DISEASE OF THE MONTH

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Evolving Concepts in Human Renal Dysplasia

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Abstract. Human renal dysplasia is a collection of disorders in which kidneys begin to form but then fail to differentiate into normal nephrons and collecting ducts. Dysplasia is the principal cause of childhood end-stage renal failure. Two main theories have been considered in its pathogenesis: A primary failure of ureteric bud activity and a disruption produced by fetal urinary flow impairment. Recent studies have documented deregulation of gene expression in human dysplasia, correlating with perturbed cell turnover and maturation. Mutations of nephrogenesis genes have been defined in multiorgan dysmorphic disorders in which renal dysplasia can feature, including Fraser, renal cysts and diabetes, and Kallmann syndromes. Here, it is possible to begin to understand the normal nephrogenic function of the wild-type proteins and understand how mutations might cause aberrant organogenesis.

Congenital anomalies of the kidney and urinary tract (CAKUT) account for one third of all anomalies detected by routine fetal ultrasonography (1). A recent UK audit of childhood end-stage renal failure reported that CAKUT was the cause in ~40% of 882 individuals (2). Acquired glomerulonephritis and congenital nephrotic syndromes, respectively, accounted for just 18% and 8% of cases, with other diseases being rare (nephronophthisis, 5%; cystinosis, 3%; polycystic kidney diseases [PKD], 3%). With improvements in dialysis and transplantation, a new cohort of children with severe CAKUT is surviving to adulthood (3,4). The spectrum of diseases encompassed by the term "CAKUT" is wide, including kidney anomalies such as aplasia, hypoplasia, multicystic dysplastic kidneys, ureteric anomalies such as megaureter, ureteropelvic junction obstruction, ureterovesical junction obstruction or incompetence, duplex kidneys/ureters, and anomalies of the bladder and urethra (5). Approximately half of the CAKUT cases associated with end-stage renal failure in children have patent urinary tracts, whereas the rest have obstructive nephropathy (2). The latter are mainly boys with bladder outflow obstruction (BOO) and posterior urethral valves (2,6). Some renal functional impairment may be superimposed postnatally from bacterial pyelonephritis and/or persistent urinary flow impairment causing renal atrophy and fibrosis. However, the primary "hit" in CAKUT is clearly a developmental one, and the main renal pathology is renal dysplasia (RD). In her landmark book *Normal and Abnormal Development of the Kidney* published in 1972 (7), Edith Potter emphasized that one must understand normal development to generate realistic hypotheses on the pathogenesis of congenital malformations. Here, we summarize normal human kidney development, using Potter's work (7) as a basis but also incorporating recent summaries (8,9).

The metanephric human kidney precursor forms 28 d after fertilization when ureteric bud (UB) branches from the mesonephric duct (MD). In the next few days, renal mesenchyme (RM) condenses from intermediate mesoderm around the UB tip, or ampulla. Ultimately, the UB lineage will form urothelium, from the renal pelvis to bladder trigone, and collecting ducts. Some RM cells undergo an epithelial conversion, through aggregation and lumen formation to form nephrons, whereas others form interstitial fibroblasts. The first 6 to 10 UB branch generations remodel, forming the pelvis and calyces, whereas the final 6 to 9 generations form collecting ducts. In humans, early UB divisions are not associated with nephrogenesis. The first nephrons are formed at 8 wk. As the ampullae divide between 8 and 15 wk, one branch continues to be associated with the already-attached nephron, whereas the other induces a new nephron. Although UB branching decelerates after 15 wk, nephrons are induced up to 32 to 36 wk. Between 15 and 20 wk, four to seven nephrons are serially induced by each nondividing ampulla; each nephron is transiently attached to an ampulla but then shifts its linkage to the connecting piece of the next-formed nephron. This results in "arcades" of nephrons. From 20 until 32 to 36 wk, elongating ampullae induce nephrons in series. Potter (7) noted that formation of a nephron always occurred near an ampulla, and Grobstein's studies in the 1950s demonstrated that murine RM did not form nephrons in organ culture when the UB was

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physically removed (10). It is now clear that RM and UB induction and differentiation depend on mutual interactions mediated by growth factors and matrix molecules, with transcription factors controlling expression of these genes (11). Potter estimated that a human kidney contained 35×10^4 nephrons at 20 wk gestation and 82×10^4 at 40 wk (7). More recent human studies suggest, however, that the majority of nephrons form in the final third of gestation and that final nephron number can be highly variable: Mean numbers range between 64×10^4 and 130×10^4 (12,13). Part of this variation, however, may be explained by different techniques used to assess glomerular number (13,14).

Human RD—Kidney Development Gone Wrong

Potter classified cystic kidneys into four categories on the basis of microdissection studies (7): Types I (autosomal recessive PKD) and III (mostly autosomal dominant PKD) do not feature RD. Potter divided RD malformations into types II and IV. Type II were termed multicystic dysplastic kidneys (MCDK) when they contain large cysts or aplastic when small. The dysplastic histology, however, is similar in both subtypes. It comprises lack of normal tissues (nephrogenic zone, glomeruli, and collecting ducts) combined with presence of primitive tubules surrounded by stroma, smooth muscle collars, metaplastic cartilage, dysmorphic nerves and vessels, and erythropoietic cells (Figure 1, A through D) (7,15–17). Clearly, these appearances fit into the CAKUT category, although probably representing the more severe end of the spectrum as they reached the pathologist. Potter thought that dysplastic tubules terminating in cysts represented early UB branches that would normally have formed the pelvis and calyces. Because she failed to observe significant numbers of normal glomeruli in type II kidneys, Potter reasoned that these organs could not produce urine and hence ruled out urinary flow impairment as a potential cause of RD. She therefore suggested that these malformations result from a primary defect of ampullary function, *i.e.*, the UB formed but normal branching and RM induction failed thereafter. Potter type IV malformations are invariably associated with urinary tract obstruction, usually BOO (7). Kidneys contain subcapsular cysts, each comprising a dilated Bowman's capsule and a primitive proximal tubule (Figure 1E); hence, cysts derive from forming nephrons ("S-shaped bodies"). Potter postulated that UB branching is initially normal in type IV malformations, with at least some filtering glomeruli generated. Only nascent nephrons became cystic because they were nearest to ampullae and experienced a "pressure (that) extends in a retrograde manner" from the obstructed lower tract; earlier nephrons located at the other end of arcades faced less "backpressure" and remained intact. Potter reasoned that a sudden, severe, obstructive event would rapidly ablate the RM, resulting in one layer of cysts, whereas a mild obstruction might allow RM to generate several generations of cysts.

Recent reports cast doubt on Potter's contention that all type

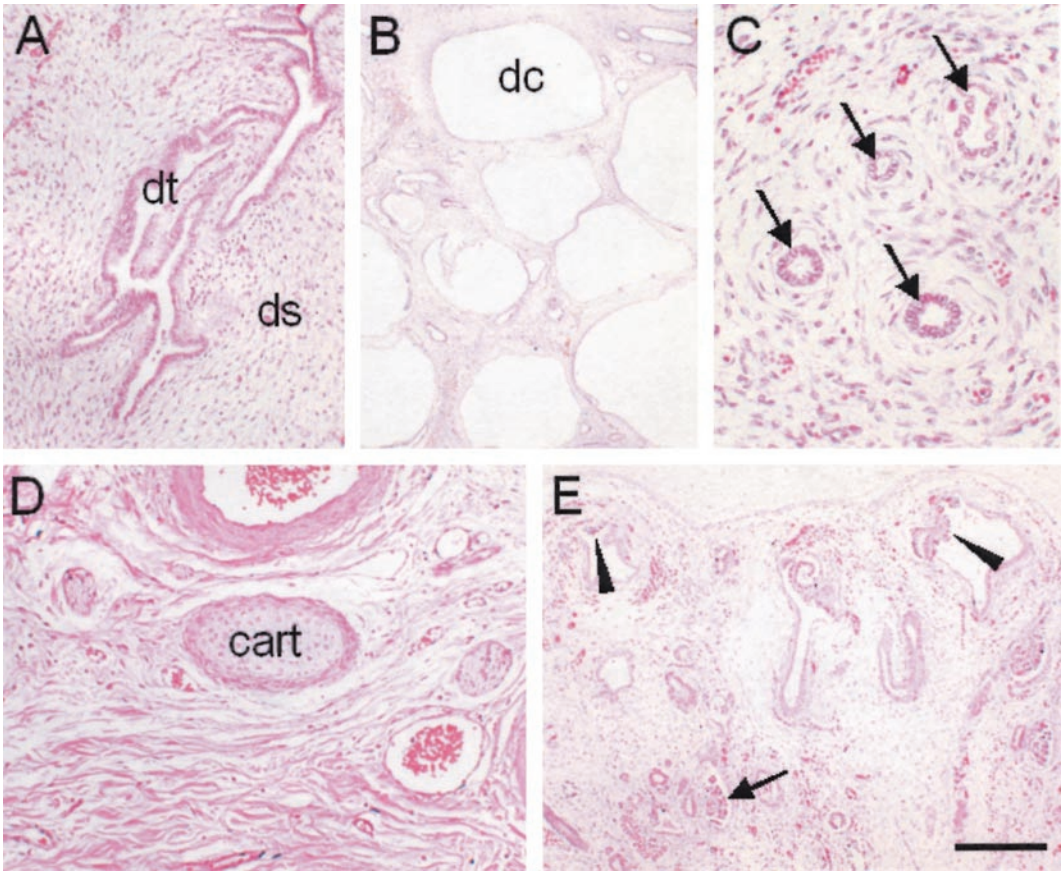

Figure 1. Histology of human renal dysplasia (RD). A through E are stained with hematoxylin and eosin; A through D are from postnatal samples with severe histologic RD, and E is from a midgestation fetus with bladder outflow obstruction. (A) RD is characterized by dysplastic tubules (dt) surrounded by stroma (ds). (B) Dysplastic cysts (dc) in multicystic dysplastic kidneys. (C) Dysplastic tubules (*arrows*) surrounded by fibromuscular collars. (D) Metaplastic cartilage (cart). (E) Cystic subcapsular glomeruli (*arrowheads*), with relative preservation of deeper, more mature, glomeruli (*arrow*). Bar = 40 μm in A, C, and D, and 200 μm in B and E.

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II malformations lack significant functional nephrons and thus represent an absolute primary failure of UB function. Matsell *et al.* (18) studied mid-trimester MCDK, reporting that disorganized tissues coexisted with relatively normal structures, including maturing glomeruli (which could be cystic, as in type IV malformations) and proximal tubules. Shibata *et al.* (19) made three-dimensional reconstructions of MCDK between 19 and 35 wk gestation, reporting that some cysts contained glomerular tufts. The two studies are consistent with the idea that some nephrons do form in fetuses with type II malformations. Coupled with the observation that nonpatent ureters are characteristic of MCDK, perhaps representing a failure of ureteric canalization that normally occurs by 8 wk gestation (20), one can speculate that the final RD phenotype might be triggered by impairment of urine flow. It is important to note that the effects of experimental obstruction differ in fetal *versus* postnatal kidneys; in the latter, nephrons do not form prominent cysts, correlating with the greater length and limited compliance of a mature *versus* a fetal nephron tubule. When fetal sheep kidneys are experimentally obstructed in midgestaion, severe RD is generated when the obstruction is prolonged (21). Similar models in fetal sheep and monkeys emphasize that formation of subcapsular cysts, some of which contain tufts of podocytes, are an early event after obstruction (22–24). The animal studies confirm that urinary flow impairment can generate type IV kidneys and also suggest that more profound grades of dysplasia might result from early obstruction. Conversely, RD kidneys generated in these experiments lack the dramatic "overgrowth" of human MCDK, which can be so pronounced that the dysplastic kidneys occupy most of the abdominal cavity and metaplastic cartilage is not formed. This suggests that additional factors, rather than just flow impairment, are operating in human disease. Furthermore, lower urinary tract obstruction does not occur in all cases of severe human RD (17) and therefore cannot be the only factor in pathogenesis.

RD Is a Dynamic Disorder

That MCDK do contain some normal-looking structures early in gestation is consistent with the concept that the phenotype of these organs is not fixed. Indeed, serial ultrasonography before and after birth demonstrates that MCDK can enlarge and then involute to an "aplastic" phenotype (25). Hiroaka *et al.* (26) described a similar tendency to involute in patients born with small noncystic kidneys that had minimal function as assessed by ^{99m}Technetium-dimercaptosuccinic acid renograms; these organs were presumably dysplastic, although histology was unavailable. Involution may represent an imbalance of programmed cell death and growth by proliferation because apoptosis in human RD is more prominent than in time-matched normal organs, especially in stroma around dysplastic tubules (27–29). By contrast, proliferation is prominent in dysplastic cyst epithelia (30,31). Disordered proliferation and death occur in malformations of other organs, for example, correlating with biliary duct dysmorphology in Meckel syndrome (32). PAX2 and BCL2 are cell survival genes (33,34) normally expressed as nephron precursors differentiate from RM (30); both are expressed in cystic RD epithelia but not in surrounding stroma, where cells die or undergo metaplasia to a smooth muscle–like phenotype (27,30) (Figure 2). TGF-β1 is overexpressed in human RD epithelia (35) (Figure 2). Yang from our group (35) created a human RD epithelial line expressing PAX2 and BCL2, and the addition of TGF-β1 induced a transition to a smooth muscle–like phenotype. On the basis of these experiments, we generated a working model of dysplasia integrating dysregulation of PAX2 and TGF-β1 with altered patterns of apoptosis/proliferation and aberrant differentiation (35). This model is highly simplified but does emphasize that common biologic pathways lead to CAKUT irrespective of underlying cause, as well as reiterating the ongoing dynamic processes within dysplastic organs. Other growth factors (*e.g.*, fibroblast growth factors [FGF], hepatocyte growth factor, IGF II, TNF-α) are expressed in human RD (36), but their functional significance in this context is unknown. Cell turnover is also altered in animal models of congenital obstructive nephropathy and uropathy (22,24,37–39). As examples, ovine fetal BOO causes apoptotic cell depletion in urinary bladder lamina propria, whereas hypertrophy and hyperplasia predominate in detrusor muscle (37), and neonatal mouse ureteric obstruction causes necrotic death in hypoxic proximal tubules, whereas collecting tubule cells are stretched and undergo apoptosis (39). Certain mutant mice with CAKUT-like phenotypes also have altered urinary tract cell turnover, *e.g.*, increased proliferation and death occur sequentially in metanephrogenesis in *glycipan-3*–deficient mice (40), and *angiotensin II type 2 receptor* (*AT2*)-deficient mice (41) show altered cell remodeling around the forming ureter. Another example, involving the Fraser syndrome gene, *FRAS1*, is discussed later. Animal CAKUT models generated by urinary obstruction also exhibit deregulated expression of PAX2, BCL2, and TGF-β1 (22,36,37,42).

UB Ectopia and RD

Kidney development is integrated with lower urinary tract morphogenesis (9). At 28 d gestation, coincident with UB formation, the urogenital sinus separates from the cloaca and fuses with the MD. In the next week, the MD below the UB dilates and this common excretory duct is absorbed into the sinus to generate the bladder trigone, with the distal end of the UB forming the ureteric orifice. Between 5 and 7 wk, the ureter becomes occluded; recanalization begins in the middle of the ureter, and by 8 wk, the structure is patent (20). An abnormal ureteric insertion into the lower tract is associated with some forms of human CAKUT (43,44). It was postulated that a more posterior UB branch point from the MD would result in a more laterally placed and incompetent ureteric-vesical junction, with vesicoureteric reflux; conversely, more anterior UB origin would result in an ectopic ureter terminating either in the bladder in an obstructing membrane (ureterocele) or in the urethra, vagina, or vas deferens. Ectopic ureters could be associated with RD, resulting either from fetal urinary obstruction or from a primary failure of UB to fully engage intermediate mesoderm. In some cases, double-ectopic UB might form, to generate duplex ureters and kidneys (45). This story

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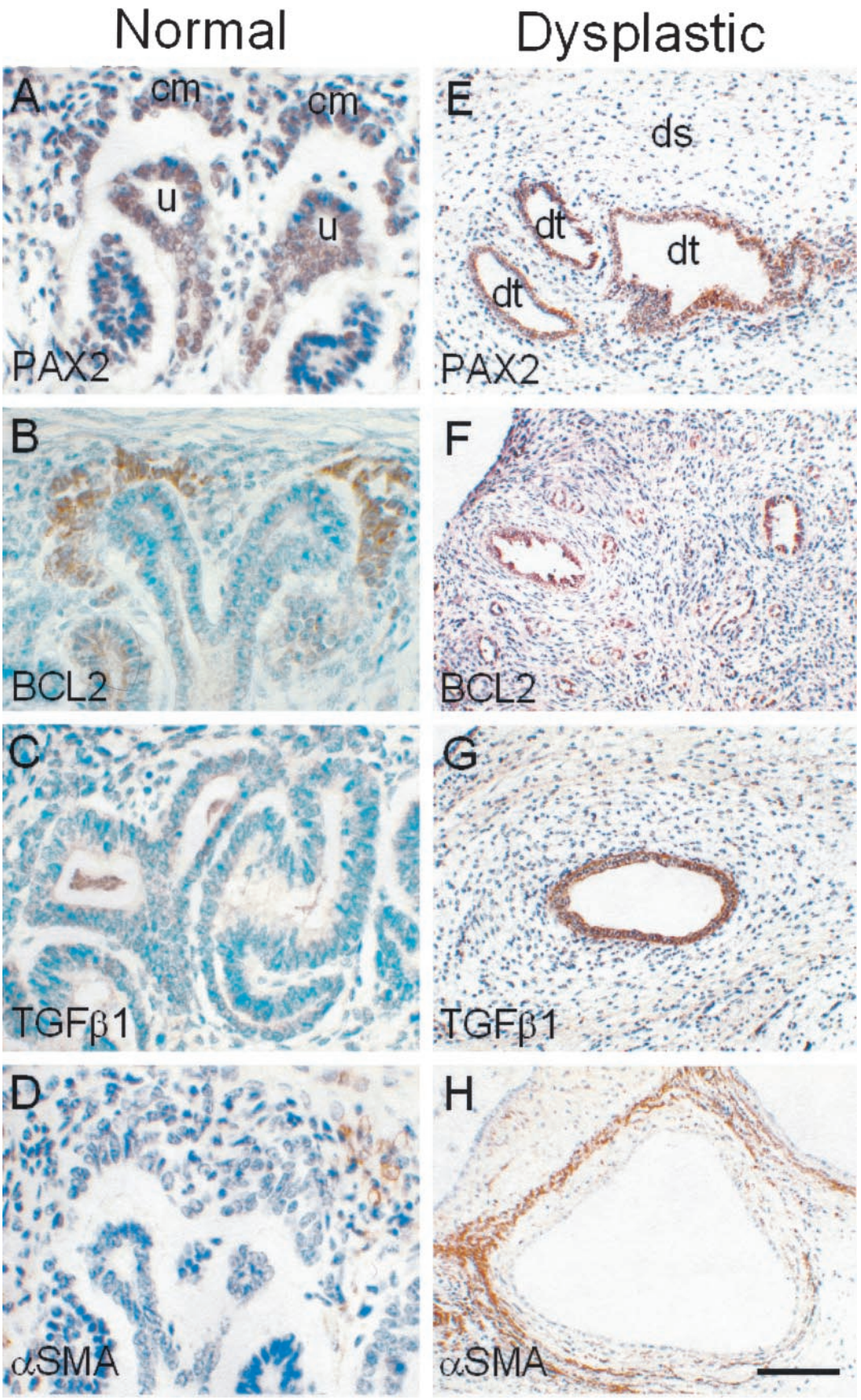

Figure 2. Gene expression in human RD. A through D are from normal midgestation kidneys, and E through H are from postnatal organs with histologically severe RD. Sections were immunostained for PAX2, BCL2, TGF-β1 and α-smooth muscle actin (α-SMA) and counterstained with hematoxylin. (A) PAX2 in ureteric bud (UB) branch tips (u) and condensing mesenchyme (cm). (B) BCL2 in condensing renal mesenchyme (RM). (C) Minimal TGF-β1 in nephrogenic cortex. (D) α-SMA in a few RM cells. (E) PAX2 in dysplastic tubules (dt); dysplastic stroma (ds) did not express this transcription factor. (F) BCL2 in dysplastic tubules. (G) TGF-β1 upregulated in dysplastic epithelia. (H) α-SMA in cells around dysplastic tubules. Bar = 40 μm in A through D; 80 μm in E, G, and H; and 160 μm in F.

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has received a novel "molecular twist," with experiments using genetically engineered mice. UB ectopia with RD-like lesions occurs in mice with ablation of *AT2* (46), *FOXC1* transcription factor (47), and bone morphogenetic protein (BMP) 4 growth factor (48) genes. Ichikawa *et al.* (49) provided schemes of how the activity of these genes might control UB formation, elongation, and kidney development.

Genetics of Human RD

Potter (7) wrote that "the type II kidney appears never to be genetic or chromosomal in origin"; we know that this statement is not correct. Although most cases of RD are sporadic, kindreds have been described with more than one affected member. Sometimes, these families have multiorgan syndromes, discussed below; in other cases, the anomaly is restricted to CAKUT. MCDK can occasionally be familial (25,50), and kindreds are reported in which some individuals have renal aplasia, or "absent kidneys," whereas others have large dysplastic organs (51,52); some of this phenotypic heterogeneity might be explained by the tendency of RD toward involution. Nishimura *et al.* (41) reported an association with a polymorphism of *AT2* in US and European patients with diverse urinary tract malformations, including MCDK. The polymorphism resulted in decreased expression of AT2, a receptor that stimulates apoptosis. However, Hiraoka *et al.* (53) could not replicate a significant association in a Japanese population, and neither study used the robust genetic strategy of transmission dysequilibrium (54) to follow segregation of alleles from parents to affected children. Another report (55), which did use transmission dysequilibrium to track the polymorphism from mother to child, failed to implicate *AT2* in primary vesicoureteric reflux, a disease that can be associated with RD (17). Although the genetic bases of isolated human RD are unclear, progress has been made in the more rare, "syndromic" cases in which the renal malformation is part of a multiorgan syndrome. In fact, Potter had noted that approximately half of the type II RD malformations that she studied were accompanied by anomalies of heart, central nervous system, anus, or uterus (7). Tens of such syndromes exist (9,56); here, we highlight three of them, and a number of others are shown in Table 1.

Fraser Syndrome

Fraser syndrome (FS) is autosomal recessive; occurs in 1:10,000 births; and presents with cryptophthalmos, syndactyly, ambiguous genitalia, and CAKUT. Of 117 cases (57), half had absent kidneys or RD. Approximately half of FS cases are stillborn or die in infancy, and kidney disease contributes to morbidity. It had been speculated that FS was a human equivalent of murine blebbing (*bl*) mutants. We recently identified loss-of-function mutations in a novel gene, *FRAS1*, in a subset of FS patients and reported that the murine homologue, *Fras1*, was mutated in *bl* mice (58). A targeted *Fras1* null mutation was found to have a blebbed phenotype and confirmed that *bl/bl* embryos lacked Fras1 protein (59). Clues regarding the metanephric roles of Fras1 can be gained from the precise type and timing of the defects seen, the expression of Fras1 transcripts and protein, and the structural domains present. FRAS1 has sequence similarity to ECM3, a component of extracellular matrix fibers that reorganize in sea urchin gastrulation (60); both have an extracellular region similar to chondroitin sulfate proteoglycan NG2, CALX-β domains, a transmembrane domain, and a short intracellular domain. NG2 core proteoglycan binds FGF2, perhaps acting as a reservoir or facilitating binding to cell surface receptors; the molecule also binds collagens. FRAS1 additionally has N-terminal chordin and furin domains, providing further possibilities for signaling functions, because chordin domains modulate BMP actions, and furin domains modulate TGF-β–related protein activities. Neonatal and postnatal renal phenotypes of *Fras1* null mutant mice mimic anomalies in FS patients. Usually, mutant mouse kidneys are absent or small, with blind-ending ureters, although they are occasionally grossly cystic (58,59). In normal mice, MD expresses Fras1 transcripts, and Fras1 immunolocalizes to the basal UB surface (58,59). In *bl/bl* mice, UB and RM are present at the inception of metanephrogenesis, but the UB generally fails to branch more than once, and RM does not form nephrons; instead, the kidney shrinks, with many pyknotic RM nuclei, reminiscent of human RD kidney involution (58). Blisters in FS mice occur after dermal separation from skin basement membrane, and Fras1 immunolocalizes to the basal surface of normal skin basement membrane; dermal collagen VI immunostaining is diminished in null-mutant mice (58,59). Thus, it is feasible that human FS external malformations (*e.g.*, cryptophthalmos, syndactyly) might arise as disruptions secondary to skin fragility. This argument cannot easily be applied to explain FS metanephric malformations; indeed, no physical separation is seen between mutant UB and RM. Instead, aberrant metanephric development in FS probably represents a breakdown of reciprocal inductive events, mediated by growth factors or matrix molecules, between UB and RM (10) and that the normal Fras1 protein somehow mediates these actions. In another multiorgan disorder with RD, the Simpson-Golabi-Behmel syndrome, *GPC3* is mutated. The wild-type protein glypican-3 is a heparan sulfate proteoglycan (HSPG) modulating kidney growth activities of BMP7, FGF7, and endostatin, a collagen XVIII cleavage product (61,62); perhaps FRAS1 has similar activities in the metanephros.

Renal Cysts and Diabetes Syndrome

Renal cysts and diabetes syndrome (RCAD) is a caused by mutations of the transcription factor gene *hepatocyte nuclear factor 1*β (*HNF1b*) (63–67). The key features are diabetes and also renal malformations of diverse phenotypes; the incidence of this recently defined syndrome has not yet been estimated. RD that can be cystic, hypoplastic kidneys (organs have fewer nephrons than normal), and polycystic/glomerulocystic kidneys all have been reported, as has solitary congenital function kidney. Lower urinary tract obstruction has not been demonstrated with any of these phenotypes. The diagnosis should be suspected in an individual who has CAKUT and glucose intolerance, especially when a first-degree relative has either disorder. Another clue, in women, is the occurrence of uterine malformations (65). Human *HNF1*β heterozygous mutations can occur *de novo* and/or be inherited in a dominant manner.

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Table 1. Genetics of human CAKUT occurring in isolation or as part of a syndrome

Apert syndrome (*FGFR2* mutation, growth factor receptor): hydronephrosis and duplicated renal pelvis with premature fusion of cranial sutures and digital anomalies
Bardet Biedl syndrome (several loci/genes implicated - includes a chaperonin and a centrosomal protein): renal dysplasia and calyceal malformations with retinopathy, digit anomalies, obesity, diabetes, and male hypogonadism
Beckwith-Wiedemann syndrome (in a minority of patients, *p57KIP2* mutation - cell cycle gene): widespread somatic overgrowth with large kidneys, cysts, and dysplasia
Branchio-oto-renal syndrome (*EYA1* mutation, transcription factor–like protein): renal agenesis and dysplasia with deafness and branchial arch defects such as neck fistulae
CAKUT (congenital anomalies of the kidney and urinary tract) syndrome (*AT2* polymorphism, growth factor receptor): diverse, nonsyndromic, renal and lower urinary tract malformations
Campomelic dysplasia (*SOX9* mutation, transcription factor): diverse renal and skeletal malformations
Carnitine palmitoyltransferase II deficiency (gene for this enzyme is mutated): renal dysplasia
CHARGE association (genetic basis unknown): coloboma, heart malformation, choanal atresia, retardation, genital and ear anomalies; diverse urinary tract malforations can occur
Denys Drash syndrome (*WT1* mutation, transcription/splicing factor): mesangial cell sclerosis and calyceal defects
Di George syndrome (microdeletion at 22q11, probably several genes involved): renal agenesis, dysplasia, vesicoureteric reflux, with heart and branchial arch defects
Duplex kidney and ureter (loci and genes unknown): nonsyndromic familial cases are recognized
Glutaric aciduria type II (*glutaryl-CoA dehydrogenase* mutation): cystic and dysplastic disease
Hypoparathyroidism, sensorineural deafness and renal anomalies (HDR) syndrome (*GATA3* mutation, transcription factor): renal agenesis, dysplasia, and vesicoureteric reflux
Fanconi anaemia (six mutant genes reported, involved DNA repair): renal agenesis, ectopic/horseshoe kidney, anemia, and limb malformations
Fraser syndrome (*FRAS1* mutation, putative cell adhesion molecule): renal agenesis and dysplasia, digit and ocular malformations
Kallmann's syndrome (X-linked form, *KAL1* mutation, cell adhesion molecule; autosomal form, *FGFR1* mutation, growth factor receptor): renal agenesis and dysplasia in X-linked form
Meckel syndrome (loci at 11q and 17q, genes unknown): cystic renal dysplasia, central nervous system and digital malformations
Nail-patella syndrome (*LMX1B* mutation, transcription factor): malformation of the glomerulus and renal agenesis
Oral facial digital syndrome type 1 (*OFD1* mutation, centrosomal protein): glomerular cysts with facial and digital anomalies
Renal-coloboma syndrome (*PAX2* mutation, transcription factor): renal hypoplasia and vesicoureteric reflux
Renal cysts and diabetes syndrome (*HNF1β* mutation, transcription factor): renal dysplasia, cysts, and hypoplasia
Simpson-Golabi-Behmel syndrome (*GPC3* mutation, proteoglycan): renal overgrowth, cysts, and dysplasia
Smith-Lemli-Opitz syndrome (*δ (7)-dehydrocholesterol reductase* mutation, cholesterol biosynthesis): renal cysts and dysplasia
Townes-Brockes syndrome (*SALL1* mutation, transcription factor): renal dysplasia and lower urinary tract malformations
Urofacial (Ochoa) syndrome (locus on 10q, gene undefined): congenital obstructive bladder and kidney malformation with abnormal facial expression
Urogenital adysplasia syndrome (some cases have *HNF1β* mutation): renal dysplasia and uterine anomalies
VACTERL association (basis unknown apart from one report of mitochondrial gene mutation): vertebral, cardiac, tracheoesophageal, renal, radial, and other limb anomalies
Vesicoureteric reflux (genetically heterogeneous, one locus on chromosome 1 but gene undefined): nonsyndromic familial cases with no secondary cause (*e.g.*, urinary flow impariment) are recognized
von Hippel Lindau disease (*VHL* mutation, tumor suppressor gene): renal and pancreatic cysts, renal tumors
WAGR syndrome (*WT1* and *PAX6* contiguous gene defect, transciption factors): Wilms' tumor, aniridia, genital and renal malformations, mental retardation
Zellweger syndrome (peroxisomal protein mutation): cystic dysplastic kidneys

HNF1β transcripts can be detected in several embryonic humans organs in which mesenchymal/epithelial interactions occur (*e.g.*, stomach, lung, pancreas, kidney), with prominent expression in fetal medullary collecting ducts but not in the UB ampullary tips (66); this suggests that the gene is active in the ureteric lineage, perhaps as a "maturation factor" rather than a "branching factor." In mice, the gene is expressed in MD, UB derivatives, forming nephrons, and the paramesonephric ducts that will differentiate into the uterus and the fallopian tubes (68). HNF1β modulates transcription of *Ksp-cadherin*, a gene

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that is expressed in a similar distribution to HNF1β within the developing urinary tract (69,70); the nephrogenic function of this adhesion molecule, however, is unknown. *HNF1β* null mutant mice die in early embryogenesis (71) and are uninformative for studying renal organogenesis. In the future, a null mutation targeted to the developing urinary tract will need to be created to study nephrogenesis; indeed, *HNF1β* inactivation in developing liver demonstrates a role in bile duct morphogenesis (72). The embryonic excretory system of *Xenopus* is an alternative model with which to study gene function (73,74); in fact, HNF1β is expressed in the embryonic region destined to form the pronephric kidney, even before overt morphologic differentiation (75). Using *Xenopus*, it has been possible to overexpress wild-type and mutant *HNF1β* human genes to study the effects on pronephric growth. In HNF1β mutants retaining DNA binding, dimerization, and transactivation activities, the pronephros generated was smaller than normal (74). In contrast, overexpression of mutants lacking these properties generally resulted in embryonic frog kidneys that were large (74). Hence, the mutated proteins that lack DNA binding seem likely to interact with regulatory components (currently unknown). At present, there is no simple correlation between specific *HNF1β* mutations and human kidney phenotypes (*e.g.*, RD, glomerulocystic kidney, hypoplasia), and the severity and the type of CAKUT can vary even within one kindred.

Kallmann Syndrome

Kallmann syndrome (KS) is characterized by the association of hypogonadotrophic hypogonadism and anosmia. It affects 1:8,000 male and 1:40,000 female individuals, and X-linked, autosomal dominant, and autosomal recessive inheritance is described (76). Renal aplasia, generally unilateral, occurs in 40% of patients (77), but MCDK is also reported (78). The X-linked form results from mutations of *KAL1*, which encodes the extracellular matrix protein anosmin-1. KAL1 transcripts occur in the human metanephros and olfactory bulb from 45 d gestation (79), and these sites are consistent with organs affected in KS. Anosmin-1 immunolocalizes to basement membrane of human UB branches (80). With increased understanding of anosmin-1 structure and function in different organisms, these observations can start to be synthesized into potential mechanisms of maldevelopment. Anosmin-1 is a modular protein consisting of an N-terminal cysteine-rich region, a whey acidic protein–like 4 disulfide core motif (WAP), four contiguous fibronectin-like type III (FnIII) domains, and a histidine-rich C-terminus. Similar WAP- and FnIII-encoding domains occur in predicted KAL proteins in birds, fish, flies, and worms. In the absence of a rodent model, KAL1 function has been investigated in *C. elegans* (81,82): Worm *Kal1* mutants have defects in ventral closure and male tail formation, partially rescued by the human gene, suggesting conservation of function across species, and neuronal targeting studies implicate FnIII domains in control of axon branching and both FnIII and WAP domains in axon misrouting. The FnIII domains are predicted to be involved in anosmin-1–HSPG interactions (83), and heparan-6-O-sulfotransferase, an enzyme required for the formation of cell membrane–associated HSPG, was identified as a modifier of KAL1-induced axonal defects in *C. elegans*. HSPG are not only important in neural development, particularly in neurite outgrowth and migration, but they also have critical roles in nephrogenesis: Mice homozygous for a gene trap mutation in heparan sulfate 2-sulfotransferase, for example, fail to initiate normal metanephrogenesis (84), as do mutants lacking glial cell line–derived neurotrophic factor or its receptors, and signaling via this pathway also requires HSPG (85). It is intriguing that loss of function mutations in *FGFR1* have recently been reported in dominantly inherited KS, and binding of HSPG to FGF and its receptors is also required for FGF signaling (86).

Conclusion

Early studies of human RD defined the anatomy and histology of affected kidneys and urinary tracts, leading to hypotheses of pathogenesis featuring UB primary dysfunction and/or ectopia and also fetal urinary obstruction. More recent clinical observations showed that the external appearance of an RD kidney can evolve pre- and postnatally, and this most likely correlates with phases of excessive growth followed by apoptotic involution. Animal experiments of fetal urinary tract obstruction generate some but not all anatomic features of human RD, and not all human RD kidneys are associated with obstruction. Histologic studies of human RD have found disordered expression of diverse growth factor, cell survival, and transcription factor genes, and some of these patterns correlate with disordered cell turnover and maturation. In some cases of RD, mutations of genes expressed in normal metanephrogenesis have been defined in multiorgan malformation syndromes. Although these observations are important, considerably more work is required to understand how any one of these mutations causes the metanephric rudiment to grow into a dysplastic kidney.

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