Advances in the Cell Biology and Genetics of Human Kidney Malformations

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In recent years there have been advances in the biology of renal malformations. Our focus is on human disease, but we will use animal paradigms when relevant. The mammalian kidney derives from two metanephric components (1–5): ureteric bud, which forms collecting ducts and uroepithelium, and renal mesenchyme, which forms nephrons. The human metanephros appears at 5 wk gestation, and glomeruli first form by 9 wk (Figure 1). Nephrons are generated until approximately 34 wk, with maturation continuing postnatally. Murine metanephros arise 11 to 12 d after fertilization, and nephrogenesis continues 2 wk postnatally.

The term "kidney malformation" describes diverse anomalies (4–5). In "renal agenesis" the kidney is absent. In "renal dysplasia," poorly branched ducts terminate in cysts and are surrounded by undifferentiated cells and metaplastic cartilage. An "aplastic" kidney is a tiny dysplastic rudiment, and the "multicystic dysplastic kidney" is distended by cysts. "Cystic dysplastic kidney" refers to a dysplastic organ with some functioning nephrons. In "renal hypoplasia" the organ is small with fewer nephrons than normal; when nephrons are large the condition is called "oligomeganephronia" (6). Lower urinary tract malformations include calyceal distortions and hypoplasia, as well as hydrenephrosis and hydroureret associated with obstruction or vesicoureteric reflux. The definition of renal malformation can be extended to microscopic abnormalities such as "tubular dysgenesis," in which proximal tubules form abnormally (7). Although polycystic diseases may present as malformations, they are disorders of terminal epithelial differentiation (8–10) and will not be discussed further in this report.

Renal malformations may occur sporadically or be familial, appearing in isolation or as part of a multiorgan syndrome commonly affecting central nervous, cardiovascular, and skeletal systems (4,11); accompanying lung hypoplasia is often secondary to oligohydramnios. Ascertainment of the occurrence of renal malformations is subject to bias: Some surveys exclude neonatal deaths; unilateral disease is often clinically silent (12); there is rarely access to tissue for histology; in adults, malformations may not be considered in differential diagnoses. However, malformations do account for most young children with chronic uremia (13,14). The following incidences have been quoted (15–18): unilateral duplex ureter, 1 in 20 births; horseshoe kidney, 1 in 200; unilateral renal agenesis, 1 in 500 to 1000; unilateral multicystic kidney, 1 in 5000. Bilateral agenesis/dysplasia occurs in 1 in 5,000 to 10,000 births, although unilateral agenesis can be associated with mild disease (e.g., hydrenephrosis, vesicoureteric reflux) of the solitary kidney (19,20). Furthermore, solitary kidneys are not biopsied at birth. These observations may be relevant to the detection, later in life, of glomerulosclerosis in congenital "normal" single kidneys (12,18,21,22).

Clues from Animal Studies

More than 40 years ago, Clifford Grobstein demonstrated that metanephric mesenchyme and ureteric bud failed to differentiate when cultured separately, but they formed nephrons and collecting ducts when recombined (23). Using genetically engineered mice and organ culture, it is now established that nephrogenesis is controlled by genes encoding diverse molecules, some of which may act as inductive signals postulated by Grobstein: (1) growth factors with positive effects include epidermal growth factor (24), bone morphogenetic protein 7 (25), fibroblast growth factors (FGF) 2 and 7 (26,27), glial cell line-derived neurotrophic factor (28,29), hepatocyte growth factor (30), insulin-like growth factors (IGF) I and II (31), platelet-derived growth factor β (32), transforming growth factor α (TGFα) (33), vascular endothelial growth factor (34), and Wnt4 (35); (2) inhibitory factors include activin (36), leukemia inhibition factor (37), tumor necrosis factor α (38), and TGFβ (39); (3) cell adhesion molecules include fibronectin, laminins, nidogen, proteoglycans, and tenasin (40–42), as well as integrins (43,44); (4) transcription factors include BFL2 (45), Hoxa11 and Hoxd11 (46), Lim1 (47), N-myC (48), PAX2 (49,50), SOX9 (51), and WT1 (52); (5) other molecules include survival factors (e.g., BCL2; references 53 and 54), retinoic acid receptors (55), enzymes (e.g., COX2; reference 56), and molecules with unknown specific functions (e.g., forms; reference 57).

Table 1 summarizes known genes affecting nephrogenesis in null mutant mice. As with human disease, the resulting malformations are agenesis, dysplasia, and hypoplasia. These re-
mouse "nephrogenesis genes" are often expressed in other organs, in which they are also critical for development (e.g., PAX2 mutants have renal and ocular defects [49], whereas WT1 -/- mice have a syndrome of kidney, gonadal, and cardiothoracic anomalies [52]).

Animal experiments also highlight the potential importance of teratogens (62). For instance, when retinoic acid is administered in large doses 1 d before the formation of the mouse metanephros, intermediate mesoderm undergoes apoptosis causing renal agenesis (63). Ethanol is a urinary tract teratogen, also inducing apoptosis (64). The metanephros is sensitive to obstruction and hydronephrosis, and dysplasia can be generated by ureteric obstruction in fetal sheep (65). Our own observations demonstrate that unilateral ureteric obstruction in ovine midgestation generates cysts expressing PAX2 with apoptosis between tubules (66). Obstruction of adult kidneys causes tubular atrophy from epithelial apoptosis (67) and interstitial scarring with TGFβ1 upregulation (68). Obstruction of neonatal murine kidneys, in which nephrogenesis is ongoing, causes apoptosis with aberrant expression of BCL2, TGFβ1, angiotensin II, and epidermal growth factor (69). It is possible to obstruct the urinary tract of fetal marsupials ex vivo: here, IGF administration abrogates damage (70).

Table 1. Null mutant mice with renal malformationsa

<table>
<thead>
<tr>
<th>Transcription factors</th>
<th>Numbers</th>
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<tbody>
<tr>
<td>BF2 (small, fused, and undifferentiated kidneys) (45)</td>
<td></td>
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<tr>
<td>Hoxa11/Hoxd11b (small or absent kidneys) (46)</td>
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<tr>
<td>Lim1 (absent kidneys) (47)</td>
<td></td>
</tr>
<tr>
<td>N-myC (poorly developed mesonephric kidneys) (48)</td>
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<tr>
<td>PAX2c (small or absent kidneys) (49)</td>
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<td>WT1 (absent kidneys) (52)</td>
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<tr>
<th>Growth factors and receptors</th>
<th>Numbers</th>
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<tbody>
<tr>
<td>EGF receptor (cystic collecting ducts) (24)</td>
<td></td>
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<tr>
<td>BMP7 (undifferentiated kidneys) (25)</td>
<td></td>
</tr>
<tr>
<td>GDNF (small or absent collecting ducts) (60)</td>
<td></td>
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<tr>
<td>PDGF B chain (mesangial cells) (32)</td>
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<tr>
<td>Wnt4 (undifferentiated kidneys) (35)</td>
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<tr>
<th>Adhesion molecules and receptors</th>
<th>Numbers</th>
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<tbody>
<tr>
<td>α3 integrin (decreased duct branching) (43)</td>
<td></td>
</tr>
<tr>
<td>α8 integrin (impaired ureteric bud branching and nephron formation) (44)</td>
<td></td>
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<tr>
<td>s-laminin/laminin β2 (nephrotic syndrome) (41)</td>
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<table>
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<tr>
<th>Miscellaneous molecules</th>
<th>Numbers</th>
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<tr>
<td>BCL2 (small kidneys) (53)</td>
<td></td>
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<tr>
<td>Formin (absent kidneys) (57)</td>
<td></td>
</tr>
<tr>
<td>COX2 (small kidneys) (56)</td>
<td></td>
</tr>
<tr>
<td>RAR αγ/αβ2 (small or absent kidneys) (55)</td>
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a Unless otherwise stated, malformations only occur in homozygous null mutants. Numbers in parentheses indicate references. EGF, epidermal growth factor; GDNF, glial cell line-derived neurotrophic factor; PDGF, platelet-derived growth factor; RAR, retinoic acid receptor.

b Null mutation of two homologous genes cause malformation.

c Heterozygous mutations also produce renal malformation.

For the table, Transcription factors are listed, including BF2, Hoxa11/Hoxd11, Lim1, N-myC, PAX2, WT1, EGF receptor, BMP7, GDNF, PDGF, and Wnt4. Growth factors and receptors include EGF, BMP7, and GDNF. Adhesion molecules are α3 integrin and α8 integrin. Miscellaneous molecules are BCL2, Formin, COX2, and RAR. Malformations are observed in homozygous null mutants, with specific references listed in parentheses.

Figure 1. Early development of human metanephros. (A through D) Sections between its inception at 5 wk gestation and 10 wk when the first glomeruli form. w, wolffian or mesonephric duct; u, ureteric bud or its branches; m, renal mesenchyme; mc, mesenchymal condensate; c and s, primitive nephrons, including comma- and S-shaped bodies, respectively; g, glomerulus.
Biology of Human Malformations

Nephrogenesis is a dynamic and tightly controlled program of cellular events. With this in mind, we investigated cell turnover and gene expression in human nonsyndromic multicystic dysplastic kidneys, a model of perturbed epithelial/mesenchymal interaction (71–73). Microdissection studies by Edith Potter revealed that dysplastic epithelia were malformed branching tubules terminating in cysts (5) surrounded by poorly differentiated cells resembling mesenchymal and stromal cells (Figure 2). Because these organs are usually associated with an atretic ureter, obstruction early in gestation has been invoked as a cause of the malformation. Dysplastic epithelia express proliferating cell nuclear antigen, PAX2, BCL2, and galectin-3, a cell signaling molecule (Figures 3 and 4). Strikingly, dysplastic organs harvested postnatally show persistent patterns of fetal gene expression, whereas normal organs downregulate proliferation, PAX2, and BCL2 in mature epithelia (72). Because transgenic PAX2 expression causes renal cysts (60), persistent expression in human epithelia may drive proliferation. PAX2 is also expressed in human Wilms’ tumors (74) and renal carcinoma (75); the gene also can transform murine cells (76) and inhibits the promoter of p53, a tumor suppressor (77). It is therefore notable that tumors occasionally arise in multicystic kidneys and that these organs may harbor nephrogenic blastema and perilobular rests, the latter being considered a Wilms’ tumor precursor (78,79). In view of these neoplastic associations, we speculate that it might be interesting to look for loss of heterozygosity in renal tumor suppressor genes (80) in these malformations. We did not detect BCL2 in normal ureteric bud branches or normal postnatal kidney (72); hence, we speculate that persistent expression in dysplastic epithelia may prevent their death. Finally, there is evidence that growth factors, including hepatocyte growth factor (81) and IGF II (82), are implicated in dysplastic epithelial growth based on their expression patterns.

Some multicystic dysplastic kidneys increase to a massive size, only to involute pre- or postnatally (83). We suggest that enhanced apoptosis contributes to regression based on our findings that the point prevalence of apoptosis was increased in undifferentiated tissues around dysplastic epithelia and “laddering” on electrophoretic gels of DNA from postnatal specimens (Figures 3 and 5; reference 71). These undifferentiated cells express WT1 (72); hence, they appear to be induced to differentiate (52), but do not stain for BCL2, which is normally expressed by mesenchyme condensing into nephrons (Figures 3 and 4; reference 72). Similar observations regarding apoptosis and absence of BCL2 staining in tissues around dysplastic tubules were subsequently reported by Granata et al. (84). On the basis of the observations that BCL2 −/− mice have fulminant apoptosis (53,54), the lack of BCL2 expression in

Figure 2. Cytoskeletal proteins in human multicystic kidneys. (A) Cytokeratin (CTK) in dysplastic tubules. (B) Vimentin (VIM) in dysplastic tubules and surrounding undifferentiated cells. (C) Smooth muscle actin (SM-ACTIN) in a few cell layers surrounding tubules. (D) von Willebrand factor (VWF) weakly expressed (arrows) by capillaries in mesenchyme (m) around dysplastic tubules (dt). Bar, 20 μm.
mesenchyme from human dysplastic kidneys may cause the untimely death of these cells, hence preventing nephrogenesis. An understanding of human dysplastic biology allows us to envisage potential therapies, e.g., administration of growth factors to enhance differentiation (70). However, deregulation of cell turnover and gene expression could be secondary events, and the question remains: What are the primary causes of human kidney malformations? We suggest three answers:

Figure 3. Cell turnover and gene expression in human multicystic kidneys. Clockwise, from top left: proliferating cell nuclear antigen (PCNA) protein; apoptosis assessed by pyknotic nuclei and in situ end-labeling; PAX2 protein; galectin-3 protein; BCL2 protein; WT1 protein. Adapted from references 71 through 73.
Teratogenic and Physical Causes of Human Malformations

In humans, glucose (maternal diabetes mellitus), angiotensin-converting enzyme inhibitors, and thalidomide are renal teratogens (62,85,86). Although it is unusual to elicit a history of teratogen exposure, it remains possible that occult or low-grade exposure is important. For example, the incidence of diverse malformations increases with a daily intake of vitamin A over levels as low as 10,000 IU; this includes a weak association with urogenital defects (87). A significant minority of kidney malformations in girls, and approximately half of malformations in boys, are associated with obstructed urinary tracts (4,5). Kidneys associated with obstruction in early gestation are usually dysplastic, whereas obstruction in the third trimester of gestation is associated with hydronephrosis and subcortical cysts. In the future, it would be interesting to seek to identify apoptotic cells and inhibitory growth factors in the urine of these patients. This might provide information regarding the severity of renal damage.

Figure 4. BCL2 in human multicystic kidneys. (A) Normal human fetal kidney, 10 wk gestation. Intense BCL2 immunostaining (brown) in condensing mesenchyme (cm). Ureteric bud branches (u), loose mesenchyme (lm), and glomeruli (g) are negative. (B) Postnatal human dysplastic tubules are malformed branches of the ureteric bud (u) and stain for BCL2, whereas the surrounding undifferentiated cells are negative. Adapted from reference 72.

Figure 5. Apoptosis in human multicystic kidneys. "Apoptotic Index" refers to point prevalence of apoptotic cells per 10 high-power fields. Data points, given as means for pre- and postnatal normal and dysplastic kidneys. Adapted from reference 71.
Genes and Renal Malformation Syndromes

Malformation syndromes are individually rare, but collectively they account for considerable morbidity (4,11). Many are associated with renal anomalies of varied type and severity. These include syndromes caused by gross chromosomal anomalies such as trisomies, 4p-syndrome, and dup (10p)/del (10q), but in most renal malformation syndromes cytogenetic aberrations are absent. Some, however, are inherited in Mendelian patterns, and these have been studied using linkage and candidate gene strategies. In several, the disease locus is known, and in a few, specific mutations have recently been defined. Table 2 lists selected syndromes with genetic bases; more comprehensive documentation can be found elsewhere (4,11). We discuss three examples in detail.

Renal-Coloboma Syndrome

The human syndrome has a striking phenotypic similarity to PAX2 +/− mice (88,89). It is characterized by blindness due to an optic nerve malformation associated with vesicoureteric reflux and hypoplastic kidneys (90). In 1995, Sanyanusin et al. described heterozygous mutations of PAX2 (10q24–q25) in one kindred (90), and other reports followed (91,92). The ocular malformations are explained by PAX2 expression during eye development. The human mutations may arise de novo or may be inherited in a dominant manner and most likely cause haploinsufficiency, a partial lack of functional protein (90). The mutation in the first-reported family (90) was predicted to code for a protein with an intact DNA-binding paired box, an interrupted octapeptide domain, and a novel, truncated carboxy terminal. It was postulated that this would perturb the transactivation of target genes (90). Other mutations affect the paired-box (91) and would therefore impair DNA binding. In humans, heterozygous PAX3 and PAX6 mutations cause Waardenburg syndrome and aniridia, respectively (93). Thus, in mice and humans, PAX2 deficiency causes impairment of nephrogenesis, whereas overexpression is associated with cyst or tumor formation (59,72,74,75,94). PAX2 −/− mice lack kidneys because the ureteric bud fails to branch from the mesonephric duct (50), whereas the absence of fallopian tubes in female embryos is explained by the expression of PAX2 in müllerian ducts (73,95). Homozygous mutations have yet to be described in humans; however, kindreds with kidney and müllerian malformations superficially resemble mouse null-mutants (96). As discussed below, research groups are now searching for PAX2 mutations in nonsyndromic cases of inherited vesicoureteric reflux (97,98). PAX8, another member of this gene family, is expressed in metanephric mesenchymal condensates (99), and perhaps PAX8 mutations might also be found in other patients with renal malformations.

Kallmann’s Syndrome

Mutations of the KAL gene (Xp22.3) cause Kallmann’s syndrome in male hemizygotes (100,101). Failure of migration of olfactory and gonadotrophin-releasing hormone neurons from the olfactory epithelium into the olfactory bulb explains the characteristic anosmia and hypogonadotrophic hypogonadism (102). Kirk et al. found that 40% of patients had unilateral renal agenesis and noted the rare occurrence of bilateral agenesis (103,104). Patients may also lack a vas deferens: in common with the ureteric bud, this derives from the mesonephric duct. KAL protein has a signal peptide but lacks sequences for membrane insertion or anchorage, suggesting that it is secreted (105). It has four fibronectin type III repeats and has homology to neural cell adhesion molecule, suggesting adhesive roles. There also is a “four disulfide core motif” with homology to antiproteinases. When KAL was expressed in mammalian cells, N-glycosylated protein was localized both on the cell surface and in conditioned medium (106). We sought KAL transcripts in early human development (107). At 11 wk, an in situ signal localized to the olfactory bulb, supporting the hypothesis that KAL enables migrating neurons to enter the brain and establish synaptic contact at this site. Intriguingly, neural cell adhesion molecule also has been implicated in olfactory bulb development (108). KAL transcripts were detected in the mesonephros and metanephros at 6 wk and continued to be expressed in the metanephric cortex (Figure 6), supporting the contention that KAL is directly involved in nephrogenesis. To date, a murine KAL homologue has not been identified, but

Table 2. Genes and human renal malformation syndromes

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Locus (Mutation)</th>
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<tbody>
<tr>
<td>Apter’s syndrome (FGFR2 mutation - growth factor receptor)</td>
<td>(133): hydronephrosis and duplicated renal pelvis (134)</td>
</tr>
<tr>
<td>Bardet Bied syndrome* (loci at 11q13, 16q22, 3p13, and 15q21)</td>
<td>(135): renal dysplasia and calyceal malformation (136)</td>
</tr>
<tr>
<td>Campomelic dysplasia (SOX9 mutation - transcription factor)</td>
<td>(137): diverse renal malformations (138)</td>
</tr>
<tr>
<td>Denys Drash syndrome (WT1 mutation - transcription/ splicing factor)</td>
<td>(139): calyceal defects (140)</td>
</tr>
<tr>
<td>DiGeorge syndrome* (locus at 22q11)</td>
<td>(141): renal agenesis, dysplasia, and vesicoureteric reflux (142)</td>
</tr>
<tr>
<td>Fanconi’s anemia (FAA mutation - DNA repair)</td>
<td>(143): renal agenesis, ectopic/horseshoe kidney (4)</td>
</tr>
<tr>
<td>Kallmann’s syndrome (KAL mutation - cell signaling molecule)</td>
<td>(105): renal agenesis, 103,104</td>
</tr>
<tr>
<td>Meckel syndrome* (locus at 17q21 to q24)</td>
<td>(144): cystic renal dysplasia (145)</td>
</tr>
<tr>
<td>Renal-coloboma syndrome (PAX2 mutation - transcription factor) (90)</td>
<td>(90): renal hypoplasia and vesicoureteric reflux (90)</td>
</tr>
<tr>
<td>Simpson-Golabi-Behmel syndrome (GPC3 mutation - proteoglycan)</td>
<td>(146): renal overgrowth and dysplasia (147)</td>
</tr>
<tr>
<td>Smith-Lemli-Opitz syndrome* (locus at 7q32 - defect in cholesterol biosynthesis)</td>
<td>(148): cystic dysplastic kidneys (4,149)</td>
</tr>
<tr>
<td>Zellweger syndrome (peroxisomal protein mutation) (150):</td>
<td>cistic dysplastic kidneys (4)</td>
</tr>
</tbody>
</table>

* Locus known, but gene unknown.
human sites of expression are similar to those observed in avian ontogeny (109,110). There are at least two important questions concerning renal malformations in Kallmann's syndrome. (1) Why are only some patients affected, even within a single kindred? Here, the action of modifying genes can be invoked, as described in mice (24,46,55). (2) Why is the malformation often unilateral? Perhaps, to adversely affect nephrogenesis, there needs to be a second perturbation in a group of cells destined to form a kidney. This "second hit" could be a somatic mutation in another nephrogenesis gene. Certainly, somatic mutations do occur in the kidney and contribute to cytogenesis in autosomal dominant polycystic kidney disease (111).

**Branchio-Oto-Renal Syndrome**

These individuals are deaf and have preauricular pits and tags, as well as neck cysts and fistulae (112). Renal agenesis, dysplasia, hydronephrosis, vesicoureteric reflux, and calyceal malformations have been reported in up to 70% of individuals, but their occurrence and severity are variable, even within one kindred (113,114). The variable penetrance and expression of the renal anomalies again suggest the influence of unidentified modifying genes or environmental factors. Early reports mapped the disease locus to human chromosome 8q12.2 to q21.2 (115), and in 1997 sporadic and autosomal dominant forms were reported to be associated with mutations of EYA1 (116). EYA1 is part of a novel human gene family with homology to the *Drosophila* eyes absent gene (117). Using *in situ* hybridization in embryonic mice, Abdelhak et al. found that EYA1 was expressed in otic vesicle and in the cochlear and vestibular neuroepithelia, as well as in condensing metanephric mesenchyme around the branching tips of the ureteric bud (116). During normal development, the same population of cells (which represent the first morphogenetic step to nephron formation) expresses BCL2 (72,84), whereas in kidneys in humans with nonsyndromic renal dysplasia, undifferentiated mesenchymal cells lack BCL2 expression and undergo enhanced apoptosis (71,84). It is therefore of interest that the *Drosophila* homologue EYA is a nuclear-located protein that enhances progenitor cell survival in the developing eye (117). We suggest that EYA1 may upregulate the expression of survival factors such as BCL2. It would be instructive to analyze expression of BCL2 in kidneys from patients with the branchio-oto-renal syndrome and study the direct effects of EYA1 expression on BCL2 transcription.

**Genetics of Isolated Renal Malformations**

Not all inherited human renal malformations are syndromic. In 1974, Cain et al. cited 12 reports of familial renal malformations and described a kindred with two siblings: the first with bilateral renal agenesis and the second with unilateral agenesis and contralateral dysplasia (118). Others reported that first-degree relatives of patients with bilateral agenesis had a tenfold higher incidence of solitary kidney compared with control subjects (17). McPherson and colleagues emphasized that nonsyndromic renal dysplasia and aplasia could be inherited within a single kindred in a probable autosomal dominant manner and that both disorders could occur in the same patient (119). Others have described kindreds with congenital single kidney with probable autosomal dominant inheritance (120,121). The genetic bases of these disorders are undefined. Primary, nonsyndromic vesicoureteric reflux occurs in 1% of children and may be associated with renal dysplasia and hypoplasia (97,98,122–124). Bailey drew attention to the fact that vesicoureteric reflux was often familial (125), and it is now accepted that inheritance in many kindreds is dominant.
with variable penetrance and expression (97,98,126,127). Hence, this is one of the most common inherited disorders (128). As discussed above, PAX2, RET, and FGFR2 have been functionally implicated in the differentiation of ureteric bud lineage; moreover, all three genes are located on human chromosome 10q. We investigated a kindred with nonsyndromic vesicoureteral reflux with 13 siblings, six of whom had radiologic reflux. One older child had renal scarring in whom the reflux was presumed to have regressed (98). Polymorphic markers along 10q were used to look for linkage; however, at each locus, two or more recombinants occurred in affected individuals. Our analysis makes it highly unlikely that mutations of these genes are important in pathogenesis in this family (98), and whole genomic linkage studies are in progress to find the relevant gene(s). Eccles et al. have also excluded PAX2 mutations in other kindreds with isolated vesicoureteric reflux (97).

Conclusions

The past decade has seen advances in the understanding of “molecular lesions” associated with human renal malformations. Perhaps the best example is provided by PAX2, a gene expressed in the metanephros and downregulated postnatally. Mutations leading to reduced PAX2 dosage cause renal hypoplasia, whereas overexpression is associated with epithelial overgrowth. Although the search for mutations in rare renal malformation syndromes has dominated genetic studies thus far, future work needs to focus on genetic influences in isolated renal malformations. In this respect, primary vesicoureteric reflux represents numerically the most important disorder, and the discovery of disease loci should facilitate early diagnosis and identification of asymptomatic carriers. It is likely that the variable penetrance and expression of familial renal malformations are the result of the action of modifying genes. In this respect, preliminary work suggesting an association of a polymorphism in an intron of the angiotensin receptor type 2 gene with diverse human malformations may be of importance (129,130). Finally, understanding the biology of human renal malformations may eventually lead to the modulation of disease by the administration of agents to prevent apoptosis and enhance differentiation of renal precursor cells (70,131,132).

Acknowledgment

We acknowledge grant support from Action Research, United Kingdom.

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