. Due to obstruction or reflux, both kidneys may show dysplasia or obstructive nephropathy. These patients may present with hypertension, pain and kidney failure. The incidence of duplication in a clinical setting is 1 in 125 and may be as high as 1 in 25 in postmortem cases [162]. The extra UBs could result from enhanced UB budding signals, failure to repress extraneous budding or aborted regression of mesonephric mesenchyme. For reasons still unknown, duplication is more common in women than in men (2:1) [162].

Agenesis

Failure of the kidneys to develop (agenesis) is frequently caused by defective/delayed WD growth or UB induction. Renal agenesis can be unilateral (1/1000) or bilateral (1/10 000) [165]. Bilateral agenesis is incompatible with life and is more common in males [165]. During embryogenesis, kidney agenesis causes oligohydramnios and abnormal lung development. Oligohydramnios or ahydramnios during fetal development often presents as Potters sequence: flat facial features, wide-set eyes, limb

Table 1. Summary of cause and treatment of lower urinary tract defects affecting kidney function

Defects	Definition	Etiology	Clinical presentation and pathological features	Diagnosis	Current treatment
Posterior urethral valves	Obstructing valve leaflets at the posterior urethra	Urogenital sinus and trigone malformation	Bilateral HN; VUR; spectrum of renal demise; UTI	VCUG	Endoscopic valve ablation
UPJ obstruction	Ureteral obstruction at the ureteropelvic junction	Atretic, narrow or aperistatic proximal ureteral segment	High-grade HN (pre- or postnatal); UTI; flank pain	Renal US; diuretic renal scan; magnetic resonance urography	Pyeloplasty—open or laparoscopic
UVJO	Ureteral obstruction at the UVJ	Atretic, narrow or aperistatic distal ureteral segment	High-grade HUN (pre- or postnatal); UTI; flank pain	Renal US; Diuretic renal scan; magnetic resonance urography	Ureteral reimplantation with or without a megaureter repair
Ureterocele	Balloon dilation of the distal ureter	Ureteral and urogenital sinus malformation	Ectopic location may result in BOO; often associated with complete ureteral duplication	Renal US; diuretic renal scan; VCUG; magnetic resonance urography	Ureterocele incision or excision
VUR	Vesicoureteral reflux	Ureteral and urogenital sinus malformation	Pre- or post-natal HN; febrile UTI	VCUG	Observation versus surgical repair (endoscopic injection or ureteral reimplantation)

HN, hydronephrosis; HUN, hydroureteronephrosis; BOO, bladder outlet obstruction; US, ultrasound.

defects, prominent epicanthal folds, hypoplastic lungs and absent to malformed kidneys [166]. Isolated unilateral agenesis may cause compensatory hypertrophy of the contralateral kidney and is commonly detected during routine sonography examinations. The incidence is equal in males and females but higher on the left than on the right side. About 50–70% of unilateral agenesis may exhibit other urogenital anomalies, including dysplasia, ectopia, reflux and proteinuria, and may present with hypertension. The term 'solitary kidney' is frequently used to describe the absence of one kidney in living patients. Without the advantage of serial radiological follow-up from early gestation, it is difficult to determine if agenesis in these patients is due to complete lack of UB induction or due to involution of a dysplastic kidney.

Hypoplasia

Hypoplasia refers to small kidneys with a decreased number of nephrons due to reduced branching morphogenesis. These kidneys exhibit preserved architecture with normal organization into cortex and medulla. Unilateral hypoplasia has an incidence of 1/1000, whereas bilateral cases are less frequent (1/4000). Most patients with bilateral hypoplasia develop end-stage renal disease (ESRD) in mid or late childhood and have a higher probability of developing hypertension [165]. Simple unilateral hypoplasia may have no consequence. Hypoplasia may accompany renal artery hypoplasia. Macroscopically they may exhibit oligomeganephronia, decreased renal lobes and secondary glomerulosclerosis.

Dysplasia

Dysplastic kidneys have abnormal architectural organization, immature nephrons, undifferentiated stroma and incomplete branching [167]. The signaling cues orchestrating nephrogenesis appear asynchronous and there is a loss of coordinated reciprocal interactions among the UB, MM and stroma during branching morphogenesis. Dysplastic kidneys can be small, normal in size or slightly larger than healthy kidneys and may show cystic changes. Dysplasia can be unilateral (1/4300 in multicystic

dysplastic kidneys and 1/1000 in dysplastic kidneys) or bilateral (1/7500) [165, 167]. Bilateral dysplasia is incompatible with life. Although definitive diagnosis of dysplasia requires histological assessment, the clinical diagnosis is often made through antenatal ultrasound. Dysplasia can occur in a portion or the entire kidney. Contralateral kidney defects may be as high as 50–70% in patients with unilateral kidney dysplasia who may also have other CAKUT phenotypes. The prognosis of unilateral dysplasia is usually good if infections and hypertension are well managed. Extreme forms of dysplasia or arrest in branching can result in involution of the kidney or rudiments, also known as aplastic kidneys. Extremely aplastic kidneys may be undetectable on radiological exam, leading to the diagnoses of solitary kidney or unilateral agenesis [168]. Microscopically the dysplastic kidneys show blastema elements; fetal glomeruli; tubular, glomerular or collecting duct cysts; smooth muscle collarettes surrounding primitive collecting ducts and cartilage in ~30% of cases (Figure 5). Multicystic dysplasia is a form of abnormal metanephric differentiation characterized by the presence of renal cysts of varying size and the absence of a normal pelvicaliceal system. Multicystic dysplastic kidneys may persist without noticeable change, increase in size or undergo spontaneous involution [169–174]. Dysplasia can be caused by primary defects in branching morphogenesis or secondary to reflux.

Position defects (horseshoe kidneys, renal ectopia and malrotation)

Position defects occur when kidneys are displaced along the anterior–posterior axis in the abdomen or mediolaterally relative to their normal location from the midline. Fusion or apposition of the growing kidneys may occur with position defects and may become clinically significant when there are associated anomalies such as refluxing ureters emanating from the fused kidneys leading to reflux nephropathy (RN). Most fusions occur near the posterior end of the kidneys. The ascent of the fused kidneys may be hindered by crossing blood vessels and other tissues. Thus the fused kidneys may position lower than normal

Table 2. A subset of genetic factors involved in CAKUT and the suspected mechanism based largely on the study of animal models

Gene/allele symbols	Gene names and functions	Defects in human patients and animal models	Likely mechanism	References
Ace	Angiotensin-converting enzyme (enzyme-converting angiotensin I to angiotensin II)	Ace$^{-/-}$ mice: hydronephrosis, renal parenchymal atrophy	Defective pyeloureteral peristalsis as a result of a ureter differentiation defect, a urine concentration defect/polyuria or both	[19]
Adamts1	A disintegrin-like and metallopeptidase with thrombospondin type 1 motif, 1 (metallopeptidase)	Adamts1$^{-/-}$ mice: UPJO, hydronephrosis, hydroureter, other urogenital defects	Unclear. Excessive collagen deposit was found at UPJ	[30]
Agt	Angiotensinogen (precursor of the peptide hormone angiotensin)	Agt$^{-/-}$ mice: hydronephrosis, renal parenchymal atrophy	Defective pyeloureteral peristalsis	[31, 32]
Agtr1a/b	Angiotensin II receptor, type 1 (1a and b) (G protein-coupled receptor)	Agtr1$^{-/-}$ (1a and b) mice: partial penetrance, hydronephrosis in older mutants, renal parenchymal atrophy	Urinary SMC developmental. Defect, renal pelvis development	[33, 34]
Agtr2	Angiotensin II receptor, type 2 (G protein-coupled receptor)	Agtr2$^{-/-}$ mice: limited incidence of hydronephrosis, megaureter, renal parenchymal atrophy	Ectopic and duplicated UB	[24, 35]
Aldh1a2	Aldehyde dehydrogenase family 1 member A2 (encodes Raldh2, an enzyme in retinoic acid synthesis)	Aldh1a2$^{-/-}$ mice rescued by maternal retinoic acid: hydroureter and hydronephrosis	Defects in ureter maturation, especially the insertion of the ureter into the bladder	[36]
Aqp2	Aquaporin 2 (water channel)	The cph mutants (Aqp2$^{S256L/S256L}$) have polyuria and hydronephrosis. Other Aqp2 mutations also cause renal damage resembling obstructive nephropathy	Polyuria overwhelms the pyeloureteral peristaltic machinery	[37–39]
β-catenin	Same as Ctnnb1 (adherens junction protein, involved in Wnt signaling)	Hoxb7-Cre$^{T/+}$; β-catenin$^{flox/flox}$ mice: hydroureter and hydronephrosis	Ectopic and supernumerary UB	[40]
BMP4/Bmp4	Bone morphogenetic protein 4 (ligand in the TGF-β superfamily)	BMP4 mutations found in human patients with anomalous kidney development. Bmp4$^{+/-}$ mice: hydronephrosis, hydroureter, other urinary tract defects	Ectopic and supernumerary UB	[41–43]
Bmp5	Bone morphogenetic protein 5 (Ligand in the TGF-β superfamily)	Short ear (Bmp5$^{-/-}$) mice have hydroureter and hydronephrosis	Spatial constraints in the lower abdominal cavity affect urinary transfer	[44, 45]
Bmp7	Bone morphogenetic protein 7 (Ligand in the TGF-β superfamily)	Renal dysplasia, hypoplasia, hydronephrosis and other defects are seen in mice deficient for Bmp7	MM differentiation and growth	[46, 47]
Bmpr1a	Bone morphogenetic protein receptor, type IA (serine/threonine–protein kinase receptor)	Mice deficient for Bmpr1a in the UB or the intermediate mesoderm has renal dysplasia, hypoplasia and other defects	Defective BMP signaling in progenitor populations	[48, 49]
CHRM3/ Chrom3	Cholinergic receptor, Muscarinic 3 (G protein-coupled receptor)	A frameshift mutation found in CHRM3 in familial congenital bladder malformation associated with prune belly-like syndrome. Bladder distension in Chrom3 mutant mice, especially in males	Defective detrusor contraction. Present in renal epithelia and bladder muscle with unknown functions	[50, 51]
Dlgh1	Same as Dlg1, Disk-large homolog 1 (scaffolding protein)	Dlgh1$^{-/-}$ mice: prenatal hydronephrosis, short ureter and defects in the ureteral insertion into the bladder	SM differentiation defect, ectopic UB	[52, 53]
Emx2	Empty spiracles homeobox 2 (transcription factor)	Mice deficient for Emx2 lack kidney, ureter, gonads and genital tracts	Defective of UB branching after it invades MM	[54]
EYA1/Eya1	Eyes absent homolog 1 (transcription factor)	Rare mutation in EYA1 found in CAKUT patients. Eya$^{-/-}$ mice: kidney agenesis	Absence or reduced Gdnf and six expression	[55, 56]

(continued)

Table 2. (continued)

Gene/allele symbols	Gene names and functions	Defects in human patients and animal models	Likely mechanism	References
Etv4 and Etv5	Ets variants 4 and 5 (transcription factors)	$Etv4^{-/-}$; $Etv5^{+/-}$ mice: kidney agenesis and severe hypodisplasia. Double homozygotes: complete agenesis	Absence of Etv4 and 5 functions downstream of Ret to promote and control branching	[57]
Fcgr2b and Pdcd1	Fc receptor, IgG, low affinity IIb and programmed cell death 1 (cell surface membrane protein of the immunoglobulin superfamily)	Some $Fcgr2b^{-/-}$; $Pdcd1^{-/-}$ mice: hydronephrosis	Autoimmune against UPKIIIA	[58]
Fgf8	Fibroblast growth factor (secreted signaling protein)	Mice with MM-specific inactivation of Fgf8 have renal agenesis and hypoplasia	Defective MM differentiation	[59, 60]
Fgfr2	Fibroblast growth factor receptor 2 (receptor tyrosine kinase)	Some $Pax3\text{-}Cre^{T/+}$; $Fgfr2^{flox/flox}$ mice have hydroureter	Supernumerary UB, abnormal ureter connection	[61]
Foxc1 and c2	Forkhead box protein C1/C2 (transcription factor)	$Foxc1^{-/-}$ and $Foxc1^{+/-}$, $Foxc2^{+/-}$ mice: duplex kidney, ureter duplication, hydroureter, hydronephrosis	Ectopic and supernumerary UB	[62]
Foxd1	Forkhead box D1 (transcription factor)	$Foxd1^{-/-}$ mice: kidney hypoplasia, fusion, malrotation	Altered signaling in the stroma. Disruption of a key role for renal capsule during kidney development	[63, 64]
FRAS1/Fras1	Fraser syndrome 1 (extracellular matrix protein)	Mice deficient for Fras1 have renal agenesis	Failure of UB to invade MM	[65, 66]
FREM2	FRAS1-related extracellular matrix protein 2 (extracellular matrix protein)	Mutations in FREM2 found in CAKUT patients	Likely similar to FRAS1/Fras1 mutations	[65]
Gata2	GATA-binding protein 2 (transcription factor)	$Gata2^{-/-}$ mice (with YAC rescue of hematopoietic defects): hydroureter, hydronephrosis	Unclear	[67]
GATA3/Gata3	GATA-binding protein 3 (transcription factor)	GATA3 mutations found in HDR (hypoparathyroidism, sensorineural deafness, renal anomaly) syndrome. $Gata3^{-/-}$ mice have kidney agenesis	Defects in nephric duct extension	[68, 69]
GDNF/Gdnf	Glial cell-derived neurotrophic factor (ligand for RET)	Mice deficient for Gdnf have renal agenesis	UB induction defect	[70–72]
GFRA1/Gfra1	GDNF family receptor α1 (glycosylphosphatidylinositol (GPI)-linked cell surface receptor for GDNF)	Mice deficient for Gfra1 have renal agenesis. Deletion of Gfra1 after UB induction causes renal hypoplasia	Defects in UB growth and branching morphogenesis	[73]
Gli3	Glioma-associated oncogene family zinc finger 3 (transcription factor)	Mice deficient for Gli3 have renal agenesis or malformed kidneys	Defective expression of key kidney patterning genes	[74, 75]
Grem1	Gremlin 1 (extracellular BMP antagonist)	Mice deficient for Grem1 have renal agenesis	Excessive BMP signaling. Defects in UB outgrowth	[76, 77]
HNF1β/Hnf1β	Hepatocyte nuclear factor 1-β (transcription factor)	Hnf1β mutant mice have severe hypoplasia and other kidney defects	Broad expression in developing kidney and urinary tract. May affect multiple processes, especially UB outgrowth and branching	[55, 78–83]
Hoxa11, Hoxc11 and Hoxd11	Homeobox a11, c11 and d11 (transcription factors)	Mice with different combination of mutations in these genes have various kidney and urinary tract defects, including hypoplasia and agenesis	UB induction defect and branching morphogenesis defects	[84–86]
Hoxa13 and Hoxd13	Homeobox a13 and d13 (transcription factors)	$Hoxa13^{+/-}$; $Hoxd13^{-/-}$ mice: UVJO, hydronephrosis, hydroureter, other urogenital defects	Patterning defects. May have homeotic transformation	[87]
HPSE2	Heparanase 2 (enzyme that degrades heparin sulfate proteoglycans)	Mutations in HPSE2 cause urofacial syndrome	Likely defects in the nerves controlling urinary voiding	[88, 89]

(continued)

Table 2. (continued)

Gene/allele symbols	Gene names and functions	Defects in human patients and animal models	Likely mechanism	References
Hspa4l	Heat-shock protein 4 like (chaperone?)	Some Hspa4l$^{-/-}$ mice have genetic background-dependent hydronephrosis	Unclear	[90]
Id2	Inhibitor of DNA binding 2	Id2$^{-/-}$ and Id2$^{+/-}$ mice have hydronephrosis	UPJ development	[91]
IL-9	Interleukin 9 (cytokine)	Overexpressing IL-9 by its own promoter in mice: hydronephrosis	Likely autoanitibodies against urinary tract components	[92]
Kcnj1	Potassium inwardly rectifying channel, subfamily J, member 1 also known as Romk (ion channel)	Romk$^{-/-}$ mice: hydronephrosis, water and electrolyte balance problem	Unclear	[93]
Isl1	Islet1 (transcription factor)	Hoxb6-Cre$^{T/+}$; Isl1$^{flox/flox}$ mice have kidney agenesis, hypoplasia and hydroureter	Abnormal UB elongation and branching. Reduction of expression	[94]
L1cam	L1 cell adhesion molecule (transcription factor)	L1cam$^{-/-}$ mice: hydroureter and hydronephrosis	Ectopic UB	[26]
Lim1	Same as Lhx1 – Lim homeobox protein 1 (transmembrane protein)	Hoxb7-Cre$^{T/+}$; Lim1$^{lz/flox}$ mice (with Lim1 deletion in the UB derivatives): hydroureter and hydronephrosis. Mice carrying homozygous germline mutations for Lim1 have renal agenesis	Ureter differentiation. Mesonephros defects in WD growth	[95–97]
Limp-2 (Lgp85)	Same as Scarb2 (scavenger receptor)	Limp-2$^{-/-}$ mice: kidney and ureter duplication, UPJO, hydroureter and hydronephrosis	Ectopic and supernumerary UB	[98]
Mdm2	Murine double minute-2 (nuclear phosphoprotein that binds p53)	Mice deficient for Mdm2 in the UB develop renal hypoplasia	Aberrant proliferation and apoptosis of UB cells	[99]
NFIA/Nfia	Nuclear factor I/A (transcription factor)	Nfia$^{+/-}$ and Nfia$^{-/-}$ mice: vesicoureteral reflux, hydronephrosis and hydroureter. Human NFIA$^{+/-}$ patients have similar defects	Abnormal development of the UPJ and UVJ	[100]
Osr1	Odd-skipped related 1 (transcription factor)	Mice deficient for Osr1 have complete renal agenesis	Establish of MM from intermediate mesoderm	[101–103]
PAX2/Pax2	Paired box gene 2 (transcription factor)	Pax2$^{1Neu/+}$ mice: vesicoureteral reflux. Other mutant alleles also cause vesicoureteral reflux in addition to renal agenesis	Delay in urinary tract maturation in the Pax2$^{1Neu/+}$ mice	[104–111]
Pbx1	Pre-B-cell leukemia homeobox 1 (transcription factor)	Kidney mispositioning, renal hypoplasia and renal agenesis have been observed in mice deficient for Pbx1	MM dysfunction	[112]
Ppp3r1	Protein phosphatase 3. Same as calcineurin (serine/threonine protein phosphatase)	The Pax3-Cre$^{T/+}$; Cnb1$^{flox/flox}$ mice (with calcineurin inactivation in the metanephric and ureteral mesenchyme): early postnatal hydronephrosis and hydroureter	Pyeloureteral peristaltic defect, defect in urinary tract SMC development	[113]
Ptprs and Ptprf	Protein tyrosine phosphatase, receptor type S & F (protein tyrosine phosphatase)	Ptprs; Ptprf double-mutant have hydronephrosis, hydroureter, duplex system and ureterocele	Defects in ureter maturation	[114]
Rara and Rarb2	Retinoic acid receptor α/retinoic acid receptor β 2 (nuclear receptors)	Rara$^{-/-}$; Rarb2$^{-/-}$ mice have hydronephrosis, hydroureter, vesicoureteral reflux	Defective differentiation of the MM	[115]
Renin	Same as Ren1 (enzyme in the rennin–angiotension system)	Renin$^{-/-}$ mice: hydronephrosis, renal parenchymal atrophy	Possibly by polyuria. It is also possible that the mutation disrupts SM differentiation	[116]
RET/Ret	Ret proto-oncogene (receptor tyrosine kinase, receptor for Gdnf)	Ret$^{-/-}$ mice: renal agenesis, defective WD insertion into the cloaca	UB initiation defect, distal WD growth	[117–119]

(continued)

Table 2. (continued)

Gene/allele symbols	Gene names and functions	Defects in human patients and animal models	Likely mechanism	References
		Mice carrying Ret alleles with specific mutation of the key tyrosines: CAKUT (hydronephrosis, hydroureter, vesicoureteral reflux, dysplasia, hypoplasia, duplication, agenesis)	Cell survival, proliferation, migration Wolffian duct patterning, UB induction, ureteral maturation	[13, 73, 120–123, 124]
		Mice overexpressing *Ret* in UB: vesicoureteral reflux	Ureter maturation defect	[125]
ROBO2/Robo2	*Roundabout homolog 2* (SLIT2 receptor)	*Robo2*$^{-/-}$ mice carrying ROBO2 mutations/variants have vesicoureteral reflux	Ectopic and supernumerary UB	[126–128]
SALL1/Sall1	*SAL-like 1* (transcription factor)	Heterozygous mutations in *SALL1* in cause Townes-Brocks syndrome with renal involvement. Mice deficient for Sall1 have renal agenesis or severe dysgenesis	Disruption of UB initiation	[129–131]
SIX1/Six1	*SIX homeobox 1* (transcription factor)	*SIX1* mutations cause certain types of bronchio-oto-renal syndrome. Mice deficient for *Six1* lack kidneys	Failure of UB invasion into MM	[132, 133]
SIX2/Six2	*SIX homeobox 2* (transcription factor)	Mice deficient for *Six2* have severe renal hypoplasia	Premature and ectopic differentiation of mesenchymal cells into epithelia; depletion of the progenitor cell population within the MM	[43, 134, 135]
Shh	*Sonic hedgehog* (secreted signaling molecule)	*Hoxb7-Cre*$^{T/+}$; *Shh*$^{flox/flox}$ mice (*Shh*$^{-/-}$ in UB derivatives): hydroureter and hydronephrosis	Mesenchymal proliferation, SMC differentiation	[136]
Slc12a1	*Solute carrier family 12, member 1.* Same as *Nkcc2* – (sodium–potassium–chloride cotransporter)	*Nkcc2*$^{-/-}$ mice: polyuria and hydronephrosis of varying severity	Possibly by polyuria overwhelming the pyeloureteral peristaltic machinery	[137]
Slit2	*Slit homolog 2* (ROBO2 ligand)	*Slit2*$^{-/-}$ mice: hydroureter and hydronephrosis	Ectopic and supernumerary UB	[126]
Smad4	*MAD homolog 4* (TGF-β signal transducer)	*Bmp7-Cre*$^{T/+}$; *Smad4*$^{flox/flox}$ mice: hydronephrosis. *Tbx18-Cre*$^{T/+}$; *Smad4*$^{flox/flox}$ mice: UPJO, hydroureter	Defective MM differentiation	[138, 139]
Spry1	*Sprouty homolog 1* (RTK/ERK antagonist)	*Spry1*$^{-/-}$ mice: hydroureter and hydronephrosis	Ectopic and supernumerary UB	[140]
Spry2	*Sprouty homolog 2* (RTK/ERK antagonist)	*Spry2*$^{-/-}$ mice: renal agenesis, hydroureter and hydronephrosis	Ectopic and supernumerary UB	[141]
Tbx18	*T-box transcription factor 18* (transcription factor)	*Tbx18*$^{-/-}$ mice: hydronephrosis, hydroureter and short ureters	Ureteral SM defects due to ureteric mesenchyme differentiation anomalies	[142]
Tensin	Same as *Tns1* (actin-binding protein)	*Tensin*$^{-/-}$ mice: cystic and hydronephrotic kidney at a few months of age	Unclear. May involve cell–cell, cell–matrix interaction	[143]
Tshz3	*Teashirt zinc finger family member 3* (transcription factor)	*Tshz3*$^{-/-}$ mice: hydronephrosis and hydronephrosis	Defects in ureteral SM differentiation	[144]
UpkII	*Uroplakin II* (glycolsylated transmembrane protein)	*UpkII*$^{-/-}$ mice: hydronephrosis, hydroureter, vesicoureteral reflux	Urothelial hyperplasia may block the urinary path. Alternatively, the urothelium defects may affect SM development	[115]
UpkIIIA	*Uroplakin III* (glycolsylated transmembrane protein)	*UpkIII*$^{-/-}$ mice: hydronephrosis, hydroureter, vesicoureteral reflux	Urothelial hyperplasia may block the urinary path. Alternatively, the urothelium defects may affect SM development	[145]
Wnt4	*Wingless-type MMTV integration site family, member 4* (secreted signaling protein)	Mice deficient for *Wnt4* have renal agenesis and hypoplasia	Failure in mesenchymal to epithelial transition	[146, 147]

Table 2. (continued)

Gene/allele symbols	Gene names and functions	Defects in human patients and animal models	Likely mechanism	References
Wnt9b	*Wingless-type MMTV integration site family, member 9b (secreted signaling protein)*	Mice deficient for *Wnt9b* have renal agenesis and hypoplasia	Defective early inductive response in MM	[148]
Wnt11	*Wingless-type MMTV integration site family, member 11 (secreted signaling protein)*	Mice deficient for *Wnt9b* have renal hypoplasia	Defects in branching morphogenesis	[149]

There are many more genes than those listed involved in congenital anomalies of the kidney and urinary tract. The information presented in this table is not meant to be complete but is an example of genes known to be involved in various types of kidney and urinary tract anomalies. We apologize to the many researchers whose work is not cited in this table due to space constraints. SMC, smooth muscle cells; BMP, Bone morphogenetic protein; YAC, yeast artificial chromosome.

Table 3. Human gene mutations, associated syndromic and nonsyndromic CAKUT and potential developmental processes contributing to the phenotype

CAKUT phenotype	Developmental process affected	Genes and genetic mechanism
Agenesis	Wolffian duct growth, pre-UB development	Autosomal dominant: *LIM1, PAX2, PAX8, GATA3, EYA1, FOXC1, RET* [5, 7, 8, 25, 150–157]
Ectopic ureters, duplex collecting system, dysplasia	Maintaining single UB	Autosomal dominant: *RET, GDNF, ROBO2, LIM1, GATA3, EYA1, BMP4* [5, 7, 8, 25, 150–152, 154, 155]
Agenesis, hypoplasia	UB induction	Autosomal dominant: *RET, GDNF, SALL1, SIX1* [5, 7, 8, 25, 150–152, 154]
		Autosomal recessive: *ITGA8* [158]
Hypoplasia, dysplasia	Branching morphogenesis, nephrogenesis	Autosomal dominant: *RET, WT1, PAX2, GDNF, BMP7, SALL1, HNF1B, MKS1, MKS2, BMP4, GLI3, SIX2, DHCR7, SIX1, SIX5, MYOG, DSTYK, WNT4, SOX17, UPK3A* [5, 7, 8, 25, 150–157]
		Autosomal recessive: *FRAS1, FREM1, FREM2, ITGA8, AGT, AGTR1* [5, 7, 8, 25, 150–152]
		Genomic disorders: 4P deletion, rare CNVs (16p13, 17q12, 22q11 and others) [159–161]
		X-linked: *KAL1, GPC3* [5, 7, 8, 25, 150–152]
Ureter defects (vesicoureteral reflux, UPJO, ureterocele)	Ureter maturation, Wolffian duct–cloaca fusion	Autosomal dominant: *RET, GREM1, EYA1, ROBO2, PAX2, UPK3A, NF1A, AT* [5, 7, 8, 25, 150–157]
		Genomic disorders: rare CNVs [159–161]
		X-linked: *AGTR2* [24, 35]

or even asymmetrically to one side of the body. The fusion may also affect rotation of the kidney. These changes can lead to tortuous ureters, predisposing to urinary tract obstruction and subsequent kidney damage. Major subtypes of positional anomalies include the following.

Horseshoe kidneys. Horseshoe kidneys are the most common fusion abnormality (1/400), resulting from abnormal positioning of the mesenchyme or the WDs. The fusion tends to affect the normal ascent of the kidneys to the upper abdomen. The kidney parenchyma may be histologically normal unless affected by reflux or obstruction during development.

Crossed fused renal ectopia. In this second most common position anomaly (1/2000), the kidney has crossed the midline and fused with the contralateral kidney. The crossed kidney is usually smaller compared with the orthotopic kidney.

Ectopia. Ectopic kidneys are not located in the renal fossa. Ectopia can be simple (ipsilateral to the pelvis) or crossed (contralateral to the ureter entry site into the bladder) [175]. This could be due to defects in ascent or an abnormal UB budding site. The incidence of simple ectopia in clinical settings is 1/ 10 000, but it is much higher in autopsies (1/1000). Solitary

crossed renal ectopia is much rarer (1/1 500 000) and the ureter crosses over and lies contralateral to its entry site into the bladder. Ectopia and fusion defects may coexist, such as in pelvic horseshoe kidneys.

Malrotation. Malrotated kidneys are abnormally rotated along their long axis. These could be due to a failure of medial rotation during ascent. As a result, the hilum is often facing anteriorly. The incidence rate is 1/500. Malrotated kidneys usually do not cause any symptoms unless accompanied by other anomalies.

Hydronephrosis

Hydronephrosis is distension and dilatation of the renal pelvis and calyces, usually caused by interruption of the free flow of urine away from the kidney. Lower urinary tract defects may block the urinary path or affect pyeloureteral peristalsis for effective urine transport, leading to hydronephrosis [176]. Defects within the kidney, such as urine concentration problems, can lead to severe polyuria that overwhelms the pyeloureteral peristalsis, leading to eventual disruption of urinary flow. Cystinuria can lead to kidney stones, which can both block urine outflow and affect ureteral peristalsis, leading to obstruction [177–179]. Thus hydronephrosis is the outcome of direct
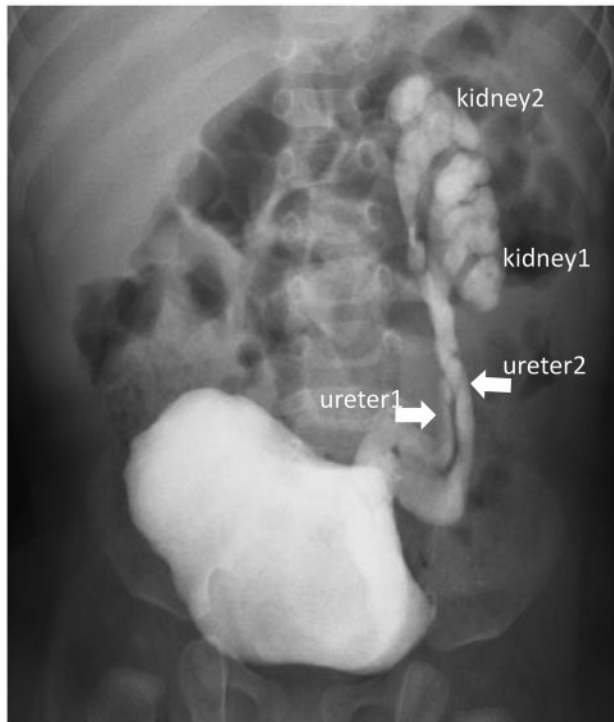
FIGURE 4: VCUG depicts complete duplication of the urinary system. The primary ureter (ureter1) inserts higher in the bladder and drains the lower kidney (kidney1). The dilated ureter2 inserts much lower in the bladder and drains the upper kidney (kidney2). Duplication can arise from failure to repress ectopic budding from the Wolffian duct or multiple UB inductions during metanephros development.

and indirect effects of conditions affecting the urinary conduit and is not a distinct disease entity by itself.

Obstructive nephropathy and obstructive uropathy

Persistence of hydronephrosis can result in tubular atrophy, inflammation and fibrosis (Figure 6) [180–182]. These pathological changes are collectively referred to as 'obstructive nephropathy' and 'obstructive uropathy'. These terms have similar meanings, with slight emphasis on pathological changes within the kidney (obstructive nephropathy) or with additional reference to involvement of the lower urinary tract (obstructive uropathy). Damage to kidney architecture and function by urinary tract obstruction is especially devastating to the developing kidneys. Even mild prenatal urinary tract obstruction can greatly affect the number of nephrons formed. Severe prenatal urinary tract obstruction can lead to the arrest of kidney development and total loss of its function. In fact, congenital obstructive nephropathy is the most common cause of chronic kidney diseases in the pediatric population. Elevated hydrostatic pressure associated with obstruction results in radial dilatation of the tubules and ducts, leading to increased epithelial apoptosis and tubular atrophy, and causes a reduction in the glomerular filtration rate. Infiltration of immune cells has been frequently reported as obstructive nephropathy progresses. Disruption of the renal architecture usually correlates with the increased severity of fibrosis [183–185]. Complete obstruction of the urinary tract is relatively rare, but when it happens, timely intervention to release the obstruction is critical for preserving kidney function. Partial obstruction is more common in the clinical setting and even partial obstruction can lead to progressive obstructive

nephropathy, ESRD and mortality, especially when obstruction is bilateral.

Ureteropelvic junction obstruction

Ureteropelvic junction obstruction (UPJO) is the junction between the kidney pelvis and the ureters. UPJO is defined as an obstruction of urine flow through the UPJ, causing progressive renal damage (Figure 7) [186, 187]. UPJ is a location where progenitor cells of different embryonic origins coalesce to form the ureter muscular layer. Due to its anatomical position and the complexity of the integration of separate progenitor cell populations, UPJO accounts for ∼50% of all antenatal hydronephrosis cases and is the most common cause of congenital obstructive nephropathy [186, 187]. Approximately, 1/100 pregnancies show fetal upper urinary tract dilation by ultrasound. Although most of these dilatations resolve spontaneously, 1/500 remains clinically significant. UPJO occurs far more frequently in males than in females (3–4:1) and more frequently on the left side. Crossing blood vessels in some patients can also cause UPJO. Currently surgical intervention remains the only option for UPJO due to intrinsic causes. In children, the procedure of choice is an Anderson–Hynes dismembered pyeloplasty in which the obstructed segment is resected and the remaining ureter is reanastomosed.

Vesicoureteral reflux

Vesicoureteral reflux (VUR) is the retrograde flow of urine from the bladder to the ureter [188]. VUR is generally diagnosed by the retrograde flow of radioopaque contrast material during a voiding cystourethrogram (VCUG) (Figure 8) [189, 190]. VUR has been observed in ∼0.1–1% of children [191–193]. This may be underestimated due to limited use of the invasive VCUG [194]. Although many patients with VUR show no kidney injury, other VUR patients develop RN, with pathological changes in advanced stages similar to obstructive nephropathy. As much as 8% of ESRD may be caused by VUR [188]. The pathophysiology of RN may be different than obstructive nephropathy, and early stages show segmental scarring of the renal parenchyma due to the propensity of reflux to damage superior and inferior lobes of the kidney. This is because these regions have compound papillae with a round orifice that facilitates retrograde flow. If untreated, the adjacent simple papillae transform into compound papillae and gradually affect the entire kidney. The scarred regions show thinning of the overlying cortex. If VUR is the only urinary tract anomaly found, then it is referred to as primary VUR. VUR is often associated with, and likely secondary to, other types of urinary tract defects, such as neurogenic bladder, posterior urethral valves (PUV) or ureterocele [195–197]. VUR can also occur as part of extrarenal syndromes [194]. VUR is frequently associated with urinary tract infection (UTI). UTIs in the setting of VUR may affect kidney function by providing access to bacteria from the bladder into the ureter and kidney and causing scarring (RN). By VCUG, ∼25–40% of screened children with UTI have VUR [198].

Ureterovesical junction obstruction and hydroureter

The ureterovesical junction (UVJ) is the site where the ureter enters the bladder. Back pressure associated with physical obstruction at the UVJ usually causes dilatation of the ureter (hydroureter or megaureter) and eventually hydronephrosis. Although less common than UPJO, persistent UVJ obstruction (UVJO) is as damaging to kidney function as UPJO. UVJO can be
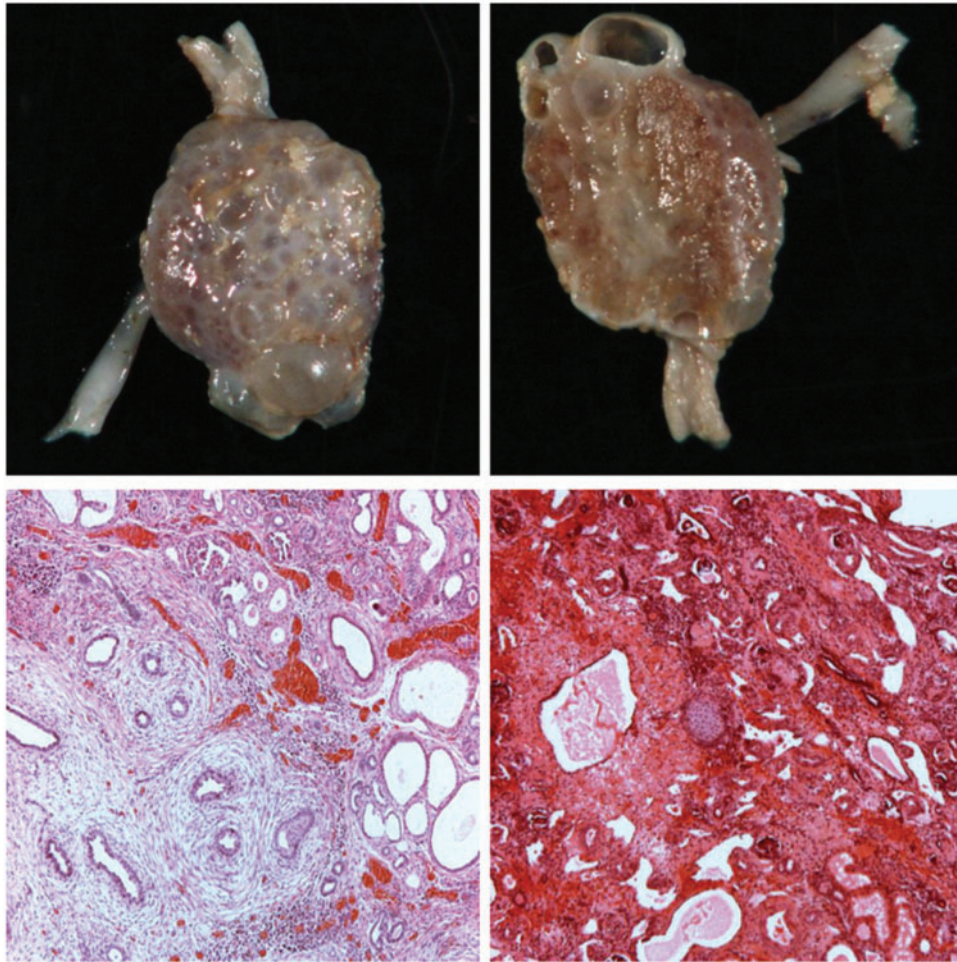
FIGURE 5: Renal dysplasia. **(A)** Gross morphology of cystic dysplastic kidneys. The image on the left shows the irregular shape of the entire kidney and the image on the right is the cut surface showing multiple cysts and no organization. **(B)** Histology of renal dysplasia. Both images show no normal renal structures or organization into cortex, medulla and papillae. Numerous cysts are scattered in the kidney. The image on the left highlights collecting ducts in the center surrounded by concentric immature mesenchymal cells (arrows). The image on the right additionally has cartilage (white arrow) in the center that can be seen in about a third of dysplastic kidneys. Dysplasia can arise from abnormal UB budding or branching morphogenesis and nephrogenesis.
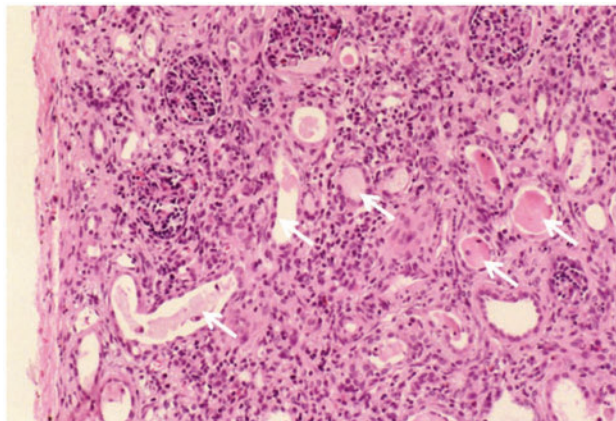
FIGURE 6: Obstructive nephropathy. Hematoxylin and eosin–stained section of a kidney from a patient with long-standing urinary tract obstruction shows significant kidney damage. Note that several tubules are dilated with no epithelial lining, thus showing atrophy (arrows). A number of the tubules show proteinaceous eosinophilic material representative of end-stage nephrons. Also note the intense inflammatory infiltrate involving almost the entire parenchyma.

caused by a poorly peristalsing ureteral segment near the bladder, abnormal insertion of the ureter into the bladder, a short intravesical ureteral segment, infection, scar tissues, kidney stones and other factors. If an obstructed segment or anatomic ureteral anomalies are present, then resection of the affected segment and refitting the ureter into the bladder is the current treatment option.

Ureterocele, ectopic ureter and duplicated ureter

Ureterocele is a saccular dilation of the terminal portion of the ureter inside the bladder (Figure 9) [176, 199]. The clinical effects of ureteroceles range from being asymptomatic to causing urinary tract obstruction and kidney damage. The normal site of ureter entry into the bladder is near the base of the bladder. The bladder trigone (a thickened muscular pad on the back of the bladder) helps to secure the intravesical segment of the ureter to prevent kinking and reflux. An abnormal ureter entry site and angle tend to nullify the function of the trigone, leading to reflux or obstruction. In rare cases, the distal ureter connects to the reproductive organs, such as the uterus, the vagina or the

FIGURE 7: Hydronephrosis and obstruction. The radiographic image shows diffuse dilation of the collecting system with dilated pelvis (arrow) due to lower urinary tract obstruction. Obstruction can result from functional or physical abnormalities that are intrinsic or extrinsic to the urinary system.
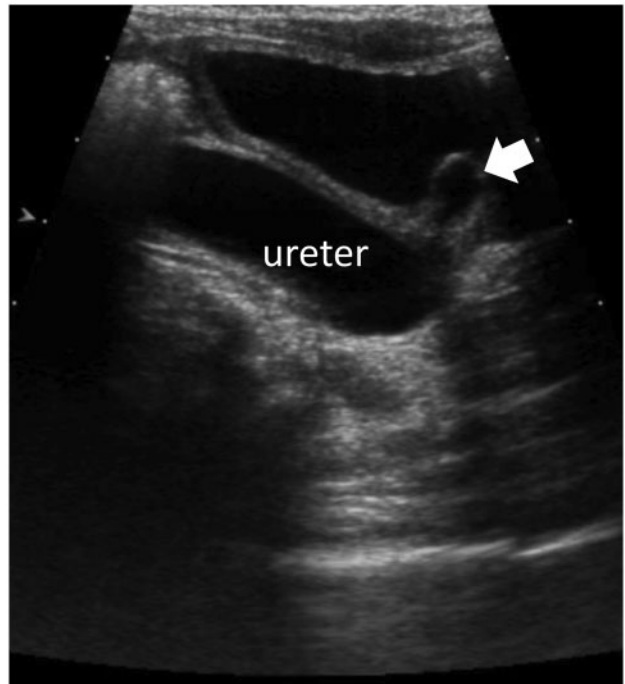

FIGURE 8: Vesicoureteral reflux (VUR). Vesicoureterocystogram shows high-grade (Grade 5) VUR. Note the dilated, tortuous ureter, with reflux involving the kidney parenchyma, highlighted by the white dye almost spanning each kidney. Primary VUR is due to abnormal development of the ureterovesicle junction so that the valve mechanism to prevent reflux from the bladder into the ureter does not function normally.

FIGURE 9: Ureterocele. The lower abdominal and pelvic ultrasonograph shows a ureterocele (arrow). Note the clear blind ending ureterocele lining (arrow) connected to the dilated ureter (long hypoechogenic tube).

FIGURE 10: Posterior uretheral valves (PUV). The radiograph shows classic findings of PUV in a male child. Note the extreme narrowing of the urethra (arrow) due to persistent valves that lead to a dilated bladder with irregular surface (trabeculations).
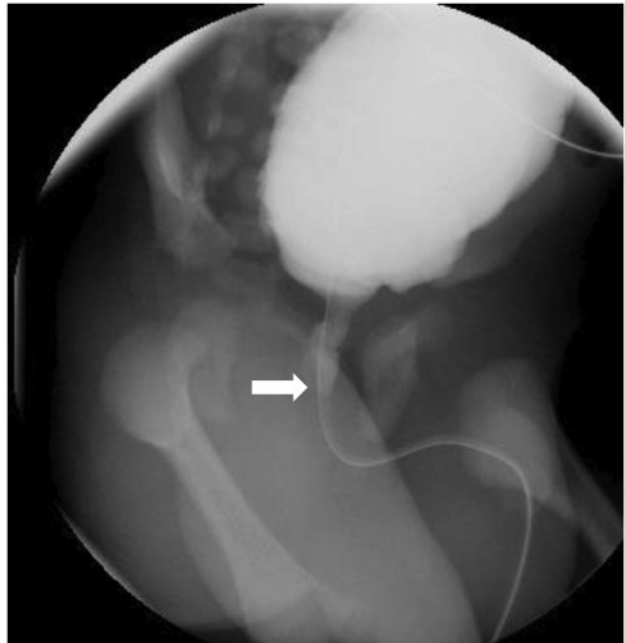
epididymis [200–203]. The resulting fistulae between the ureter and the reproductive organs tend to be obstructed, leading to hydroureter, hydronephrosis and kidney damage.

Bladder outlet obstruction and posterior urethral valves

Bladder outlet obstruction is the blockage of urine passage from the bladder to the urethra caused by benign prostate hyperplasia, bladder tumor, bladder stones, PUV or other causes. PUV, a congenital blockage of the posterior urethra [204, 205], is a common cause of urinary tract obstruction in male infants, with an estimated incidence rate of 1/5000–8000 male births and may account for 10% of all prenatally detected hydronephrosis [206–208]. PUVs can cause bilateral kidney damage, kidney failure and even death. It is one of the leading causes of kidney failure

in children. PUV is typically detected by prenatal ultrasound and subsequently diagnosed definitively after birth. Fetuses with PUV can have bilateral hydroureter/hydronephrosis with a thick trabeculated bladder wall and keyhole sign in the bladder neck (Figure 10). A VCUG and/or cystoscopic evaluation can be

used to demonstrate the presence of the 'valves' or 'membranes' that block urine passage. Although a bladder catheter can provide immediate relief, endoscopic ablation can be performed to permanently correct the defects.

CONCLUSIONS

A prominent feature of the development of the urinary system is the dynamic temporal and spatial integration of progenitor tissues of distinct embryonic origins. Such integration requires precise control of proliferation, apoptosis, migration and differentiation of all the progenitor cells involved to create junctional complexes, which if malformed result in bottlenecks for urine passage [9]. Research in animal models, especially transgenic mouse models, has contributed to a better understanding of the genetic factors and mechanisms of the pathogenesis of CAKUT (Table 2) that help us understand the genotype–phenotype association and mechanism in CAKUT patients (Table 3). Of note, many CAKUT cases have a developmental basis even before the metanephric kidney begins to develop. A deeper understanding of the embryonic processes underlying normal and abnormal development of the urinary tract will inform potential targetable therapies with small molecules and provide necessary knowledge to build kidneys that can be transplanted into patients. Genetic studies have taught us that CAKUT is a genetically heterogeneous disorder and the phenotype is influenced by gene interactions and epigenetic pathways. A major challenge in patient care is determining the pathogenicity of potentially deleterious variants identified in patients. Advances in the field of genome editing and induced pluripotent cell-derived kidney organoids will surely overcome this hurdle in the near future and ultimately bring precision medicine to patients with CAKUT.

CONFLICT OF INTEREST STATEMENT

None declared. The content presented in this article has not been published previously in whole or part.

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