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Cystic Kidney Diseases – many ways to form a cyst

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Abstract

Renal cysts are a common radiological finding in adults and children. They occur in a variety of conditions and the clinical presentation, management and prognosis varies widely. In this article, we discuss the major causes of renal cysts in children and adults with a particular focus on the most common genetic forms. Many cystoproteins have been localised to the cilia centrosome complex (CCC). We discuss the evidence for a universal 'cilia hypothesis' for cyst formation and the evidence for non-ciliary proteins in cyst formation.

Introduction

Renal cystic diseases comprise one of the most common genetic causes of kidney disease in man. As a group, they are however remarkably heterogenous and may present as part of rare syndromes. Autosomal dominant polycystic kidney disease (ADPKD) is the most common inherited cause of end-stage renal disease (ESRD) in adults and accounts for 10% of all ESRD. Nephronopthisis, an autosomal recessive condition is the most common inherited cause of ESRD in children. In this article, we summarise the major genetic causes of cystic disease in children and adults. Due to space considerations, non-genetic and syndromic causes are only mentioned in brief but should be borne in mind as part of the differential diagnosis (Table 1).

Autosomal Recessive Polycystic Kidney Disease (ARPKD)

Autosomal recessive polycystic kidney disease (ARPKD) is caused by mutations in a single gene, *PKHD1*. The incidence is 1 in 20,000 live births and the gene frequency is 1 in 70. Over 300 mutations have been identified and genotype-phenotype

correlations have been described [1] *PKHD1* is located on chromosome 6p12 and encodes the protein fibrocystin/polyductin.[2, 3]

Pathophysiology and Histopathology

The exact function of fibrocystin is unknown. It is expressed on primary cilia and the cytoplasmic tail contains a ciliary targeting sequence.[4, 5] ARPKD is one of a number of conditions grouped together as 'ciliopathies'[6]. Cystogenesis is probably caused by aberrant cell proliferation and apoptosis but it is still unclear how this is regulated. Down regulation of *PKHD1* induces cell apoptosis [7]. Fibrocystin binds to and functionally interacts with the PKD2 protein, polycystin 2 [8, 9]. A genetic interaction between *Pkd1* and *Pkhd1* has been reported though no direct interaction was demonstrated between fibrocystin and the PKD1 protein, polycystin 1 [10].

Patients with ARPKD have diffuse dilatation and elongation of the renal collecting ducts. Cysts are usually small (<3mm) but as their number increases, the kidneys enlarge. At autopsy, there is poor corticomedullary differentiation due to the extension of the collecting ducts from the medulla to cortex. In foetuses and neonates, there is a correlation between genotype and the degree of collecting duct extension and cortical tubule lesions.[11]

All patients with ARPKD have congenital hepatic fibrosis (CHF) or Caroli disease. The histological basis of CHF is a ductal plate malformation which consists of portal fibrosis, bile duct proliferation and hypoplasia of portal vein branches leading to portal hypertension [12]. The pathognomonic feature of Caroli disease is the presence of non-obstructive dilated intrahepatic bile ducts.

Clinical Presentation

ARPKD affects males and females equally and can affect all racial groups. There is a wide spectrum in the age of presentation which correlates with disease severity. Those with the most severe phenotype present in the neonatal period with oligohydramnios, pulmonary hypoplasia and Potter facies. Although ARPKD has been classically reported in childhood or adolescence, mild or late onset disease can present in adult life, occasionally as isolated CHF [13]. In a single centre retrospective study, the actuarial renal survival of ARPKD children surviving the first month of life was 86% at one year [14]. Similarly, a second retrospective study showed that overall survival 20 years after diagnosis depended largely on the age at presentation ie 36% (< 1yr), 80% (1-20yrs) and 88% (>20yr) [13]. In a study of 164 neonatal survivors with ARPKD, the renal survival rates were 86% at 5 years, 71% at 10 years, and 42% at 20 years [15]. Thus apart from severe neonatal presentation, overall survival is surprisingly good.

Individuals may develop urinary concentrating defects and present with polyuria and polydipsia. Recurrent urinary tract infections (UTIs) may occur and hypertension is common, leading to cardiac hypertrophy and congestive cardiac failure in severe cases. Portal hypertension due to congenital hepatic fibrosis leading to splenomegaly and varices can be the presenting feature. Although hepatocellular function is usually preserved, ascending suppurative cholangitis can lead to hepatic failure [12]. Progression to end stage renal disease (ESRD) is common.

Investigations

The diagnosis of ARPKD relies mainly on imaging. Ultrasound can make the diagnosis prenatally by showing bilaterally enlarged echogenic kidneys. In the neonate, ultrasound shows bilateral smooth enlarged kidneys which are diffusely echogenic with poor corticomedullary differentiation. The liver may also show an increase in parenchymal echogenicity. Studies have suggested that the kidney size stays stable or reduces with increasing age with increased echogenicity in the cortex.[16] There may be macrocysts in the liver and pancreas and splenomegaly. Portal hypertension is associated with reversal of hepatic blood flow detectable by Doppler ultrasound.

Several studies have shown a clear genotype-phenotype correlation for ARPKD. In one study, the presence of a single truncating *PKHD1* mutation was associated with death in the first month of life whereas the presence of a missense mutation was associated with survival beyond the first month. All patients inheriting two truncating mutations were uniformly associated with perinatal or neonatal death [17].

Mutation testing is now available with an overall detection rate of 77% [13, 15]. Most mutations are private and numerous polymorphisms have been reported in *PKHD1*. In European populations, T36M is the most common mutation reported (15-20%) and could represent a founder mutation [15]. Linkage analysis could be unreliable since other genes may phenocopy ARPKD.

Treatment

ARPKD is not curable. In the neonatal period, mechanical ventilation may be required for pulmonary hypoplasia or respiratory compromise due to enlarged kidneys.

Bilateral nephrectomy may be indicated. In anuric individuals, continuous veno-venous haemofiltration (CVVH) or peritoneal dialysis can be used. Hypertension and urinary tract infections should be treated adequately.

Hepatic complications are common. Bacterial cholangitis is serious and must be treated promptly. Oesophageal varices can be treated by sclerotherapy, banding or insertion of a porto-caval shunt. A final option is partial liver transplantation, sometimes combined with renal transplantation.[18]

The mTOR pathway is activated in ARPKD kidneys suggesting that mTOR might be a potential target to slow cyst development.[19] In animal models of experimental polycystic kidney disease, mTOR inhibition was shown to reduce cyst growth and slow the loss of renal function.[20] (but see later).

Prognosis

Currently it is estimated that 23-30% of affected individuals die in the first year of life.[14, 15] For those that survive the first year of life, 10 year survival is estimated to be 82%.[15]. Significant intrafamilial variability has been reported in some families indicating the influence of modifying genes [17].

Autosomal Dominant Polycystic Kidney Disease

Autosomal dominant polycystic kidney disease (ADPKD) is among the most common inherited diseases in man. Its prevalence is 1 in 400 to 1 in 1000. 85% of affected families have mutations in *PKD1* (located on the short arm of chromosome 16) which encodes for Polycystin 1. The rest have mutations in *PKD2* (located on the long arm of chromosome 4), which encodes for Polycystin 2. Some studies have proposed a

third gene but this has not been identified.[21, 22] Individuals with *PKD2* mutations present later and have a slower rate of progression to ESRD than individuals with *PKD1* mutations.[23] Transheterozygotes with mutations in both *PKD1* and *PKD2* have been reported; their clinical course is more severe than for individuals with mutations in simple heterozygotes.[24]

Pathophysiology and Histopathology

Polycystin 1 and 2 form a functional receptor-channel complex and a defect in either protein leads to renal cyst formation and an overlapping clinical phenotype [25, 26]. Both proteins have overlapping subcellular distribution including in primary cilia [27, 28]. However, polycystin-2 is mainly resident in the ER where it can function as a Ca^{2+} release channel. [25, 26] Unlike ARPKD, cysts can arise from any part of the nephron. Cysts arise as outpouchings connected to the tubular lumen which eventually disconnect. Over time, they enlarge, destroying normal parenchyma and result in bilateral kidney enlargement.

Clinical Presentation

Most patients present between 20-40 years of age but can present in childhood (early onset, under 15 years of age) or even *in utero* (very early onset, less than 2 years of age). Common renal symptoms include abdominal pain, polyuria, UTIs, haematuria and hypertension. Extra-renal features are rare in children. They include hepatic, pancreatic, ovarian, splenic and intestinal cysts. There is an increased prevalence of mitral valve prolapse, aortic aneurysms and intracranial aneurysms.[29]

Investigations

Age banded ultrasound criteria have been established for the diagnosis of ADPKD in families with a positive family history.[30] CT and MRI are more sensitive than ultrasonography in the detection of cysts but have not been formally evaluated against ultrasonography.[31] Genetic testing for *PKD1* and *PKD2* by direct DNA sequencing are now readily available for predictive and diagnostic testing.[32, 33] In a research setting, positive detection rates of up to 89% have been reported [34]. Of these, 60-65% had definite *PKD1* mutations, 4% had large deletions/duplications while 20-26% were missense changes; in this latter group, it may be difficult to assign pathogenicity in the absence of a functional test. Evolutionary conservation, predicted effects on secondary structure or splicing, the absence of other pathogenic changes and segregation analysis within the pedigree will inform the likelihood whether a particular change is pathogenic (but see later). *PKD1* is also highly polymorphic (average 10 neutral variants per patient) and this complicates the interpretation of any changes found [34].

Predictive testing is indicated in potential live related kidney donors from ADPKD families where imaging is negative or equivocal in the under 40 year age group.[35] Diagnostic testing is indicated in families with very early-onset disease (under 2 years of age) where a very high recurrence rate of (~45%) has been reported [36]. This could facilitate pre-implantation genetic diagnosis where indicated.

Some early-onset cases may relate to the co-inheritance of an incompletely penetrant or hypomorphic *PKD1* allele from the 'normal' parent which in combination with an inactivating allele, leads to the severe early-onset phenotype [37, 38]. Since the penetrance of a single hypomorphic allele is low, segregation may appear as an

apparent 'de novo' mutation or recessive (phenocopying ARPKD) inheritance. The prevalence of hypomorphic alleles as disease modifiers in early-onset or typical onset disease is not known.

The co-inheritance of germline mutations in other cystic disease genes (eg *HNF1β, PKHD1*) alongside *PKD1* or *PKD2* alleles may similarly lead to a more severe renal phenotype [39]. The rate of new mutation for PKD1 has been estimated at 4-5% of cases though the possibility of mosaicism or non-paternity should be considered in the absence of a positive family history [40]. Other diseases that may phenocopy ADPKD if present in the carrier state (OFD-1 females) or if other systemic features are mild (eg HNF1b, TSC) should form part of the differential diagnosis.

The screening of asymptomatic at risk children is presently not recommended. However it has been reported that the prevalence of hypertension (15%), borderline hypertension (15%) and microalbuminuria (36%) in children with ADPKD could be higher than previously thought [41] and associated with increased left ventricular mass in children with borderline hypertension [42]. A reasonable course of action would therefore be to monitor at risk children for the development of hypertension and proteinuria and institute antihypertensive treatment early. In future, screening could be offered at an earlier age once an effective intervention is identified.

Treatment

The mainstay of treatment is controlling hypertension, reducing proteinuria and treating infections. Two recent trials failed to demonstrate an improvement or slower

rate of decline of eGFR with mTOR inhibition [43, 44]. Several other interventional studies are in progress.[45, 46].

Prognosis

Heart disease is the most common cause of death among patients with ADPKD, followed by infection and neurological events.[47, 48] Renal function does not usually start to decline until the fourth decade.[49]

Nephronophthisis

Nephronophthisis (NPHP) is an autosomal recessive condition caused by more than 13 genes [50]. It has been reported worldwide with an incidence of 9 per 8.3 million in the USA and 1 in 50,000 live births in Canada [51]. Clinically, three forms of NPHP (infantile, juvenile and adolescent) are recognised based on the age of presentation (Table 2). Extra-renal features are present in 10-20% of cases of NPHP [52]. A number of syndromes with nephronophthisis and prominent extra-renal features associated with mutations in NPHP genes have been described. These include Joubert's syndrome (cerebellar ataxia), Senior-Loken syndrome (tapetoretinal degeneration) and Cogan's syndrome (oculomotor apraxia) [53]. In addition, some NPHP genes (NPHP6, 8, 11) can phenocopy the lethal Meckel-Gruber syndrome (occipital encephalocele, polydacytyly, enlarged dysplastic kidneys).

Pathophysiology and Histopathology

On ultrasound, patients with NPHP may have normal or reduced kidney size, corticomedullary cysts or loss of corticomedullary differentiation. On renal biopsy, tubular atrophy, interstitial fibrosis and changes in the tubular basement membranes

(TBM) are prominent features. The TBM is irregularly thickened and often there is an abrupt transition between a thick segment and a normal or disintegrated one.[54]. In infantile NPHP, there are typically no TBM changes; the features are those of moderate renal enlargement with cortical microcysts. [55]

A total of 13 recessive genes (NPHP1-13) have been linked to the NPHP phenotype, some in single families; these account for less than 30% of all patients indicating that the majority of NPHP genes are yet to be discovered [56]. In a world-wide cohort of 365 NPHP families, NPHP1 mutations were the most frequent and accounted for 64% of all identified alleles [50]. The identification of these genes has led to the recognition that mutations in some 'NPHP' genes (eg NPHP 6, 8, 11, 12) can give rise to both mild (NPHP), intermediate (Joubert's syndrome, JBTS) and severe (Meckel-Gruber syndrome, MKS) phenotypes. The genetic mechanisms determining phenotype are complex with evidence of gene locus heterogeneity, allelic effects (NPHP6) and modifier genes, all of which interact to determine disease severity and the extent of extrarenal involvement [50].

A common finding in NPHP proteins is their localisation to primary cilia or centrosomes [57]. Mutations in these genes therefore impair ciliary function both in renal tubular epithelial cells and in other organs.[52] Some NPHP proteins (NPHP1, 2, 4, 10) also localise to cell-cell junctions or focal adhesions (NPHP1) where they regulate junction integrity and polarity [58-60]. In some cells, distinct ciliary sub-compartment localisation has been reported for different NPHP proteins [61]. Of interest, NPHP1 has also been reported to bind polycystin-1 and may regulate apoptosis [62].

The NPHP proteins do not share a high degree of sequence homology but rather form interacting protein complexes which function in distinct pathways or subcellular compartments. A recent study has shown that the NPHP proteins co-purify in at least 3 separate protein complexes with distinct subcellular locations and functions [63]. NPHP1, 4 and 8 are present in the transition zone of primary cilia and regulate apical junction formation, NPHP 5 and 6 are located at the centrosomes and regulate ciliogenesis whereas the MKS proteins, MKS1 and MKS6 regulate hedgehog signalling. NPHP2/INVS and the JBTS3/AHI1 protein, Jouberin act as molecular bridges between the three modules. These findings provide a molecular link between NPHP, JBTS and MKS and an explanation for the overlapping spectrum seen in these diseases. However, the proteins that make up the transition zone could vary between cell types and organisms [61, 64-66].

Clinical Presentation

Juvenile nephronophthisis (ESRD ≥ 4yr) is the most common form of NPHP and the usual age at which NPHP presents (except for NPHP2/INVS). The first symptoms usually develop at 4-6 years of age. Reduced urinary concentrating capacity and increased urinary sodium loss leads to polyuria, polydipsia, enuresis and dehydration. Chronic dehydration and eventually renal insufficiency causes growth retardation and failure to thrive [52]. Due to the mild nature of the initial symptoms, there can often be a delay in diagnosis. As there is salt wasting, blood pressure does not tend to be raised until individuals develop renal failure. A normochromic, normocytic anaemia is common and may occur prior to renal insufficiency. [67] ESRD occurs at a mean age of 13 years. [68]

The **adolescent** form was described after identification of the NPHP3 gene in a large Venezuelan family. ESRD occurred at a mean age of 19.[69] However the histological features are very similar to the juvenile form and often they are regarded as part of the same disease. The age of ESRD in NPHP3 appears more variable than other forms of NPHP, ranging between 3 to 13 yrs.

Infantile NPHP (ESRD ≤ 4yr) is usually caused by mutations in *NPHP2/INVS* although patients with other NPHP mutations can present with infantile ESRD [50, 70]. *Situs inversus* and ventricular septal defects are commonly associated with NPHP2 [52].

Investigations

Urinalysis shows low specific gravity in early morning samples. Careful ophthalmoscopy should be performed and an MRI to look at the cerebellum if neurological symptoms are present [53].

Genetic testing is possible in many cases, negating the need for renal biopsy. Screening for gene mutations can be guided by the age of presentation and the presence or absence of specific extra-renal features.[50, 52] Asymptomatic siblings are screened for urinary concentrating defects and abnormalities on USS rather than undergoing genetic testing.

Treatment

There is no specific treatment. NPHP does not recur in the transplanted kidney. Live related heterozygous carriers can donate.

Prognosis

The prognosis depends on the age of presentation and whether there are extra-renal features.

Medullary Cystic Kidney Disease

Medullary cystic kidney disease (MCKD) is a rare autosomal dominant condition leading to ESRD. It generally presents in adulthood but can occur in children.[71] It was once thought to be the same disease entity as juvenile NPHP due to the overlapping phenotypes.[72] The condition is caused by mutations in several genes.[73, 74] The MCKD1 locus has been mapped to chromosome 1q21 but the gene has yet to be identified. The MCKD2 locus on chromosome 16p12 has been identified as the *UMOD* gene [74].

Recently, it was proposed that MCKD be reclassified as one of four types of autosomal dominant interstitial kidney disease (ADIKD) based on the underlying gene mutation: (1) <u>*UMOD*</u>: mutations in UMOD are the most common and can present as MCKD2, familial juvenile hyperuricemic nephropathy (FJHN), uromodulin-associated kidney disease (UAKD) and glomerulocystic kidney disease (GCKD); (2) <u>*REN*</u>: mutations in *REN*, which encodes renin, have been identified in a few ADIKD families [75]; (3) <u>Chromosome 1q21</u>: also known as MCKD1; (4) <u>Unidentified genes</u>: some families without *UMOD* or *REN* mutations and unlinked to chromosome 1 have been reported [76]. This classification does not require the

presence of cysts for diagnosis and reflects the highly variable cystic phenotype in

ADIKD which is most prominently expressed as MCKD.

Pathophysiology and Histopathology

MCKD1

Renal biopsy shows tubular atrophy, interstitial fibrosis, lymphocytic infiltration,

splitting or lamellation of the thickened and irregular tubular basement membranes

[77]. The glomerular basement membranes are usually unaffected though glomerular

sclerosis can occur.

MCKD2

The *UMOD* gene on chromosome 16p12 encodes for uromodulin, the most abundant

protein found in normal human urine and which is expressed specifically in the thick

ascending loop of Henle. Its functions are not well understood but it is thought to

maintain the watertight properties of the thick ascending loop of Henle and/or protect

against UTIs.[78, 79] Mutant uromodulin accumulates in the endoplasmic reticulum

leading to tubular cell atrophy and death.[80] One study has reported uromodulin

expression in primary cilia and centrosomes. [81] *UMOD* mutations are associated

with hyperuricaemia and early-onset gout: FJHN is allelic to MCKD2. On biopsy,

diffuse tubulointerstitial fibrosis is prominent with occasional tubular dilatations or

cysts [82].

Clinical Presentation

MCKD1

The clinical picture of MCKD1 is that of a slowly progressive chronic kidney disease. There is minimal proteinuria and haematuria. Hypertension becomes more common as the kidney disease progresses, as does hyperuricaemia.[77] The course of the disease is variable with ESRD occurring between 25 and 55 years of age.[77, 83]

MCKD2

Hyperuricaemia is characteristic of MCKD2. In females, this is often asymptomatic but commonly presents as gout in teenage males.[84] As with MCKD1, progressive renal impairment occurs. Hypertension can occur but proteinuria is minimal. Mild concentrating defects can also occur [85].

Investigations

MCKD1

The absence of significant proteinuria in a patient with renal impairment and a strong family history should be enough to consider MCKD. Cysts are sometimes seen on ultrasound but are not essential for the diagnosis.[77] Renal biopsy can be performed but the findings are non-specific.[86] A definitive diagnosis can be made through linkage analysis if there is linkage to chromosome 1q21.

MCKD2

As with MCKD1, diagnosis often relies on clinical suspicion. Patients with MCKD 2 often have hyperuricaemia. Medullary cysts may be seen on ultrasound. The biopsy findings are non-specific. Mutational analysis of the *UMOD* gene can confirm the diagnosis.

Treatment

MCKD1

Treatment is mainly supportive. The disease does not recur in the transplanted kidney but family members need to be screened if they come forward as live donors.

MCKD2

The management of MCKD2 is the same as MCKD1 except for the possible benefits of allopurinol. Allopurinol can be used to prevent gout but there is conflicting evidence as to whether early allopurinol therapy can also prevent progression to ESRD. [82, 84, 87]

Prognosis

The age of progression to ESRD varies between 20 and 70 years of age.

Hepatocyte Nuclear Factor 1-beta (HNF1β) Mutations

Mutations of *HNF1β* were first identified as a rare cause of maturity-onset diabetes of the young type 5 (MODY5).[88] It is now recognised that *HNF1β* mutations are responsible for a range of different renal abnormalities including cystic diseases. The *HNF1β* gene is located on chromosome 17q12.

Pathophysiology and Histopathology

HNF1β is a member of the homeodomain-containing superfamily of transcription factors. It encodes the transcription factor 2 (TCF2) and functions as a homodimer or heterodimer with *HNF1α*.[89] *HNF1β* appears to be a master regulator controlling the

transcription of multiple cystic genes including *PKHD1, PKD2, UMOD* and *Tg737/polaris*.[90]

The pleiotropic features of *HNF1β* mutations can be explained by its role in the development of pancreas, kidney, liver, lung and gut and expression in the neural tube and genital tract.[91, 92] In the embryonic kidney, *HNF1β* is expressed in the ureteric bud, the comma and s-shaped bodies and in the proximal and distal tubules [91] Although it is not expressed in glomeruli, glomerulocystic kidney disease has been associated with *HNF1β* mutations (see later). It has been suggested that the formation of glomerular cysts could result from transient obstruction of immature nephrons.[93]

Several studies have not found a clear genotype-phenotype correlation between the type of mutation and the severity and/or type of renal disease. There is strong intrafamilial variability suggesting that non-allelic or environmental factors must be important.[89, 94] Mutations may involve heterozygous deletion of the whole gene or small mutations including missense, nonsense, frameshift and splice site mutations. In the studies to date, *de novo* mutations accounted for a third to half of all cases.[88, 94]

Clinical Phenotypes

Renal cysts are present in most *HNF1β* carriers, including some with glomerulocystic kidney disease (GCKD). Renal malformations are also common eg single and horseshoe kidneys.[89, 94] *HNF1β* mutations have been identified in all cases of familial hypoplastic glomerulocystic kidney disease examined so far. This condition is inherited in an autosomal dominant fashion.[93] Not all individuals with *HNF1β* mutations have diabetes but renal cysts and diabetes (RCAD) is a common

phenotype.[94] Prenatally, bilateral hyperechogenic kidneys of normal or moderately enlarged size is the most frequent finding. Other prenatal phenotypes include bilateral multicystic kidney disease (MCD), unilateral MCD, unilateral renal agenesis, unilateral renal hypoplasia, renal macrocysts and isolated upper urinary tract dilation. All patients with unilateral MCD developed postnatal abnormalities in the contralateral kidney.[89] The degree of renal impairment varies widely with some cases of ESRD presenting in childhood or prenatally but other adult cases with normal renal function.

Other features of *HNF1β* mutations include early onset gout and/or hyperuricaemia, genital tract malformations, pancreatic atrophy, abnormal liver function tests and hypomagnesaemia. [89, 93]. The underlying pathogenesis of hyperuricemia in some patients is unknown though rarely, it may phenocopy FJHN (see above) [95]. In a seminal study, hypomagnesemia was found in 44% of children with *HNF1β* mutations [96] and was associated with urinary magnesium wasting and hypocalciuria in a subset of patients. The likely pathogenesis of this abnormality is a defect in *HNF1β* mediated transcription of *FXYD2*, which encodes the γ subunit of Na^+-K^+-ATPase; mutations in *FYXD2* are associated with autosomal dominant hypomagnesemia and hypocalciuria [97].

Investigations

HNF1β mutations should be considered in all individuals with an unidentified cause of cystic kidney disease. Since a significant proportion of mutations are de novo, the absence of a family history should not preclude genetic testing.

Treatment

The treatment is dependent on the degree of renal impairment and the presence of
other features such as diabetes.

Prognosis

The prognosis varies widely and is difficult to predict. Genetic counselling is also
challenging due to the lack of phenotype-genotype correlation.

Glomerulocystic Kidney

The term glomerulocystic kidney (GCK) refers to a kidney with more than 5% cystic
glomeruli.[98] Lennerz proposed a useful classification system and suggested that the
term glomerulocystic kidney disease (GCKD) is used for the familial subtypes
only.[99]

Type I: GCK in PKD

Early onset ADPKD sometimes presents as GCK.

Type II: Hereditary GCK (GCKD)

GCKD includes autosomal dominant GCKD (ADGCKD) due to *UMOD* mutations,
familial hypoplastic GCKD due to *HNF1β* mutations and GCKD due to mutations
that have not yet been classified.

Type III: Syndromic GCK

Syndromic GCK is when GCK occurs as part of a known syndrome without dysplasia,
the most common being tuberous sclerosis. Other examples include Zellweger

cerebrohepatorenal syndrome, von Hippel Lindau disease and X-linked dominant oral-facial-digital syndrome type 1 (OFD-1).

Type IV: Obstructive GCK

Obstructive GCK is GCK associated with renal dysplasia or urinary obstruction without dysplasia and no evidence of a heritable condition. It is a common cause of GCK.

Type V: Sporadic GCK

Included in this category are ischaemic GCK and drug induced GCK. The ischaemic causes are often due to systemic sclerosis or haemolytic uraemic syndrome. Lithium is a recognised cause of drug-induced GCK.

Pathophysiology and Histopathology

Glomerular cysts are defined as Bowman space dilatation of more than 2 to 3 times the normal size.[98] Glomerular tufts help to distinguish glomerular cysts from cysts of tubular origin but may be absent if the tufts degenerate. [99] The pathogenesis of GCK is unknown although a number of theories have been proposed.[99] There is some evidence that primary cilia dysfunction may be involved.[100]

Clinical Presentation

The presentation of GCK varies. Infants may present with an abdominal mass or renal insufficiency. In later childhood or in adulthood, the presentation may be with haematuria, hypertension or abdominal pain. In cases of syndromic GCK, patients are

likely to present with other features. UTIs may precede diagnosis of GCK in obstructive causes.

Investigations

GCK is not easy to diagnose by ultrasound in the foetus or neonate. It is difficult to distinguish GCK from other cystic renal conditions.[101] In adults, glomerular cysts are often missed by ultrasound or CT. MRI is much more reliable.[102] Renal biopsy may be necessary to distinguish GCK from tubular cystic disease. Genetic testing is possible for certain subtypes of GCK.

Treatment

The treatment will depend on the underlying cause of GCK. Most treatments will be symptomatic.

Prognosis

The prognosis is variable and depends on the underlying cause of GCK and the rate of decline in renal function.

The ciliary hypothesis and cystic disease

Primary cilia as sensory organelles

Primary cilia are hair-like organelles expressed by almost every cell and tissue in the body [103]. Unlike motile cilia, primary cilia are generally non-motile though they are sensitive to bending or flow [104]. Sensory cilia involved in vision and smell are modified primary cilia showing that they can sense visual and olfactory stimuli.

In non-dividing polarised epithelial cells, cilia extend as apical structures consisting of a microtubule core enveloped by a membrane lipid bilayer. Ultrastructurally, all cilia can be classified as '9+2' (motile) or '9+0' (primary) depending on the presence or absence of a central pair of microtubules. Prior to entering mitosis, cilia are resorbed and both centrosomes form the mitotic spindle poles. As cells become quiescent, cilia reform. More recently, ciliary sub-compartments have been described associated with specific locations of different proteins (Figure 1A).

Cilia, flagella and intraflagellar transport

Evolutionarily, cilia are structurally related to (motile) flagella expressed by single cell organisms such as the green algae, *Chlamydomonas reinhardtii*. Remarkably, proteins involved in the formation and maintenance of flagella structure, a microtubule-dependent process called intraflagellar transport (IFT) are highly conserved throughout evolution, being also expressed in mammalian cilia [27]. IFT is essential for the assembly, disassembly and maintenance of cilia. In brief, an IFT-B complex (at least 15 proteins) is transported from the cilia base to the cilia tip through the action of the microtubular motor protein kinesin. An IFT-A complex (6 proteins) is transported from the ciliary tip to the base through the action of dynein (Figure 1A).

Mutations in human IFT proteins have been associated with several skeletal dysplasia syndromes such as Sensenbrenner syndrome (cranioectodermal dysplasia, MIM 218330), Jeune syndrome (asphyxiating thoracic dysplasia, MIM 611263) and short-rib polydactyly (MIM263510). Mutations in two IFT-A proteins (IFT139, 144) syndrome have been reported with in patients with isolated nephronopthisis (NPHP12, 13) indicating a phenotypic overlap between Sensenbrenner syndrome and NPHP.

Cilia, centrosomes and the cell cycle

The link between cilia and cystic disease came from several co-incidental findings [28]. Since these seminal discoveries, many more proteins associated with a cystic kidney phenotype have been localised to primary cilia and their associated structures, the centrosomes. This has led to the formulation of the 'ciliary hypothesis' as a unifying pathogenic mechanism for cyst formation [27]. A link to cell cycle control is also implied by the fact that the mother centriole (or basal body) enucleates the primary cilium (present in non-dividing cells) and that both centrioles also form the mitotic spindle poles (in dividing cells). Some cystoproteins remain localised at the spindle poles during mitosis. These cilia-associated diseases have been termed 'ciliopathies' [57].

Cilia signalling in extrarenal tissues

Abnormalities in cilia structure or function could explain some of the unusual extrarenal features reported in some of these diseases such as *situs inversus*, retinitis pigmentosa, skeletal or digital abnormalities and CNS malformations.

Left-right patterning of the body axis is determined by the function of nodal cilia which are motile and transmit an asymmetric Ca^{2+} signal. The findings of *situs inversus* in *Pkd2* null mice [105] and in several other ciliopathy mutants (eg *nphp2/invs*) indicated that a more general abnormality in cilia function could explain the systemic features of the ciliopathies. In the retina, the connecting cilium represents a modified transition zone which controls the transport of rhodopsin containing vesicles between the inner and outer photoreceptor segments. The finding of retinitis

pigmentosa in many ciliopathies correlates with their localisation to this structure. Finally, a clear link between hedgehog signalling, a key developmental signalling pathway, and primary cilia signalling has been shown in mouse models [106]. Abnormalities in hedgehog signalling probably underlie the digital and CNS abnormalities seen in some of the ciliopathies. Other signalling pathways that have been linked to primary cilia are the Wingless (Wnt) and Notch pathways, cAMP/PKA, PDGF-α, somatostatin receptor 3 (SSTR3) and mTOR kinase (Figure 1A). Although these are not associated with discrete phenotypes and may vary between tissues, they do indicate that a variety of ligand-gated receptors can signal through cilia.

Cilia signalling in the kidney

How abnormalities in cilia or centrosome function lead to renal cysts is still unclear. Apart from intercalated cells, it is thought that all renal cells throughout the nephron express primary cilia. Motile (9+2) cilia are expressed in the pronephros of lower vertebrates and have been occasionally detected in human kidney [107, 108]. In the latter, they could represent a recapitulation to an embryonic phenotype or a dedifferentiation phenotype to injury.

Planar cell polarity (PCP) and oriented cell division (OCD) are two key processes that are critical for maintaining tubular diameter during tubular elongation in development or repair following injury. Renal epithelial cell cilia are sensitive to flow [104]. Defects in OCD have been reported in several cystic mouse mutants linked to cilia structure (Kif3a) or function (HNF1b) [109, 110]. The non-canonical Wnt pathway is likely to be important in PCP regulation in the kidney [111] and the switch between the two limbs of Wnt signalling mediated through primary cilia flow sensing [112].

Pkd1 mutant tubular cells have defects in cilia-mediated flow-induced Ca^{2+} signalling [113]. There is conflicting evidence as to whether abnormalities in OCD or PCP are critical to the onset of cyst formation in ADPKD or ARPKD [114, 115].

Non-ciliary mutants and renal cysts

It is helpful to consider that in the vast majority of the ciliopathies, renal cysts are rare unless associated with organ dysplasia (Meckel's) or of late-onset when associated with degeneration (NPHP). These phenotypes appear distinct from those of more 'classical' cystic diseases such as ADPKD and ARPKD, even though these are included in the ciliopathies. This could mean either that the ADPKD or ARPKD proteins serve more distinct ciliary functions (from the other ciliopathy proteins) or that their non-ciliary functions may be more important in preventing cyst formation. In this regard, it is worth noting that polycystin proteins are also prominently expressed at the basolateral membrane in epithelial cells (where they may regulate cell adhesion) and that polycystin-2 can also function as an ER located Ca^{2+} release channel. [25] We cannot easily differentiate the relative importance of ciliary and non-ciliary functions of the two proteins at present. Similarly, several of the NPHP genes (NPHP1, 2, 4, 10) are clearly expressed at the basolateral epithelial membrane where they could regulate epithelial morphogenesis independent of their cilia function.

Other cystogenic proteins that have exclusive non-ciliary locations are the ER proteins, Sec63 (MIM 608648) and PRKCSH (MIM 177060), which are associated with autosomal dominant polycystic liver disease (ADPLD), the mitochondrial protein XPNPEP3 (MIM 613553) which is associated with a nephronopthisis-like phenotype (NPHP-L1) with occasional cysts, the basement membrane proteins, Laminin α5

(LAMA5, MIM 608648) and collagen IVα1 (COL4A1, MIM 601033) which when mutated, can be associated with renal cysts [6].

These observations suggest two possibilities. First, normal ciliary structure or function is essential in the pathogenesis of all cystic diseases and that even 'non-ciliary' cystogenic proteins may somehow interfere with the processing, trafficking or function of key ciliary mediators. An alternative explanation is that there are both ciliary and non-ciliary pathways involved in the pathogenesis of cysts.

Conclusions

Mutations in genes that affect ciliary structure or function are increasingly recognised as an important group of diseases (the ciliopathies). Nonetheless, they are highly heterogenous and it may be helpful to think of a phenotypic spectrum ranging from dysplasia to degeneration or cystic change (Figure 1B). The occasional phenotypic overlap between NPHP, JBTS and MKS illustrates this well. The mechanistic link between cilia dysfunction and cystic transformation in the kidney remains to be fully elucidated.

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Figure legends

Figure 1

(A) <u>Cilia structure and signalling</u>. Primary cilia extend as apical structures with a microtubular core in polarised kidney epithelial cells. They are assembled, disassembled and mainatained by a process called intraflagellar transport (IFT). Complex B proteins undergo anterograde transport and complex A undergo retrograde transport. The transition zone (orange) and inversin (green) ciliary sub-compartments are shown. Cilia signalling can be activated by mechanical bending or flow or ligand binding to a variety of membrane receptors expressed in the ciliary membrane. Cilia signalling can be usefully divided into Ca^{2+} or non- Ca^{2+} mediated pathways. Apart from stimulating Ca^{2+} release from intracellular stores, Ca^{2+} increases could activate protein kinase C (PKC), protein kinase A (PKA) and phospholipase C (PLC) signalling. Non- Ca^{2+} signalling could involve multiple receptors including developmental pathways such as Hedgehog, Wnt and Notch, as well as those regulating cell division or cell size such as PDGF-α (platelet-derived growth factor-alpha), SSTR3 (somatostatin receptor 3) or mTOR (mammalian target of rapamycin).

(B) <u>Disease spectrum of the ciliopathies</u>. The phenotypic spectrum of the ciliopathies may overlap and ranges from organ dysplasia, degeneration or fibrosis to cystic change. A number of the common ciliopathies and their typical phenotypes are shown on the diagram.

Table 1   **Diseases commonly associated with a cystic phenotype**

MIM Gene/locus number	Disease	Inheritance, genes	Incidence. Male; Female	Age at presentation	Renal features	Extra-renal features
Genetic Disorders						
*606702	Autosomal Recessive Polycystic Kidney Disease	A.R. *PKHD1* (6p21.1-p12)	1 in 20,000 (gene frequency 1 in 70) M:F 1:1	Neonatal, childhood.	Abdominal masses, polyuria, polydipsia, UTIs, ESRD.	Oligohydramnios if severe, hypertension, ascending cholangitis.
*601313	Autosomal Dominant Polycystic Kidney Disease	A.D. *PKD1* (16p13.3-p13.12), *PKD2* (4q21-q23)	1 in 400-1 in 1000 M:F 1:1 but renal phenotype may be more severe in males	Usually 20-40 years.	Clinical findings in children rare. In adults- abdominal pain, UTIs, ESRD.	Clinical findings in children rare. In adults- hypertension, sub-arachnoid haemorrhage.
*607100 *243305 *608002 *607215 *609237 *610142 *608539 *610937 *609799 *609884 *613524 *612014 *614377	Nephronophthisis	A.R. 13 causative genes *NPHP1-13*	1 in 50,000 M:F 1:1	3 forms. Infancy, childhood, adolescence	Polyuria, polydipsia, enuresis, ESRD.	Growth retardation, anaemia, (visual loss, liver fibrosis, cerebellar ataxia if associated with another syndrome).

%174000, *191845	Medullary Cystic Kidney Disease	A.D. *MCKD1*, *MCKD2*/UMOD	Rare. M:F 1:1	Early adulthood	Clinical findings in children rare. In adults-ESRD	Clinical findings in children rare-may develop gout. In adults-gout.
*189907	HNF1β-related diseases	*HNF1β* (17q12)	? M:F 1:1	Any age	Highly variable. Hyperechogenic kidneys, multicystic kidney disease, renal agenesis, renal hypoplasia, cystic dysplasia, or hyperuricaemic tubulointerstitial nephropathy not associated with *UMOD* mutation[89]	Congenital anomalies of the urinary tract, pancreas atrophy, liver abnormalities, maturity-onset diabetes of the young type 5 and genital malformations.
*608537	Von Hippel-Lindau Disease	A.D. *VHL* (3p25.3)	1 in 36,000 M:F 1:1	Childhood, adolescence or adulthood. Mean age 26.	Renal symptoms rare during childhood. Adults-renal cysts, renal cell carcinoma (RCC).	Clinical findings in children rare. In adults- CNS haemangioblastomas, retinal haemangioblastomas, phaeochromocytoma, pancreatic cysts.
*605284 *191092	Tuberous Sclerosis Complex	A.D. High rate of spontaneous mutations. *TSC1* (9q34), *TSC2* (16p13.3)	1 in 1000 M:F 1:1 but female morbidity and mortality rates higher	Childhood	Renal symptoms rare during childhood. Renal angiomyolipomas, renal cysts, ESRD.	Numerous systemic findings. Facial angiofibromas, cardiac rhabdomyomas, lymphangioleiomyomatosis, retinal hamartomas.
	Renal Cysts in Malformative	Varies according to syndrome (including Meckel-Gruber, Ehlers-Danlos, Trisomy 13,18 and 21, and Zellweger syndromes).				

	syndromes				
Non-genetic disorders-developmental					
	Medullary Sponge Kidney	Mutations in *GDNF* have been linked. May be part of other syndromes.	1 in 2000-20,000 M:F 1:1 (but may be more severe in females)	20-50yr but may present younger.	Haematuria, UTI, calculi.	
	Multicystic Renal Dysplasia	Usually sporadic but familial disease has occurred (*PAX 2*). Also associated with many syndromes.	1 in 4000 M:F 2:1	Usually detected pre-natally or soon after birth	Abdominal mass, flank pain, UTI.	Hypertension
Non-genetic disorders-acquired					
	Acquired Renal Cystic Disease	Acquired	7-22% of pre-dialysis patients. >90% 10 years post dialysis.	Any age depending on age of development of ESRD.	Flank pain, bleeding, RCC.	
	Simple Renal Cysts	Acquired	Very common. Incidence increases with age. M:F 2:1	Any age. Usually incidental finding.	Clinical findings rare especially in children. In adults - pain, bleeding, infection.	Clinical findings rare especially in children.
	Multilocular Renal Cysts	Acquired	Rare	Any age but often early	Often asymptomatic. Can present with	Hypertension

				childhood	abdominal mass, abdominal pain or haematuria	
	Hypokalaemic renal cysts	Acquired		Any age.	Usually cysts do not cause symptoms.	
Genetic and non-genetic forms						
	Glomerulocystic Kidney					
	GCK in PKD	ADPKD and ARPKD	M:F 1:1.	Any age	As per primary disease	As per primary disease
	Hereditary GCKD	ADGCKD and HNF1β mutations	M:F 1:1	Any age.	Abdominal masses, renal insufficiency, flank pain, haematuria.	Hypertension
	Syndromic GCK	As per syndrome	As per syndrome	Any age	As per syndromes e.g. X-linked dominant oral-facial-digital syndrome type 1, tuberous sclerosis	
	Obstructive GCK			Any age	Associated with renal dysplasia. Urinary tract infections.	
	Sporadic GCK	May be a de novo mutation, ischaemic or drug induced.		Any age	Abdominal masses, renal insufficiency, flank pain, haematuria. Described post haemolytic uraemic syndrome[116]	Hypertension

MIM = Mendelian Inheritance of Man; AD = autosomal dominant, AR = autosomal recessive.

Table 2   Cystoproteins and their putative functions

Disease	Gene	Protein	Localisation	Function
Autosomal Recessive Polycystic Kidney Disease	PKHD1	Fibrocystin/ polyductin	6p21.1-p12	Exact function unknown. Expressed in apical membrane, primary cilia and centrosomes. Interacts with polycystin-2.
Autosomal Dominant Polycystic Kidney Disease	PKD1	Polycystin-1	16p13.3-p13.12	Mechanosensitive or ligand-activated receptor; functionally complexed with polycystin-2. Expressed in basolateral plasma membrane, cilia, centrosomes.
	PKD2	Polycystin-2	4q21-q23	A non-selective Ca^{2+} channel. Functionally complexed with polycystin-1. Expressed in ER, basolateral plasma membrane, cilia, centrosomes.
Nephronophthisis Infantile, Juvenile/Adolescent	NPHP1/SLSN1 (J)	Nephrocystin 1	2q13	Involved in primary cilia function and the cell cycle. Some
	NPHP2/INVS (I)	Inversin	9q31.1	
	NPHP3/SLSN3 (I,J,A)	Nephrocystin 3	3q22.1	

(I/J/A)	NPHP4/SLSN4 (J)	Nephrocystin 4	1p36.31	localise to cell-cell junctions (1, 2, 4, 10) or focal adhesions (1).
	NPHP5/IQCB1/SLSN5 (J)	Nephrocystin 5	3q13.33	
	NPHP6/CEP290/LCA10/SLSN6/JBTS5/MKS4 (J)	Nephrocystin 6	12q21.32	
	NPHP7/GLIS2 (J)	GLIS 2 protein	16p13.3	
	NPHP8/RPGRIP1L/JBTS7/MKS5 (I,J)	Nephrocystin 8	16q12.2	
	NPHP9/NEK8 (I/J)	Nephrocystin 9	17q11.2	
	NPHP10/SLSN7/SDCCAG8 (J)	Centrosome Colon Cancer Autoantigen Protein (CCCAP)	1q43	
	NPHP11/MKS3/TMEM67 (J)	Meckelin	8q22.1	
	NPHP12/TTC21B/JBTS11 (I,J)	IFT139	2q24.3	
	NPHP13/WDR19 (A)	IFT144	4p14	
Medullary Cystic Kidney Disease	MCKD1		1q21	Not known
	MCKD2 (UMOD)	Uromodulin	16p12	Possible role in maintaining integrity of thick ascending loop of Henle. Localisation to cilia and centrosomes.
HNF1β/TCF2 range	HNF1β	HNF1β protein or Transcription Factor 2 (TCF2)	17q12	Regulates the transcription of several key cystic genes.
Von Hippel Lindau Disease	VHL	VHL protein	3p26-p25	Tumour suppressor gene acting through HIF and non-HIF dependent pathways. Localisation to cilia

				and role in cilia length. [117]
Tuberous Sclerosis Complex	TSC1	Hamartin	9q34	Complexes with tuberin to inhibit mammalian target of mTOR. [118]
	TSC2	Tuberin	16p13.3	Complexes with hamartin. Localises to primary cilia and regulates cilia length [119]

I = infantile, J = juvenile, A = adolescent

Key Summary Points
1. Cystic kidney disease can be genetic, developmental or acquired.
2. Many genetic cystic diseases have been termed ciliopathies due to the colocalisation of multiple cystoproteins in primary cilia.
3. The age at presentation and clinical features are wide-ranging.
4. Many cystic kidney diseases have extra-renal features or form part of a syndrome.
5. The mainstay of treatment at present is the management of the complications of renal impairment.

Key Research Points
1. Two negative trials of mTOR inhibitors in ADPKD were recently reported.
2. Other interventional studies are looking at V2 receptor antagonists, somatostatin, renin-angiotensin system blockade and statin use in slowing cyst development in ADPKD.
3. The function of the primary cilium and its dysfunction in disease remains a focus of intense research investigation.

Questions
1. The PKHD1 gene found on chromosome 6p21 encodes for
   a. Polycystin
   b. Fibrocystin
   c. Inversin
   d. Nephrocystin 1
   e. Neurofibromin

2. Hepatic involvement is associated with
   a. HNF1β mutations
   b. ARPKD
   c. Nephronpohthisis
   d. Medullary sponge kidney
   e. All of above

3. Individuals with juvenile nephronophthisis
   a. Generally have enlarged kidneys
   b. Have glomerular cysts
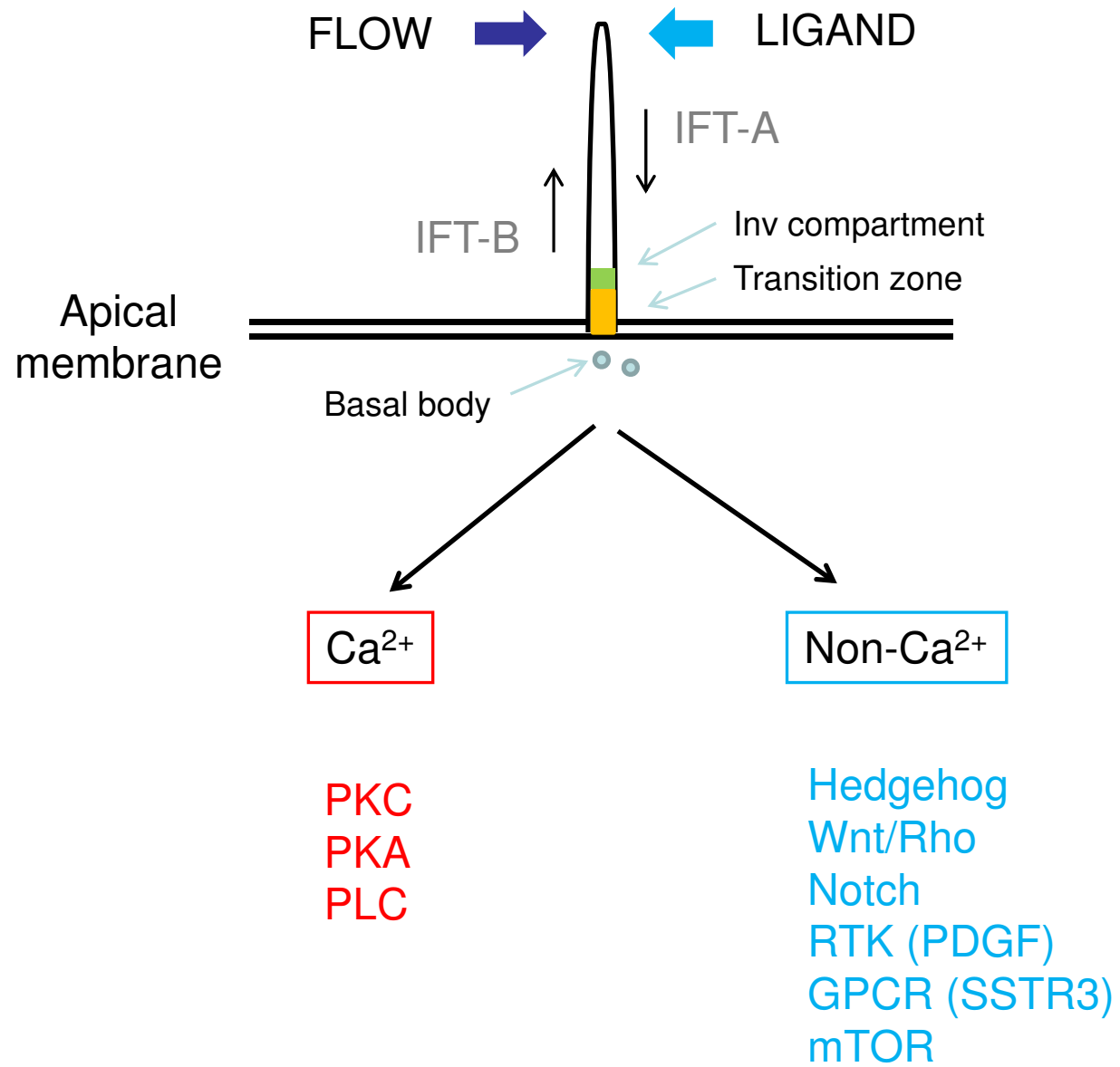   c. Usually have tubular cell hypertrophy on renal biopsy

d. Usually have an irregularly thickened tubular basement membrane on biopsy

e. Rarely present before 10 years of age

4. The following condition is never inherited in an autosomal dominant fashion
   a. Tuberous sclerosis complex
   b. Medullary cystic kidney disease
   c. Von Hippel Lindau disease
   d. Nephronophthisis
   e. Hereditary glomerulocystic kidney disease

5. The HNF1β gene is located on
   a. Chromosome 13
   b. Chromosome 14
   c. Chromosome 15
   d. Chromosome 16
   e. Chromosome 17

6. Multicystic dysplastic kidney
   a. More commonly affects the left kidney
   b. Is more common in girls
   c. Is usually bilateral
   d. Is rarely detected ante-natally
   e. Is usually diagnosed by biopsy

7. Familial hypoplastic glomerulocystic kidney disease is associated with mutations of
   a. MCKD2
   b. HNF1β
   c. TSC1
   d. TSC2
   e. NPHP1

8. Early onset gout is a feature of
   a. ADPKD
   b. ARPKD
   c. Nephronopthisis
   d. Medullary cystic kidney disease
   e. Acquired cystic kidney disease

9. The incidence of autosomal recessive polycystic kidney disease is approximately
   a. 1 in 5000 live births
   b. 1 in 20,000 live births
   c. 1 in 40,000 live births
   d. 1 in 80,000 live births
   e. 1 in 100,000 live births

10. Polyuria and polydipsia are often present in
    a. Autosomal recessive polycystic kidney disease
    b. Juvenile nephronophthisis
    c. Medullary sponge kidney
    d. a,b and c
    e. None of above

Answers
1b, 2e, 3d, 4d, 5e, 6a, 7b, 8d, 9b, 10d

B