Chapter 1
Congenital Anomalies of the Kidney and Urinary Tract: An Overview

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Abbreviations

CAKUT	*C*ongenital *a*nomalies of the *k*idney and *u*rinary *t*ract
CKD	Chronic kidney disease
ESRD	End-stage renal disease
VCUG	Voiding cystourethrogram
VUR	Vesicoureteral reflux

Introduction

Congenital anomalies of the kidney and urinary tract (CAKUT) are the most common cause of all birth defects, constituting 23 % of all such defects [1]. As a group, CAKUT are the cause of 30–50 % of all cases of end-stage renal disease (ESRD) in children [2]. Further, they are the most frequent malformations detected by ultrasound in utero [3]. Lower urinary tract abnormalities can be identified in approximately 50 % of affected patients and include vesicoureteral reflux (VUR) (25 %), ureteropelvic junction obstruction (11 %), and ureterovesical junction obstruction (11 %) [4]. Renal malformations, other than mild antenatal pelviectasis, occur in association with non-renal malformations in about 30 % of cases [3]. This chapter is an overview of issues related to the etiology, pathobiology, diagnosis, and clinical management of CAKUT and serves as a foundation for more detailed presentation in subsequent chapters.

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Clinical Classification

Renal–urinary tract malformations are classified under the rubric *c*ongenital *a*nomalies of the *k*idney and *u*rinary *t*ract (CAKUT). An overarching classification for these malformations was proposed due to recognition that (1) multiple structures within one or both kidney–urinary tract units may be affected within any given affected individual, (2) mutation in a particular gene is associated with different urinary tract anomalies in different affected individuals, and (3) mutations in different genes give rise to similar renal and lower urinary tract phenotypes. Within the CAKUT rubric, a spectrum of phenotypes exist ranging from aplasia (agenesis), defined as congenital absence of kidney tissue; to simple hypoplasia, defined as renal length <2 s.d. below the mean for age and normal renal architecture; dysplasia ± cysts, defined as malformation of tissue elements; and isolated dilatation of the renal pelvis ± ureters (collecting system). Any malformation phenotype can be observed for a kidney in an orthotopic (normal) position or an ectopic kidney.

Pathogenesis of CAKUT

Genetic Mechanisms

The genetics of CAKUT are complex (Refer to Chap. 15). The incidence of gene mutations in patients with CAKUT is unknown since population-based genome-wide sequencing studies are only now being performed. In the majority of affected patients, congenital renal malformations occur as sporadic events. In approximately 30 % of affected individuals, CAKUT occurs as part of a multiorgan genetic syndrome. Over 200 distinct genetic syndromes feature some type of kidney and urinary tract malformation. More than 30 genes have been identified as mutant in multiorgan syndromes with CAKUT (Table 1.1). Incomplete penetrance with variable expressivity is frequent in affected families. Studies of patients with CAKUT but without evidence of a multiorgan syndrome indicate that a minority of such patients will manifest mutations in genes which have been associated with genetic syndromes. For example, a study in which a small number of genes were examined in 100 patients with renal hypodysplasia and renal insufficiency demonstrated a gene mutation in genes including *TCF2* and *PAX2* in 16 % of affected individuals [5]. Some of the mutations were de novo mutations, explaining the sporadic appearance of CAKUT. Careful clinical analysis of patients with *TCF2* and *PAX2* mutations revealed the presence of extrarenal symptoms in only 50 %, supporting previous reports that *TCF2* and *PAX2* mutations can be responsible for isolated renal tract anomalies or at least CAKUT malformations with minimal extrarenal features [6, 7]. It is not uncommon for first-degree relatives of individuals with bilateral renal agenesis or bilateral renal dysgenesis and without evidence of a genetic syndrome or a family history to have ultrasound evidence of a renal–urinary tract malformation of some type. Studies have suggested an incidence ranging from 9 to 23 % [8, 9].

Table 1.1 Human gene mutations associated with syndromic CAKUT

Primary disease	Gene	Kidney phenotype
Alagille syndrome	*JAGGED1*	Cystic dysplasia
Apert syndrome	*FGFR2*	Hydronephrosis
Beckwith–Wiedemann syndrome	*p57^{KIP2}*	Medullary dysplasia
Branchio-oto-renal (BOR) syndrome	*EYA1*, *SIX1*, *SIX5*	Unilateral or bilateral agenesis/ dysplasia, hypoplasia, collecting system anomalies
Campomelic dysplasia	*SOX9*	Dysplasia, hydronephrosis
Duane-radial ray (Okihiro) syndrome	*SALL4*	UNL agenesis, VUR, malrotation, cross-fused ectopia, pelviectasis
Fraser syndrome	*FRAS1*	Agenesis, dysplasia
Isolated renal hypoplasia	*BMP4*, *RET*	Hypoplasia, VUR
Hypoparathyroidism, sensorineural deafness and renal disease (HDR) syndrome	*GATA3*	Dysplasia
Kallmann syndrome	*KAL1*, *FGFR1*, *PROK2*, *PROK2R*	Agenesis
Mammary–ulnar syndrome	*TBX3*	Dysplasia
Meckel-Gruber syndrome	*MKS1*, *MKS3*, *NPHP6*, *NPHP8*	Dysplasia
Nephronophthisis	*CEP290*, *GL1S2*, *RPGR1P1L*, *NEK8*, *SDCCAG8*, *TMEM67*, *TTC21B*	Dysplasia
Pallister–Hall syndrome	*GLI3*	Agenesis, dysplasia, hydronephrosis
Renal coloboma syndrome	*PAX2*	Hypoplasia, vesicoureteral reflux
Renal tubular dysgenesis	*RAS* components	Tubular dysplasia
Renal cysts and diabetes syndrome	*HNF1b* (*TCF2*)	Dysplasia, hypoplasia
Rubinstein–Taybi syndrome	*CREBBP*	Agenesis, hypoplasia
Simpson–Golabi–Behmel syndrome	*GPC3*	Medullary dysplasia
Smith–Lemli–Opitz syndrome	*7-Hydroxy-cholesterol reductase*	Agenesis, dysplasia
Townes–Brock syndrome	*SALL1*	Hypoplasia, dysplasia, VUR
Ulnar–mammary syndrome	*TBX3*	Hypoplasia
Zellweger syndrome	*PEX1*	VUR, cystic dysplasia

Embryologic Mechanisms

CAKUT arises from disrupted renal development. Formation of renal–urinary tract structures is initiated at 5-week gestation and concludes by about 34-week gestation. Here, the morphologic and genetic events that control kidney development are summarized. At 5-week gestation in humans, the ureteric duct is induced to undergo lateral outgrowth from the Wolffian duct and to invade the adjacent metanephric

mesenchyme. After invading the metanephric mesenchyme, the ureteric bud then undergoes repetitive branching events, so termed because each event consists of expansion of the advancing ureteric bud branch at its leading tip and division of the ampulla, resulting in formation of new branches and elongation of the newly formed branches. This process results in formation of approximately 65,000 collecting ducts. During the latter stages of kidney development, tubular segments formed from the first five generations of ureteric bud branching undergo remodeling to form the kidney pelvis and calyces [10].

Identification of genes mutated in humans with CAKUT coupled with analyses of genes expressed in the developing kidney and urinary tract has provided critical insights into the mechanisms that govern mammalian renal–urinary tract morphogenesis in health and disease. Here, examples of how the study of genes mutated in human CAKUT has informed our understanding of renal development are discussed as a framework for a more detailed discussion of such studies elsewhere in this book.

Outgrowth of a single ureteric bud in the correct position is a critical initial stage of renal development. Without this process, induction of the metanephric mesenchyme does not occur. The budding process is dependent on a signaling axis comprised of *Ret,* a proto-oncogene and tyrosine kinase receptor, and its ligand, *Gdnf*. RET is expressed on the surface of ureteric cells [11], while GDNF is expressed by metanephric mesenchyme cells [12]. Homozygous deletion of either *Ret* or *Gdnf* in mice causes failure of ureteric outgrowth and renal agenesis. Patients with CAKUT have mutations in the RET/GDNF signaling pathway [13–16]. A study of 122 patients with CAKUT identified heterozygous deleterious sequence variants in *GDNF* or *RET* in 6/122 patients, 5 %, while another group screened 749 families from all over the world and identified three families with heterozygous mutations in RET [13]. Similar findings have been reported in studies of fetuses with bilateral or unilateral renal agenesis [14, 16].

The site of ureteric bud outgrowth from the Wolffian duct is normally invariant and the number of outgrowths is limited to one. Outgrowth of more than one ureteric bud can result in renal malformations including a double collecting system and duplication of the ureter. The position at which the ureteric bud arises from the Wolffian duct relative to the metanephric mesenchyme influences the interactions between the ureteric bud and the metanephric mesenchyme; ectopic positioning of the ureteric bud is associated with renal dysplasia and is also thought to contribute to the integrity of the ureterovesical junction. Mackie and Stephens postulated [17] that an abnormal position of the ureteral orifice in the bladder is associated with vesicoureteral reflux in humans. This hypothesis is supported by the discovery that mutations in *ROBO2*, a cell surface receptor expressed in the metanephric mesenchyme, are associated with vesicoureteral reflux in humans [18, 19]. Mice deficient in *Robo2* exhibit ectopic ureteric bud formation, multiple ureters, and hydroureter [20].

Branching of the ureteric bud is initiated immediately following invasion of the metanephric mesenchyme by the ureteric bud. The number of ureteric bud branches elaborated is considered to be a major determinant of final nephron number since each ureteric bud branch tip induces a discrete subset of metanephric mesenchyme cells to undergo nephrogenesis. Regulation of ureteric branch number has been

informed by complementary studies in humans and mice. Mutations in *PAX2* cause renal coloboma syndrome (also named papillo-renal syndrome), an autosomal dominant disorder characterized by the association of renal hypoplasia, vesicoureteric reflux, and optic nerve coloboma [21]. During renal development, *Pax2* is expressed in the Wolffian duct, the ureteric bud, and the metanephric mesenchyme. Studies in the *1Neu* mouse strain, which is characterized by a *Pax2* mutation, demonstrated decreased ureteric branching in association with decreased nephron number. Decreased ureteric branch number and nephron number are rescued by inhibition of apoptosis in the ureteric lineage [22, 23]. Studies in normal term newborns suggest that loss of PAX2 function may also contribute to generating a lower number of nephrons within the range of nephron number (approximately 250,000–1,600,000) observed in humans [24]. Goodyer hypothesized that gene polymorphisms that generate loss of PAX2 function could contribute to mild reductions in nephron number and discovered that a *PAX2* haplotype ($PAX2^{AAA}$) is associated with an approximately 10 % decrease in kidney volume in a cohort of newborn infants [25].

As discussed above, GDNF expression by metanephric mesenchyme cells is critical to ureteric branching. In the metanephric mesenchyme, *Sall1, Eya1,* and *Six1* positively control *Gdnf* expression. *Sall1*, a member of the Spalt family of transcriptional factors [26], is expressed in the metanephric mesenchyme prior to and during ureteric bud invasion. Mutational inactivation of *Sall1* in mice causes renal agenesis or severe dysgenesis and a marked decrease in GDNF expression [27]. Mutations in *SALL1* are associated with Townes–Brock syndrome, an autosomal dominant malformation syndrome characterized by imperforate anus, preaxial polydactyly and/or triphalangeal thumbs, external ear defects, sensorineural hearing loss, and, less frequently, kidney, urogenital, and heart malformations [28, 29]. EYA1, a DNA-binding transcription factor, is expressed in metanephric mesenchyme cells in the same spatial and temporal pattern as GDNF. EYA1 functions in a molecular complex with SIX1 [30] to control expression of *Gdnf* [31]. Both EYA1 and SIX1 are also expressed in developing otic and branchial tissues [32, 33]. Mice with EYA1 deficiency demonstrate renal agenesis and failure of GDNF expression [32]. Mutations in *EYA1* and *SIX1* occur in humans with branchio-oto-renal (BOR) syndrome [30, 34], which consists, in its classic form, of conductive and/or sensorineural hearing loss, branchial defects, ear pits, and renal anomalies [35, 36]. Renal malformations include unilateral or bilateral renal agenesis, hypodysplasia, as well as malformation of the lower urinary tract including vesicoureteral reflux, pyeloureteral obstruction, and ureteral duplication.

While the genome was originally conceived as consisting of two copies of each gene, the situation is more complex. Within the genome, there exist stretches of DNA that exist in less than or more than two copies. These genomic regions are termed copy number variants (CNV) and are defined as stretches of DNA that are larger than 1kb in length. Rare CNVs, that is, CNVs that are detected with a very low frequency in a human population, have recently been implicated in syndromes with CAKUT [37, 38]. For example, Sanna-Cherchi et al. examined the frequency of rare CNVs in individuals with CAKUT and identified such variants in 10 % of affected individuals compared to 0.2 % of population controls [38]. Deletions at the *HNF1* locus (chro-

mosome 17q12) and the locus for DiGeorge syndrome (chromosome 22q11) were most frequently identified, suggesting these are "hotspots" for copy number variation. Interestingly, 90 % of the CNVs associated with congenital renal malformations were previously reported to predispose to developmental delay or neuropsychiatric disease, suggesting that there are shared pathways implicated in renal and central nervous system development. Similarly, Handrigan et al. demonstrated that copy number variants at chromosome 16q24.2 are associated with autism spectrum disorder, intellectual disability, and congenital renal malformations [37].

Mechanisms Related to the Environment and Exposures in Utero

A substantial body of evidence, derived from human epidemiological studies and animal models, demonstrates an important role for the intrauterine environment in the pathogenesis of renal hypoplasia and predisposition to later kidney disease (reviewed in [39]). Renal hypoplasia with low nephron number is associated with low birth weight or intrauterine growth retardation (IGUR) and maternal undernutrition in animals [40, 41]. While the underlying mechanisms are not well defined, there is some evidence suggesting that the maternal diet programs the expression of critical genes required for embryonic kidney development, cell survival, and renal function [42–44].

Maternal diabetes is associated with renal hypoplasia in the absence of reduced birth weight. In animal models, offspring of hyperglycemic or diabetic mothers demonstrate a significant nephron deficit [45]. In utero exposure to drugs and alcohol has also been associated with renal hypoplasia. Maternal intake of angiotensin-converting enzyme inhibitors during the first trimester in humans is associated with an increased risk of renal dysplasia as well as cardiovascular and central nervous system malformations [46]. Human infants exposed to cocaine in utero have an increased risk of renal tract anomalies [47]. Similarly, infants with fetal alcohol syndrome have a higher incidence of CAKUT [48].

Diagnosis of CAKUT in Utero

The human kidney does not exhibit a capacity to accelerate the rate of nephron formation in children born prematurely or to extend the period of nephrogenesis beyond the equivalent of 34-week gestation [49]. Thus, the integrity of nephron formation in utero is absolutely critical to postnatal life. The number of functional nephrons formed by 32–34-week gestation has been implicated in short- and long-term renal function. Infants with a moderate to severe degree of hypodysplasia exhibit renal insufficiency. A more subtle deficiency in nephron number has been

associated with adult-onset hypertension [50], consistent with the "Barker hypothesis," which is based on epidemiologic evidence showing a correlation between birth weight and the incidence of cardiovascular diseases and proposes that adult-onset diseases such as hypertension have a fetal origin [51, 52]. Growth of renal tubules and expansion of glomerular cross-sectional area in utero and after birth is critical to renal functional capacity. The observation in animal models that tubule number, cross-sectional area, and cellular maturation are abnormal in renal dysgenesis is consistent with clinical observations that infants with moderate to severe renal hypoplasia or dysplasia demonstrate a limitation of GFR and tubular function.

The widespread use and 80 % sensitivity of fetal ultrasound in identifying renal–urinary tract anomalies has led to the frequent diagnosis of these anomalies in utero [53]. The fetal kidney can be visualized at 12–15 weeks of human gestation. Corticomedullary differentiation is distinct by 25 weeks of gestation and sometimes earlier. The fetal ureters are not normally detected by ultrasound. Visualization of ureters may be indicative of ureteric or bladder obstruction, or VUR. A urine-filled bladder is normally identified at 13–15-week gestation [54]. Development of the kidney in utero is commonly assessed using fetal renal length standardized for gestational age as a surrogate marker [55]. The volume of amniotic fluid is a surrogate measure of renal function. Fetal urine production begins at 9 weeks of gestation. By 20-week gestation and thereafter, fetal urine is the primary source of amniotic fluid volume [56]. A decrease in amniotic fluid volume, termed oligohydramnios, at or beyond the 20th week of gestation is an excellent indicator of a critical defect in both kidneys, for example, bilateral renal dysplasia (or a critical defect in one kidney where a solitary kidney exists), bilateral ureteral obstruction, or obstruction of the bladder outlet. Severe oligohydramnios in the second trimester can result in lung hypoplasia since an adequate amniotic fluid volume is critical for lung development [57].

Fetal urine is also used as a marker of kidney function in utero and after birth. Levels of sodium and beta-2-microglobulin in fetal urine decrease with increasing gestational age, while urine osmolality increases [58, 59]. Impaired resorption occurs in fetuses with bilateral renal dysplasia or severe bilateral obstructive uropathy, resulting in abnormal high urine levels of sodium and beta-2-microglobulin and high urine osmolality [60]. In general, sodium and chloride concentration greater than 90 meq/l (90 mmol/l), urinary osmolality greater than 210 mosmol/kg H_2O (210 mmol/kg H_2O), and urinary beta-2-microglobulin levels >6 mg/l raise concern as to postnatal renal prognosis [61, 62]. However, the predictive value of these indices is by no means 100 %, providing motivation for the development of other biomarkers to predict renal function. A recent study of fetuses with posterior urethral values demonstrates the promise of such approaches. Analysis of the fetal urine proteome in affected fetuses vs. controls generated a peptide profile that correctly predicted postnatal renal function with 88 % sensitivity and 95 % specificity in affected fetuses and was superior to fetal urine biochemistry and fetal ultrasound in this group of patients [63].

Clinical Sequelae and Management of CAKUT

Because CAKUT play a causative role in 30–50 % of cases of CKD in children [64], it is important to diagnose and initiate therapy to minimize renal damage, prevent or delay the onset of ESRD, and provide supportive care to avoid complications of ESRD. Counseling of families during pregnancy is a key element in the management of CAKUT. Coordinated consultation among professionals in the disciplines of obstetrics, pediatric nephrology, pediatric urology, and neonatology is critical. Consistent and clear clinical information regarding diagnosis and prognosis should be provided during pregnancy and after birth. The level of certainty regarding the severity of the diagnosis and prognosis has a major impact on decision-making during pregnancy and in the immediate postnatal period. To date, little evidence exists that relief of urinary tract obstruction in utero prevents the development of associated renal dysplasia or renal scarring. In contrast, insertion of a bladder–amniotic cavity shunt in the fetus with obstruction below the bladder neck can rescue oligohydramnios and pulmonary hypoplasia [65, 66]. Diagnostic and therapeutic management after birth should be anticipated via the coordinated actions of obstetricians, neonatologists, pediatric nephrologists, and pediatric urologists and should include an immediate assessment in the postnatal period of the need for specialized imaging, assessment of renal function, and management of nutrition and electrolytes.

After delivery, a detailed history and careful physical examination should be performed in all infants with an antenatally detected renal malformation. The examination should include the respiratory system to assess the presence of pulmonary insufficiency; the abdomen to detect the presence of a mass that could represent an enlarged kidney due to obstructive uropathy or multicystic dysplastic kidney or a palpable enlarged bladder, which could suggest posterior urethral valves; the ears, since outer ear abnormalities are associated with an increased risk of CAKUT; and the umbilicus, since a single umbilical artery is also associated with an increased risk of CAKUT.

In newborns with bilateral renal malformation, a solitary malformed kidney, or a history of oligohydramnios, an abdominal ultrasound is recommended within the first 24 h of life since an intervention such as decompression of the bladder with a transurethral catheter may be required. Newborn infants with unilateral involvement do not need immediate attention. In these infants, a renal ultrasound is generally performed after 72 h of age and within the first week of life. Ultrasound examination before 72 h of age may not detect collecting system dilatation since a newborn is relatively volume contracted during this period of time [67]. The serum creatinine estimates the extent of renal impairment and should be utilized when there is bilateral renal disease or an affected solitary kidney. The serum creatinine concentration at birth is similar to that in the mother (usually $\leq$1.0 mg/dl [88 μmol/l]). Thus, serum creatinine should be measured after the first 24 h of life. It declines to normal values (serum creatinine 0.3–0.5 mg/dl [27–44 μmol/l]) within approximately 1 week in term infants and 2–3 weeks in preterm infants.

Management of CAKUT is further guided by the characteristics of specific phenotypes.

Renal anomalies are frequently associated with collecting system abnormalities including VUR. Because of the frequent association of upper urinary tract anomalies including dysplasia and ectopy with a collecting system anomaly in the affected and in an apparently normal contralateral renal unit, a VCUG should be considered in such patients. A DMSA radionuclide scan can provide further information on the differential function of each kidney, which may be useful in management decisions regarding surgical interventions. Also refer to Chap. 14.

Clinical Outcomes of CAKUT

Clinical outcomes in CAKUT vary widely from no symptoms whatsoever to CKD, resulting in a need for renal replacement during a period ranging from the newborn period to the 4th and 5th decades of life. Risk factors for mortality during infancy and early childhood include coexistence of renal and nonrenal disease, prematurity, low birth weight, oligohydramnios, and severe forms of CAKUT (agenesis, hypodysplasia) [68]. In a case series of 822 children with prenatally detected CAKUT that were followed for a median time of 43 months, Quirino et al. reported a mortality of 1.5 % and morbidities including urinary tract infection, hypertension, and CKD in 29, 2.7, and 6 % of surviving children, respectively [69]. A faster rate of decline of renal function in patients with CAKUT and CKD has been associated with a urine albumin to creatinine ratio greater than 200 mg/mmol compared to less than 50 mg/mmol (eGFR: −6.5 ml/min/1.73 m^2/year vs. −1.5 ml/min/1.73 m^2/year), and with more than two (vs. <2) febrile urinary tract infections (eGFR −3.5 ml/min/1.73m^2 vs. −2 ml/min/1.73 m^2 year). A greater decline in eGFR occurs during puberty (eGFR: −4 ml/min/1.73 m^2/year vs. −1.9 ml/min/1.73m^2/year) [70]. A study examining the risk for dialysis in patients with CAKUT demonstrated a significantly higher risk for patients with a solitary kidney compared to non-disease controls [71]. These results raise the possibility that the prognosis for a solitary apparently normal kidney may not be as “normal” as previously thought. Finally, a study of CAKUT patients receiving some form of replacement therapy and registered within the European Dialysis and Transplant Association Registry showed that some of these patients only require renal replacement in the 3rd, 4th, or 5th decade of life. The finding that the mean age at which patients with CAKUT require dialysis and/or transplantation is 31 years indicates that children with CAKUT are at risk of developing a requirement for dialysis and/or transplantation as adults [72].

Conclusions

A majority of CAKUT can be identified in utero. However, the ability to predict the natural history of particular phenotypes is limited, and therapies, beyond surgical correction that treats the primary cause of these disorders, are nonexistent. New

developments in human genetics and rapid evolution of DNA sequencing technology provide a basis to identify genetic variants in affected individuals using tools such as next-generation genomic sequencing. The knowledge gained will inform new genotype–phenotype correlation and natural history studies and the development of nongenetic disease biomarkers. This, in turn, can provide a basis for biological signatures that inform the pathobiology of specific disorders, predict their natural history, and guide personalized therapy. Further, with such knowledge, it may be possible to design new interventions to extend the current repertoire of interventions which can be used to relieve or correct urinary tract obstruction but are otherwise limited in their ability to address tissue malformation at more fundamental level using regenerative medicine strategies.

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