EDUCATIONAL REVIEW

Glomerulocystic kidney disease

John J. Bissler · Brian J. Siroky · Hong Yin

Abstract Glomerulocystic disease is a rare renal cystic disease with a long descriptive history. Findings from recent studies have significantly advanced the pathophysiological understanding of the disease processes leading to this peculiar phenotype. Many genetic syndromes associated with glomerulocystic disease have had their respective proteins localized to primary cilia or centrosomes. Transcriptional control of renal developmental pathways is dysregulated in obstructive diseases that also lead to glomerulocystic disease, emphasizing the importance of transcriptional choreography between renal development and renal cystic disease.

Keywords Basal body · Cilia · Glomerulocystic kidney disease · Polycystic kidney disease · Tuberous sclerosis complex

Introduction

Although glomerulocystic kidney disease is somewhat rare, it is far from a new entity. As early as 1941, Roos described an infant with failure to thrive, rickets, and renal failure associated with cystic glomeruli [1]. Approximately 20 years later, Bialestock used microdissection to further characterize glomerular cysts associated with renal dysplasia and failure in an infant [2]. Baxter noted that glomerulocystic kidney disease could be limited to the cortex or be associated with medullary cysts [3], while Taxy and Filmer first used the term 'glomerulocystic kidney disease' to describe this dilatation of Bowman's space [4]. Bernstein added significant clarity to the diagnoses by defining the glomerular cyst as the dilatation of Bowman's space in the plane of section of two- to threefold that of normal [5]. Furthermore, he used the occurrence of glomerular tufts, within at least 5% of otherwise identifiable cysts, as being consistent with the diagnosis of glomerulocystic kidney and, like Baxter, he did not exclude associated tubular dilatations or cysts. Bernstein originally classified glomerulocystic kidney disease into three categories: (1) glomerulocystic kidney disease comprising nonsyndromal inheritable and sporadic forms of severely cystic kidneys in children and adults, (2) glomerulocystic kidneys associated with inheritable malformation syndromes, and (3) glomerular cysts in dysplastic kidneys [5]. His work served as the basis for a working descriptive classification of glomerulocystic disease (Table 1) [6]. Recent scientific progress offers new insight into the pathobiology of glomerulocystic disease and builds upon the Bernstein classification. A greater understanding of the developmental and genetic pathobiology of glomerulocystic disease will likely refine the classification system and may also reveal new therapeutic targets.

Inherited and syndromic forms of glomerulocystic kidney disease

In describing glomerulocystic kidney disease, Bernstein noted that many patients had a family history of autosomal

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Table 1 Classification of glomerulocystic disease

Classifications of glomerulocystic kidney disease	Example
Familial nonsyndromic	Autosomal dominant polycystic kidney disease in young infants
Associated with inheritable malformation syndromes	Tuberous sclerosis complex
Syndromic, non-Mendelian	Trisomy 9, 13, or 18
Sporadic	New mutations
Acquired and dysplastic kidneys	Hemolytic uremic syndrome and obstructive uropathy

dominant polycystic kidney disease (Fig. 1). He based the diagnosis of glomerulocystic kidney disease on anatomical findings and did not distinguish between familial and sporadic disease, in part because of the possibility of new mutations in known polycystic disease loci. The autosomal dominant inheritance of glomerulocystic kidney disease is well documented in the literature and can be associated with autosomal dominant polycystic kidney disease (ADPKD) genes [7]. An autosomal dominant glomerulocystic kidney disease that is not linked to the autosomal dominant polycystic kidney disease genes (PKD1 and PKD2) or the human homolog of mouse jcpk locus also exists [8]. While the presentation of glomerulocystic kidney disease is more common in newborns and young children, it also occurs in older children and adults. A developmental aspect of renal cystic disease has recently been identified, and it is possible that the glomerulocystic kidney disease phenotypic may manifest because of developmental timing and the effects of specific mutations [9, 10]. These effects

may hinge on cell proliferation during organogenesis that then slow but which can then increase again following acute renal injury [11]. Glomerulocystic kidney disease also can be found in patients diagnosed with other identifiable diseases, such as tuberous sclerosis complex, medullary cystic kidney disease, Jeune syndrome, nephronophthisis, Meckel-Gruber syndrome (Fig. 2), orofaciodigital syndrome, brachymesomelia-renal syndrome, trisomy 9, 13, and 18, the short rib-polydactyly syndromes, and Zellweger's syndrome (Table 2).

Dysplastic and acquired forms of glomerulocystic kidney disease

Glomerulocystic kidney disease also can be seen as a component of renal dysplasia (Fig. 3) and following significant fetal renal damage, such as that caused by maternal intake of drugs such as phenacetin [12], or following hemolytic uremic syndrome [13]. Tubular obstruction is postulated to play a role in the development of some forms of glomerulocystic kidney disease. This link to obstruction is not a simple relationship and appears to involve transcriptional reprogramming as well as changes in cilia length, as discussed below (Fig. 4).

Specific genetic diseases associated with glomerulocystic kidney disease

Tuberous sclerosis complex

Tuberous sclerosis complex (TSC) is a tumor suppressor syndrome associated with solid and cystic renal lesions. Glomerulocystic kidney disease associated with TSC was described almost 60 years ago [14] and is a well-

Fig. 1 An example of glomerulocystic disease in a child with autosomal dominant polycystic kidney disease. **a** Coronal section of a polycystic kidney, **b** histology demonstrating glomerular cysts (magnification 20×). Note the normal-sized glomeruli with the enlarged Bowman's space and tubular cystic changes
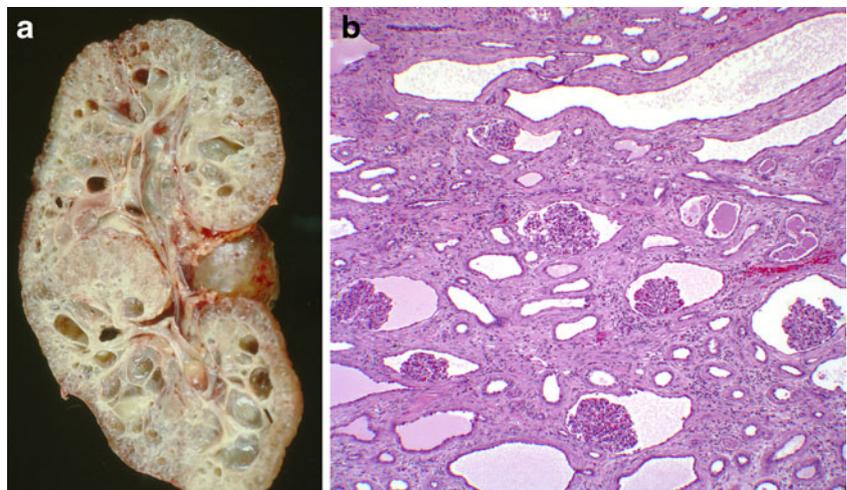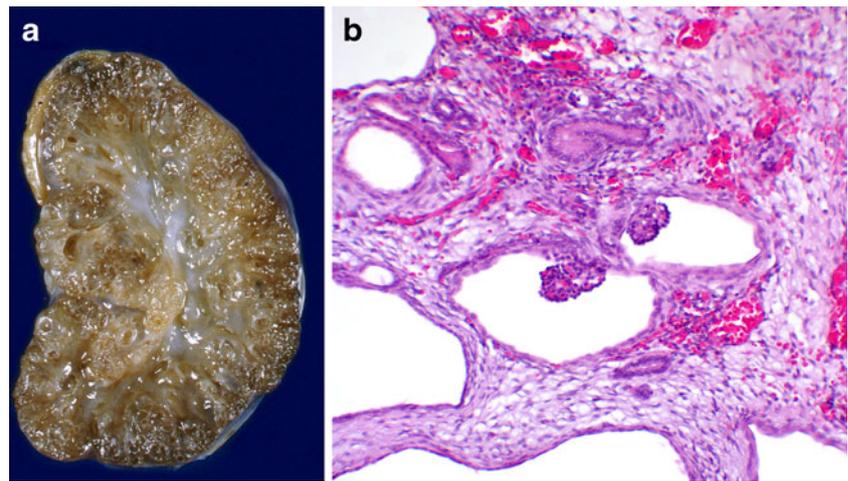
Fig. 2 An example of glomerulocystic disease in an infant with Meckel–Gruber syndrome. **a** Coronal section of the affected kidney, **b** histology demonstrating glomerular cysts (magnification 20×). Note the fetal glomeruli and surrounding dysplastic tissue with tubular cystic changes

documented phenomenon [5, 15, 16]. In one study, among ten patients with TSC, four exhibited glomerulocystic kidney disease [16]. Only one of these patients was a teenager and the other three were infants. In each case, the glomerulocystic involvement was unilateral. The glomerular spaces exhibited large, bizarre parietal epithelial cells piled up against Bowman's capsule, and the glomerular tufts exhibited similarly atypical podocytes. The lining in the large cysts in TSC is also different from that in other renal cysts insofar as the epithelial cells are hypertrophic and hyperplastic with strongly eosinophilic cytoplasm [17, 18]. This type of hypertrophy is reminiscent of the phenotype seen in the eye cell of the *Drosophila* gigas mutant, which also lacks *Tsc2* and cannot make tuberin [19]. The protein products of the TSC loci, the tumor suppressors tuberin and hamartin, function together to integrate cellular growth, nutritional, and energy status signals to gate cell growth and facilitate proliferation. Cellular loss of one of the TSC gene products results in constitutive activity of the mTORC1 growth pathway [20].

Table 2 Inherited and genetic malformation syndromes with glomerulocystic disease

Syndrome	OMIM number[a]	Disease reference
Arthrogryposis-renal dysfunction-cholestasis (ARC)	#208085	[46]
Brachymesomelia-renal syndrome	113470	[47]
Cornelia de Lange syndrome	#122470, #300590, #300590	[5]
Congenital nephrotic syndrome Finnish type (microcystic disease)	#256300	[48]
Down syndrome	#190685	[49]
Asplenia with cardiovascular anomalies	%208530	[50]
Multiple acyl-CoA dehydrogenase deficiency	#231680	[51]
Jeune's syndrome	%208500	[5]
Marden-Walker's syndrome	%248700	[52]
Maturity-onset diabetes of the young	#606391	[27, 28, 41, 42]
Meckel-Gruber syndrome	#249000	[26]
Medullary cystic kidney disease	#603860	[24]
Nephronophthisis	#256100	[53]
Orofaciodigital syndrome-type I	#311200	[54]
Phocomelia syndrome or Robert's syndrome (pscudothalidomide syndrome)	#269000	[5]
Short-rib-polydactyly syndrome	%263530, %263520	[55]
Smith-Lemli-Opitz's syndrome	#270400	[5]
Tuberous sclerosis complex	#191100	[5, 14–16]
Zellweger's cerebrohepatorenal syndrome	#214100	[56]

[a] OMIM numbering symbols: #, indicates that a descriptive entry, often a phenotype, and does not represent a unique locus; %, indicates a confirmed Mendelian phenotype or phenotypic locus for which the underlying molecular basis is unknown; no symbol, indicates a phenotypic description for which the Mendelian basis has not been clearly established or that the phenotype may also be in other entries

Fig. 3 An example of glomerulocystic disease in a child with a multicystic dysplastic kidney. **a** Coronal section of a multicystic dysplastic kidney, **b** histology demonstrating glomerular cysts (*arrow*) and a focus of cartilage (*asterisk*) associated with the multicystic dysplastic kidney (magnification 20×)
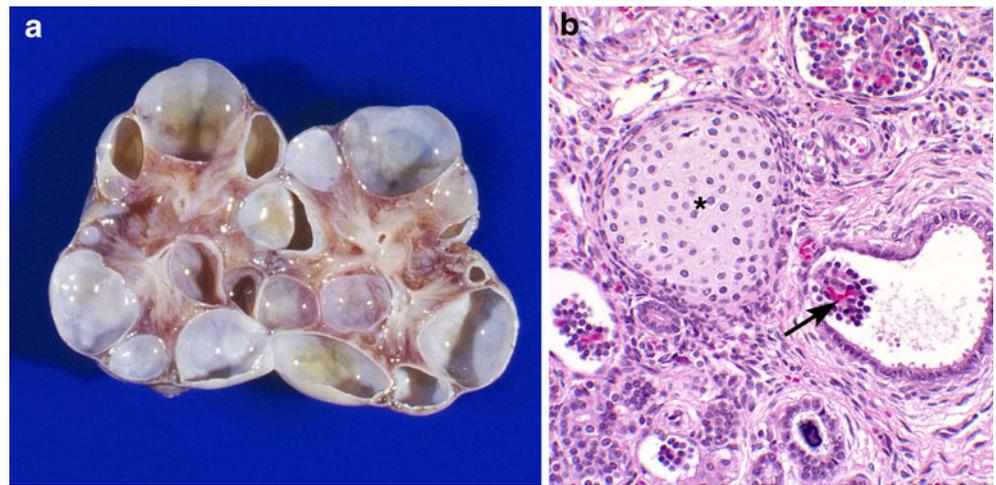

The *TSC2* and *PKD1* genes are adjacent on chromosome 16p13, and a contiguous germline deletion or mutation involving both genes results in a severe polycystic kidney phenotype at birth [21]. Children with this contiguous gene syndrome can be genetically mosaic; for example, DNA obtained from the peripheral white blood cells may show a different fraction of mutant allele when compared to DNA isolated from the kidney [21, 22]. The cystic disease can demonstrate rapid expansion, and the children can have very significant hypertension. This rapid progression may be due to developmental timing of the mutation [11] or its effects on the translation of critical genes. This latter possibility may also be compounded by RNA interference involving translation from the mutated alleles or possibly due to altered gene expression a result of the convergent transcription of genes on the unaffected allele [23]. Although the reason why these affected children have such an accelerated disease is unknown, the cellular morphology in the glomerular and medullary cysts provides strong

evidence that the cysts are very unlike those found in ADPKD. The large size of the cells likely betrays the underlying defect in the mTORC1 signaling pathway for cell growth as well as the role of this pathway in renal development.

Medullary cystic kidney disease

Medullary cystic kidney disease (MCKD) type 2, familial juvenile hyperuricemic nephropathy, and glomerulocystic kidney disease are associated with mutations in the *MCKD2* gene encoding uromodulin. Benetti et al. reported a family with an affected father and son. The son exhibited reduced bilateral kidney volumes, cortical hyperechogenicity, and two cysts in the left kidney, and the renal biopsy revealed the typical enlargement of Bowman's space with fibrosis and alpha actin positivity. At the corticomedullary junction, histological examination revealed immature tubules with cytokeratin and paired box gene 2 (*PAX2*)-positive immu-

Fig. 4 An example of glomerulocystic disease with obstruction. **a** Coronal section of a dysplastic kidney demonstrating a ureteropelvic junction obstruction, **b** histology demonstrating glomerulocystic disease (magnification 40×). Note the normal size of the glomerulus and dense interstitial lymphoplasmic infiltrate and tubular dilatation
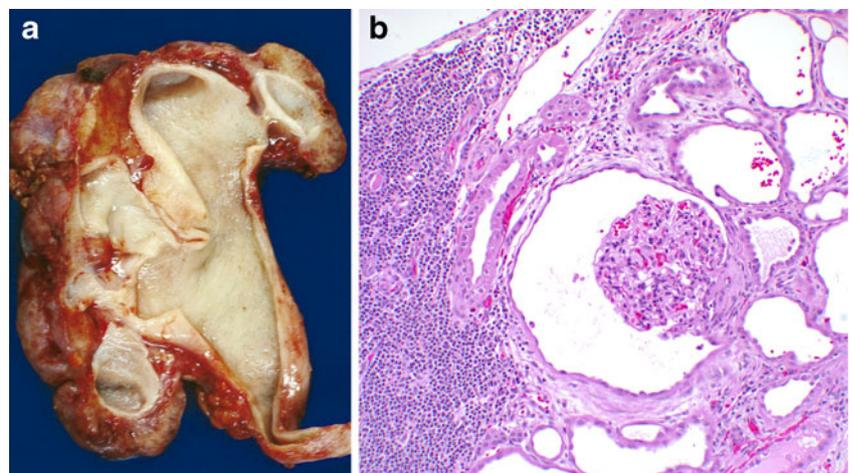
nostaining surrounded by vimentin-positive mesenchymal tissue. The patient did not excrete uromodulin, and a sequencing analysis showed a novel heterozygous sequence change in the *UMOD* gene [24]. Mutations in the *MCKD2* gene often lead to earlier disease manifestation compared to mutations in the *MCKD1* gene [25].

Nephronophthisis

Bergmann et al. studied a mouse model of nephronophthisis as well as families with the disease to understand the phenotypic spectrum of mutations in the *NPHP3/Nphp3* gene and to garner insight into the functional role of the nephrocystin-3 protein [26]. The *pcy* mouse model results from a hypomorphic *Nphp3* allele causing a slowly progressive renal cystic disease, while a complete loss of the locus function results in a more severe, multi-organ phenotype that includes *situs inversus*, congenital heart defects, and embryonic lethality.

The study of these families revealed that *NPHP3* mutations caused a broad clinical spectrum of early embryonic patterning defects that likewise resulted in *situs inversus*, polydactyly, central nervous system malformations, structural heart defects, preauricular fistulas, and a variety of congenital anomalies of the kidney and urinary tract. Importantly, the authors noted glomerulocystic kidney disease in at least one of the patients. There are numerous *NPHP* genes, but only the *NPHP3* gene is currently associated with glomerulocystic disease. The authors further demonstrated that nephrocystin-3 directly interacted with another renal cystic kidney disease-related protein called inversin and that nephrocystin-3 inhibited the inversin-mediated canonical Wnt signaling. Wnt signaling is critical in renal development and has a role in renal cystogenesis. Wnt signaling occurs through the canonical and non-canonical pathways (Fig. 5), and switching between these pathways appears to be controlled by cilial deflection and cilioproteins. Using a Xenopus model, Bergmann et al. demonstrated that nephrocystin-3 deficiency led to planar cell polarity defects, supporting a role for nephrocystin-3 in the control of renal canonical and non-canonical Wnt signaling and establishing the importance of this pathway in renal cystic disease.

Maturity-onset diabetes of the young

Mutations in the gene encoding hepatocyte nuclear factor (HNF)-1β are associated with early-onset diabetes (maturity-onset diabetes in the young) and non-diabetic renal disease, including renal cystic disease. Bingham et al. sequenced the *HNF-1β* gene in four unrelated families with autosomal dominant glomerulocystic kidney disease and identified mutations in two families [27]. The protein
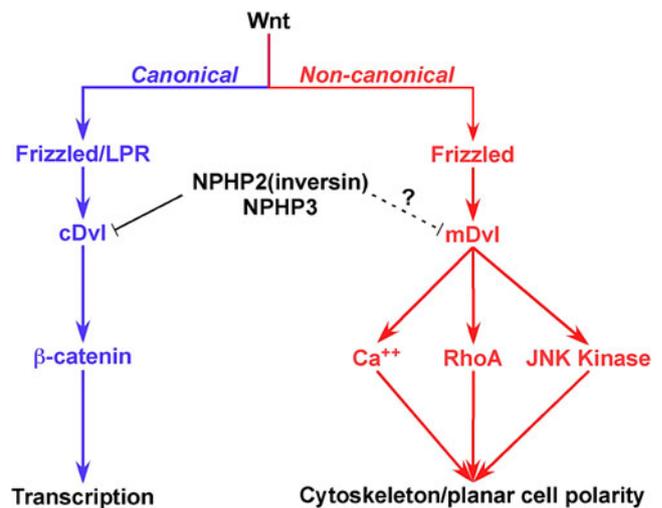

Fig. 5 Wnt signaling pathways. The canonical pathway is mediated through the cystoplasmic protein disheveled (*Dvl*) and ultimately effected through β-catenin-mediated transcription. The non-canonical pathway is mediated through membrane-bound Dvl and ultimately controls planar cell polarity. Inversin, the *NPHP2* gene product, in concert with the NPHP3 protein, appears to facilitate development by controlling the Wnt pathway signaling. *RhoA* Ras homolog gene family, member A

product of this gene, HNF-1β, is a widely expressed transcription factor that is critical for embryonic development of the kidney, pancreas, liver, and Mullerian duct. The affected families exhibited a dual phenotype that included hypoplastic glomerulocystic kidney disease and early-onset diabetes or impaired glucose tolerance. The authors concluded that there was genetic heterogeneity in familial glomerulocystic kidney disease and that the hypoplastic subtype was part of the clinical spectrum of the renal cysts and diabetes syndrome that are associated with *HNF-1β* mutations. Edghill et al. sequenced the *HNF-1β* gene in 160 unrelated subjects with renal cystic disease. Of these patients, only 64 had a personal or family history of diabetes mellitus. They identified 23 different heterozygous *HNF-1β* gene mutations. Despite the original association of the *HNF-1β* gene with diabetes, they emphasized the relationship to renal cystic disease, including glomerulocystic kidney disease [28].

Mechanistic insights into glomerulocystic pathobiology

Associations with the primary cilium

Glomerulocystic disease is an anatomically descriptive term and is associated with cystic disease syndromes, such as autosomal dominant and recessive polycystic kidney disease, maturity onset diabetes in the young, orofaciodigital syndrome, Bardet Biedl syndrome, and nephronophthi-

Table 3 Ciliopathy-related renal disease

Syndrome	Mutated gene	Cilia/centrosome references
Autosomal dominant polycystic kidney disease (ADPKD)	PKD1 PKD2	[57]
Autosomal recessive polycystic kidney disease	PKHD1	[58, 59]
Jeune	IFT80	[60]
Orofaciodigital (type 1)	OFD1	[61]
Meckel–Gruber	MKS1 MSK3	[62]
Nephronophthisis	NPHP1 NPHP2 (inversin) NPHP3 NPHP4 NPHP5 NPHP6 NPHP7 NPHP8 (RPGRIP1L) NPHP9 (NEK8)	[63]
Tuberous sclerosis complex (TSC)	TSC1 TSC2	[64–67]
Bardet–Biedl	BBS1 BBS2 BBS3/ARL6 BBS4 BBS5 BBS6/MKKS BBS7 BBS8 BBS9 BBS10 BBS11/TRIM32 BBS12	[63]

sis, to name a few (Table 3). These syndromic renal cystic diseases are also associated with mutations in genes whose proteins are expressed in the renal tubular primary cilia or centrosome, and this association has lead to a 'unifying theory' of renal cystic disease involving these structures [29].

Primary cilia and the requisite centrosome are found in a variety of cells throughout the body where they serve a predominantly sensory role, including mechanosensation, chemosensation, and receptor-mediated signal transduction [30]. A recent comparative analysis of genomic and proteomic data sets enriched for basal body and ciliary proteins support the suggestion that the vertebrate cilium may require over 1000 different polypeptides [31]. These ciliary and basal body proteins are strongly linked to renal

cystic disease as well as other cellular proliferation-associated diseases, including certain cancers [32]. The number of different proteins associated with cilia begins to shed light on the variety of signaling processes involved. Cilia facilitate signaling through the transient receptor potential (TRP) channels (notably polycystin-2) [33], the Wnt, hedgehog, and mitogen and growth factor pathways [30, 33–35]. Mouse models with disrupted cilia expression (Table 4) lead to a very clear glomerulocystic phenotype (Fig. 6), and cilia are expressed in parietal epithelial cells of Bowman's space (Fig. 7). The Wwtr transcription factor and Glis3, a cilia-related protein, have been shown to interact by co-immunoprecipitation and mammalian two-hybrid systems, and dysfunction of the Glis3 or Wwtr1 signaling pathways results in aberrant gene regulation and the development of glomerulocystic kidney disease [36, 37].

Cilia are crucial for proper embryonic development. During development, the temporal and spatial expression of ciliopathy proteins are tightly controlled, and failure of proper expression can lead to renal cystic disease. Even non-renal manifestations can be explained on the basis of primary cilia; for example, eye findings are a logical extension of the nephronophthisis phenotype because ocular rods and cones are modified cilia. These critical cilial functions help explain the association of some renal cystic disease with such unusual features as retinal abnormalities and situs inversus [38]. The cilial involvement in development and the timing and extent of mutations may also impact the phenotypic expression of renal cystic disease. Glomerulocystic disease, at least in some cases of inherited cystic disease, is often identified in the very young patient, usually by ultrasound studies revealing increased renal cortical echogenicity. The timing of such glomerulocystic disease onset suggests that the pathogenesis may be developmentally regulated, as has been identified for certain murine models of renal cystic kidney disease [39]. In such a case, it is possible that disruptions in specific gene and signaling pathways at critical points during renal development could manifest in the glomerular region in a similar fashion to that of other regions of the kidney. Such temporal and spatial regulation may help explain the wide phenotypic variability of, for

Table 4 Mouse models of glomerulocystic disease

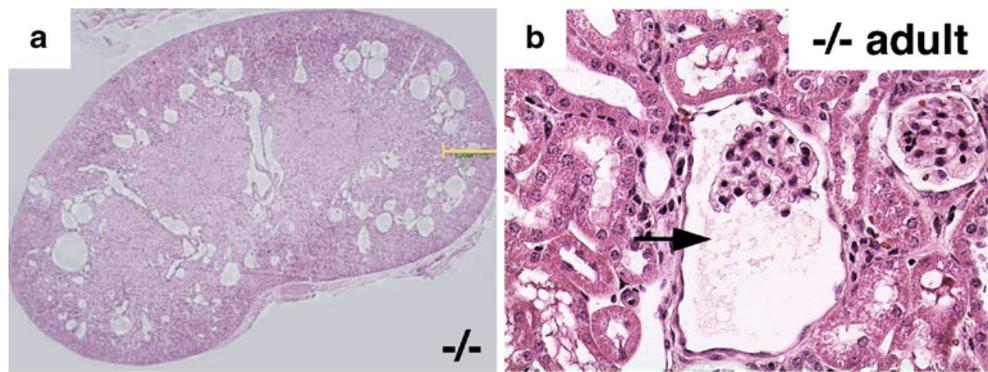| Mouse model	Gene	Reference
pcy mouse	Nphp3	[26]
Wwtr1 mutant	Wwtr1	[36]
Glis3 mutant	Glis3	[37]
jcpk mouse	Bicc1	[8]
Pkd1 over expression	Pkd1	[68]

Fig. 6 Hematoxylin and eosin staining showing glomerulocystic disease in an 8-week old $Wwtr1^{-/-}$ mouse. **a** Coronal kidney sections showing numerous cysts in the corticomedullary region of the kidney from the knockout mouse (magnification 20×), **b** higher magnification showing clear glomerulocystic disease with a reasonably normal glomerulus (*arrow*, magnification 40×). Modified with permission from [36]

example, ADPKD, in which there can be significant pediatric involvement in the cases of very early onset disease and glomerulocystic disease, or geriatric onset disease.

Glomerulocystic disease associated with aberrant expression/signaling of HNF-1β may be indirectly related to primary cilia by virtue of recently described roles for the transcription factor in regulating the expression of certain cystoproteins that are expressed in cilia and in cilia-related cell signaling pathways. Hiesberger et al. recently demonstrated a role for HNF-1β in the transcription of the autosomal recessive polycystic kidney disease protein

PKHD1 [40]. Using a mouse model, these researchers identified an evolutionarily conserved HNF-1-binding site that mapped in a region of deoxyribonuclease hypersensitivity. They also demonstrated the binding of both HNF-1β and HNF-1α to the *Pkhd1* promoter and that this binding stimulated gene transcription. Transgenic mice expressing a dominant-negative HNF-1β controlled by a kidney-specific promoter developed renal cysts, and *Pkhd1* transcripts were not expressed in the cells lining the cysts but were present in normal surrounding tubules. Gresh et al. also noted that renal-specific *HNF-1β* inactivation resulted in polycystic kidney disease, but they further observed a significant

Fig. 7 Immunohistological example of normal glomerular cilia. **a** *Arrowheads* indicate glomerular cilia on visceral and parietal epithelium, **b** magnification of cilia from **a** for a better visualization of the cilia. **c** Glomerular cilia; *arrow* depicts tubular cilia as a control, **d** magnification of cilia seen in **c**. Images were obtained using a Zeiss Axiovert 200 M microscope equipped with a 40× lens; acetylated alpha-tubulin 1:250, Alexa-488 chicken anti-mouse immunoglobulin G 1:250; nuclei stained with DAPI. *Scale bar*: 20 μm
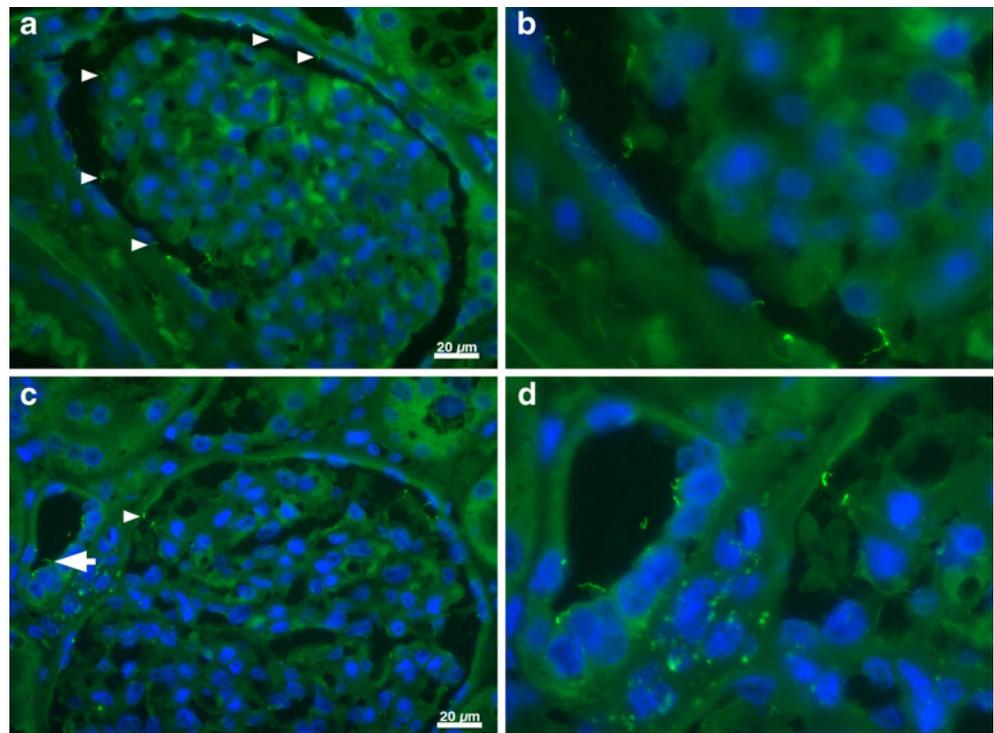
transcriptional defect in the *Umod*, *Pkhd1*, and *Pkd2* genes. These three genes when mutated alone also lead to distinct cystic kidney syndromes [41]. Using immunoprecipitation, they identified that HNF-1β binds to several DNA elements in murine *Umod*, *Pkhd1*, *Pkd2*, and *Tg737/Polaris* genomic sequences, further asserting the link between HNF-1β and cystoproteins. The findings from these murine studies are compelling, but they do not indicate that the neonatal cystic disease is caused solely by reduced expression of these cystoproteins. Haumaitre et al. characterized two human fetuses with novel mutations, one in exon 2 and the other in exon 7 of the *HNF-1β* gene, that exhibited severe bilateral enlarged glomerulocystic kidneys, severe pancreas hypoplasia, and abnormal genital tracts. In contrast to the murine studies, a significant proportion of cysts expressed polycystin-1, polycystin-2, fibrocystin/polyductin complex, and uromodulin. The authors concluded that cyst formation in these cases may have resulted from a deregulation of cell–cell adhesion and/or the Wnt/β-catenin signaling pathway. This contention was supported by the fact that the fetuses exhibited strongly down-regulated β-catenin and E-cadherin in the hypoplastic pancreas [42].

Urinary tract obstruction

The association of glomerulocystic kidney disease with renal dysplasia likewise may be rooted in transcription and developmental gene regulation. Renal malformations are often associated with urinary tract obstruction. Using an ovine model, Attar and colleagues unilaterally obstructed the ureter at a developmental point where only a few layers of glomeruli had formed and then characterized the renal development in the context of the un-obstructed kidney. They identified ureteric and pelvic dilatation and an increased renal parenchymal weight on the operated side compared to the contralateral organs or those from un-operated fetuses. The renal cortex on the obstructed side exhibited glomerulocystic disease [43]. The cystic epithelia strongly expressed *PAX2*, a growth-stimulating transcription factor down-regulated during normal maturation. The cysts also exhibited increased cell proliferation and apoptosis, as had been previously reported in human kidney malformations. Dressler and Woolf described an association between renal cysts and increased *PAX2* expression [44]. One could speculate that the increased proliferation of cells would also be associated with a reduction in the number of primary cilia because the centriole cannot be involved in cytokinesis and cilia formation and maintenance at the same time. In light of these findings, it would be interesting to investigate the potential relationship between primary cilia and *PAX2* expression, particularly whether the persistence of *PAX2* expression beyond its developmental usefulness impacts proper cilia expression and signaling. Unilateral ureteral

obstruction has also been shown to result in rather impressive changes in cilia morphology, supporting a link between cilia structure and function and glomerulocystic kidney disease [45].

Conclusions

The classification of glomerulocystic kidney disease has been almost exclusively descriptive up to this point in time, and for good reason. The different phenotypes are rare and associated with a wide array of additional features. Recent findings regarding gene and protein associations with some forms of glomerulocystic diseases have shed some light on the mechanisms that may underlie disease pathogenesis, indicating that primary cilia dysfunction may be involved. Based on current knowledge, the pivotal role of renal development in renal phenotypic cystic disease expression is to clarify the roles of developmental genes not only in cystogenesis but also ultimately in the link between renal cysts and renal neoplasms.

Questions
(Answers appear following the reference list)

1. Which of the following statements about glomerulocystic kidney disease are true?

   a. Glomerulocystic kidney disease can be associated with autosomal dominant polycystic kidney disease.
   b. Glomerulocystic kidney disease can only be said to occur in otherwise normal kidneys.
   c. Glomerulocystic kidney disease can be associated with tuberous sclerosis complex.
   d. a and c.
   e. a, b, and c.

2. Which statements about glomerulocystic kidney disease and ureteral obstruction are true?

   a. Ureteral obstruction has been shown to be associated with glomerulocystic kidney disease.
   b. Ureteral obstruction has an effect on *PAX2* expression.
   c. Ureteral obstruction has an effect on cilia expression.
   d. a and b.
   e. a, b, and c.

3. Which of the following statements about glomerulocystic kidney disease is false?

   a. Glomerulocystic kidney disease is an anatomically descriptive term.

b. Glomerulocystic kidney disease can be inherited as an autosomal dominant or recessive disorder.

c. Glomerulocystic kidney disease is associated with several different genetic loci.

d. Mouse models of glomerulocystic kidney disease do not resemble the human disease state.

e. Glomerulocystic kidney disease can be associated with changes in Wnt signaling.

4. Which of the following statements about glomerulo-cystic kidney disease is most true?

a. Glomerulocystic kidney disease can be associated with nephronophthisis.

b. Glomerulocystic kidney disease can be associated with medullary cystic kidney disease.

c. Glomerulocystic kidney disease can be associated with tuberous sclerosis complex.

d. Glomerulocystic kidney disease can be associated with maturity onset diabetes in the young.

e. All of the above are true.

5. Which of the following statements about glomerulo-cystic kidney disease is false?

a. Glomerulocystic kidney disease may manifest in some patients because of developmental timing effects.

b. Glomerulocystic kidney disease may manifest because of a change in ureteral patency.

c. Glomerulocystic kidney disease may develop be-cause of changes in Wnt or hedgehog signaling.

d. Glomerulocystic kidney disease may develop fol-lowing Henoch–Schönlein purpura.

e. Glomerulocystic kidney disease may develop fol-lowing nephrotoxin exposure.

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Answers

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2. e
3. d
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5. d