Early and Severe Polycystic Kidney Disease and Related Ciliopathies: An Emerging Field of Interest

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Abstract
Early and severe forms of polycystic kidney disease (PKD) do already manifest during childhood or adolescence. They are characterized by enlarged kidneys and diminished renal function that prenatally may result in Potter’s oligohydramnios sequence. Genetically, various defects can mimic this phenotype. Most common are PKHD1 mutations that lead to autosomal recessive PKD (ARPKD). About the same number of children do carry mutations in the dominant autosomal dominant polycystic kidney disease (ADPKD) genes, PKD1 and less frequent PKD2, often arise de novo or may affect both disease alleles in a recessive mode. Mutations in DZIP1L have been recently described to result in an ARPKD-like phenotype. Likewise, mutations in several other cystogenes can phenocopy early and severe PKD. Early and reliable prenatal diagnosis for which there is a strong demand in ARPKD and related diseases is feasible only by genetics. A comprehensive knowledge of disease-causing genes is essential for the correct diagnosis and parental counselling. The increasing number of genes that need to be considered benefits from the advances of next generation sequencing and allows the simultaneous analysis of all genes of interest in a single test, which is now the mainstay for genetic diagnosis. Interpretation of data is challenging and requires expert knowledge in data handling, bioinformatics and clinical genetics.

Polycystic Kidney Disease and Ciliary Dysfunction

Polycystic kidney disease (PKD) is a clinically and genetically heterogeneous group. Manifestations vary widely and range from beginnings in utero to clinically silent disease during adulthood. Both, dominant (Autosomal dominant PKD [ADPKD]) and recessive (Autosomal Recessive PKD [ARPKD]) inheritance patterns are possible. In addition to those 2 typical forms of PKD, cystic kidney disease is a common feature of syndromic ciliopathies. Overall, PKD and ciliopathies represent a significant proportion of all patients with end-stage renal disease.
Early and Severe PKD and Related Ciliopathies

Corresponds to a carrier frequency of approximately 1:70. Males and females are equally affected. The recurrence risk for subsequent pregnancies of parents of an affected child is 25%. Given its autosomal recessive mode of inheritance, the recurrence risk for subsequent pregnancies of parents of an affected child is 25%. However, the spectrum for phenotypic severity can be much broader than widely assumed with some cases of elderly people with ARPKD reported who were only moderately affected [2, 3].

Ultrasound examination typically reveals enlarged hyperechoic kidneys with retained reniform contour, poor corticomedullary differentiation, and multiple tiny cysts confined to distal tubules and collecting ducts (Fig. 1). With advancing clinical course, the kidney structure might increasingly resemble the pattern observed in ADPKD with renal cysts that vary considerably in size and appearance, often also accompanied by some degree of interstitial fibrosis [4]. Arterial hypertension, which is often difficult to control despite multi-drug treatment invariably develops during the first months of life and affects up to 80% of children with ARPKD. Close monitoring of blood pressure is crucial to avoid further hypertension-driven damage to the kidney [3].

Every ARPKD patient shows hepatic fibrosis and biliary hyperplasia from embryonic age on. These histological changes are the result of defective remodelling of the ductal plate and summarized as ductal plate malformation [5–7], (Fig. 1f). Notably, ductal plate malformation is also a common feature of various other ciliopathies. With increasing age of the patient, the hepatobiliary changes often result in significant clinical problems (e.g., portal hypertension and its complications such as hypersplenism and oesophageal varices) [3, 8]. ARPKD is one of the 2 major indications (besides primary hyperoxaluria) for combined liver and kidney transplantation (CLKT) during childhood. There is only scarce long-term outcome data for CLKT in children and controversy exists as to whether simultaneous CLKT is beneficial. In line, the best timing and strategy for combined transplantation is still a matter of debate and usually requires individualized decision making on a case by case basis.

In contrast to, for example, HNF1β-related diseases, liver enzymes are typically within normal ranges in ARPKD, with the exception of cholestasis parameters, which might be elevated. In the literature, there is some preliminary evidence that adult ARPKD patients beyond the age of 40 years may have a slightly increased risk to develop hepatic tumours, especially cholangiocarcinoma [6, 9].

Autosomal Recessive PKD

ARPKD occurs in about 1 in 20,000 live births, which corresponds to a carrier frequency of approximately 1:70 in non-isolated populations. Given its autosomal recessive mode of inheritance, the recurrence risk for subsequent pregnancies of parents of an affected child is 25%. Males and females are equally affected.

Notably, among children with polycystic kidneys the total number of patients with early-onset ADPKD may be comparable to those of children with ARPKD and the phenotypes are often quite similar in those individuals. However, typically ADPKD manifests much later in life and is less severe than ARPKD. Most children with ARPKD are identified late during pregnancy or at birth. Affected individuals display a “Potter” phenotype (that refers to a group of features associated with a lack of amniotic fluid and kidney failure in an unborn infant) with massively enlarged kidneys, pulmonary hypoplasia, characteristic facies and contracted limbs with club feet. Approximately 30–50% of affected neonates die shortly after birth from respiratory insufficiency due to pulmonary hypoplasia and thoracic compression by the excessively enlarged kidneys. However, the spectrum for phenotypic severity can be much broader than widely assumed with some cases of elderly people with ARPKD reported who were only moderately affected [2, 3].

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While a preponderance of ARPKD patients show consistent disease progression, individual patients may present with atypical phenotypes, such as exclusive or predominant phenotypes of either the liver or kidneys. Accordingly, in certain cases of isolated congenital hepatic fibrosis (Caroli’s disease), PKHD1 has been demonstrated to be the causative gene [10]. Similarly, in mouse models for PKHD1, the liver phenotype is stronger than renal involvement [11–14]. Overall, ARPKD is associated with a significant portion of liver and kidney associated morbidity.

**PKHD1 Is the Major, but not the Only Gene for ARPKD, and Encodes the Ciliary Type I Transmembrane Protein Fibrocystin/Polyductin**

The PKHD1 gene extends over almost 0.5 Mb. The longest transcript comprises 67 exons and encodes a 4,074 amino acid (aa) integral membrane protein (fibrocystin/polyductin), which contains a signal peptide at the amino terminus of its extensive, highly glycosylated extracellular domain, a single transmembrane (TM)-spanning...
ning segment, and a short cytoplasmic C-terminal tail containing potential protein kinase A phosphorylation sites (Fig. 2). Targeting to the ciliary membrane is facilitated by an 18-residue motif in the cytoplasmic tail [15]. From structural and histological characteristics in ARPKD, fibrocystin can be hypothesized to be involved in cell-cell adhesion and proliferation processes and may act as a membrane-bound receptor [16]. Like polycystin-1 and polycystin-2, fibrocystin is localized to the primary cilium and basal body. Its spatio-temporal subcellular localization pattern, as well as interactions with polycystin-2 and CAML, suggests that fibrocystin might be involved in cell-cell adhesion and proliferation processes and may act as a membrane-bound receptor [16]. Like polycystin-1 and polycystin-2, fibrocystin is localized to the primary cilium and basal body. Its spatio-temporal subcellular localization pattern, as well as interactions with polycystin-2 and CAML, suggests that fibrocystin might be involved in cell-cell adhesion and proliferation processes and may act as a membrane-bound receptor [16].

PKHD1 mutation analysis is characterized by vast allelic heterogeneity and a huge number of private mutations and missense changes [20]. With the advance of Next-Generation Sequencing (NGS)-based testing options, many patients primarily clinically diagnosed as ARPKD have been re-classified. It is becoming increasingly apparent that the characteristics of ARPKD can be mimicked by mutations in a number of other genes [21]. ARPKD is not as homogeneous as still widely proposed and evidence for genetic heterogeneity has been found in a number of cases. NGS streamlines the previously cumbersome screening process and allows the simultaneous analysis of all genes that need to be considered in a single test at relatively low cost.

Genotype-phenotype correlations for PKHD1 have been established for the type of mutations. Typically patients with 2 truncating mutations are severely affected and display peri- or neonatal mortality. Patients with at least 1 missense mutation tend to be less severely affected and are more likely to survive the neonatal period. However, as to be expected, some missense changes affect critical residues and can clinically impress as severe as truncating mutations. No significant clinical differences could...
be observed between patients with 2 missense mutations and those patients harbouring a truncating mutation in trans; thus, the milder mutation obviously defines the phenotype [3]. Loss of function probably explains the rather uniform phenotype and early demise of patients with 2 null alleles. A critical amount of proper full-length protein seems to be required for normal development and function. Recent evidence suggests that multiple alternatively spliced transcripts exist and aberrant PKHD1 splicing may represent an unappreciated pathogenic mechanism. Alternative splicing patterns might disrupt a critical stoichiometric and temporal balance between different protein products and complex transcriptional profiles may thus play a role in defining the patient’s phenotype [22, 23].

**ARPKD Can be Caused by Mutations in the Gene Encoding the TZ Protein DZIP1L**

Recently, mutations in DZIP1L have been described in patients with a moderate clinical course of ARPKD [24]. DZIP1L encodes a ciliary TZ protein (DZIP1L, DAZ interacting protein 1-like) that in line with other PKD proteins localizes to centrioles and the distal end of basal bodies. DZIP1L was demonstrated to interact with septin2 (SEPT2), a key ciliary TZ protein implicated in the maintenance of the periciliary diffusion barrier. Consistent with a diffusion barrier defect, ciliary membrane translocation of both ADPKD proteins (polycystin-1 and -2) were shown to be compromised in DZIP1L mutant cells suggesting a requirement for DZIP1L in regulating TZ integrity.

DZIP1L spans about 53 kb of genomic DNA with 16 exons (ATG start codon in exon 2) and encodes a protein of 767 amino acids. Mutations in DZIP1L are considerably rarer than variants in PKHD1. Our limited data suggest that the N-terminus of DZIP1L might be more susceptible to mutations, a concept supported by in silico data that predict pathogenicity scores to decay towards the C-terminus.

The clinical course so far described patients who harbour DZIP1L mutations were invariably moderate. While clinical manifestations in all patients were invariably detected already prenatally or during early childhood, none showed perinatal demise. Thus far, the data suggest that the type or location of DZIP1L mutation does not determine the severity of the clinical course. Patients bearing missense mutations on both parental alleles displayed a comparable phenotype to patients with 2 truncating DZIP1L alleles. Although we have not screened large numbers of embryonically lethal patients, in view of homozygous truncating mutations in moderately affected patients we hypothesize that it is unlikely that DZIP1L mutations play a major role in this cohort of most severely affected individuals.

**ARPKD Due to Mutations in PKD1 and PKD2**

From a clinical point of view, ARPKD can also be mimicked by either dominant or recessive mutations in PKD1 and PKD2, the genes usually causing ADPKD. Typically, ADPKD symptoms do not become apparent before adulthood. However, a small proportion (2–5%) of ADPKD patients do already manifest during childhood or prenatally. While the clinical course in most ADPKD families is comparable, considerable phenotypic variability among affected individuals is a challenge in some pedigrees. Notably, families in which one child displays early manifestations of ADPKD have a high recurrence of early onset in any further affected children suggesting a common familial background modifier that leads to early disease expression [25].

Stochastic, epigenetic and environmental factors are thought to modify the phenotype. More complex genotypes with second-site modifying alleles may exert an aggravating effect and contribute to early and severe disease expression. A reduced dosage of disease proteins (“dosage-sensitive network”) can be expected to disturb cell integrity and may result in the more severe clinical course observed in those patients [26].

Early disease manifestation in ADPKD is the most important differential diagnosis of ARPKD and many patients with allegedly ARPKD carry mutations, in particular, in PKD1 (Fig. 3). Parenteral renal ultrasound is a must and should be performed in every child with cystic kidney disease of unknown origin. However, it needs to be emphasized that the family history often is negative mainly because a considerable proportion of mutations in ADPKD genes (approximately 15–20%) arise de novo, an information that bears a major impact for those families. Another reason for an unremarkable pedigree tree is recessive inheritance of incompletely penetrant hypomorphic mutations in PKD1 and PKD2.

Though there is significant overlap between ARPKD and ADPKD, there are a number of complications associated with each disease that are relevant for proper clinical management. ADPKD patients rarely develop hepatobiliary complications like congenital hepatic fibrosis or...
DPM. Patients with ARPKD, on the other hand, will almost certainly develop some complications due to CHF and DPM over time. In a similar vein, ADPKD patients require special considerations for cardiovascular co-morbidities, in particular, intracerebral aneurysms (ICAs), which do not typically occur in ARPKD. While general screening for ICAs is usually not recommended, it might be good to know both from the patient’s as well as from the doctor’s side whether there is a positive family history that can lead to an increased risk [27–29]. Typically, aneurysm rupture is quite rare in children and young adults, so screening is usually not necessary until patients reach the age of 20 years.

**Autosomal Dominant PKD**

Overall, in ADPKD patients, that is, in typically adult-onset cases, most mutations affect the *PKD1* gene encoding polycystin-1, whereas 15–20% harbour a mutation in *PKD2* leading to alterations of the polycystin-2 protein [17]. Allelic heterogeneity is a challenge in ADPKD too with a significant proportion of mutations being private. However, the majority of known *PKD1* and *PKD2* mutations are predicted to be of truncating nature (70 and 80% respectively) [17].

Screening for *PKD1* mutations is confounded by the 6 pseudogenes adjacent to the *PKD1* locus. However, optimization of targeted sequence capture approaches or the methodological advantages of WGS now allow mutation analysis by NGS of even highly confounding loci such as *PKD1* [30]. NGS approaches are nowadays the gold standard for genetic screening for ADPKD and should encompass a number of other genes besides the ones discussed above such as *GANAB* or *HNF1β* that were recently described to be mutated in a subset of patients with ADPKD [31].

Polycystin-1 and polycystin-2 are TM proteins that interact with each other through their C-terminal tails containing coiled-coil motifs (Fig. 2). Polycystin-2 is a divalent cation channel involved in cellular Ca$^{2+}$ signalling [32]. Polycystin-1 forms a complex with Polycystin-2 and when bound to an as yet unidentified ligand, facilitates conformational changes in Polycystin-2 opening the Ca$^{2+}$ channel. The polycystin complex is hypothesized to be activated by mechanical strain. Some functional and mu-

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**Fig. 3.** a, b Typical sonographic picture of ADPKD in a 10-month-old girl (a) and an 11-year-old boy (b). c ADPKD resembling ARPKD in a 3-year-old boy with enlarged echogenic kidneys and small sized cysts. d Three-week-old girl with previous oligohydramnion, arterial hypertension and small cysts in massively enlarged kidneys with a calculated total kidney volume of about 100 mL (normal age-related value <40 mL). Her mother’s phenotype resembled ADPKD, but the family was shown to carry an *HNF1β* germline mutation (from Bergmann, Ped Nephrol 2015).
tational data suggest fibrocystin to be part of the polycystin complex [33–36]. The role DZIP1L plays in ciliary translocation of the polycystin proteins has been described before.

PKD2 is usually significantly milder than PKD1 with the development of ESRD at a later age and a lower prevalence of arterial hypertension and urinary tract infections. Patients with PKD1 develop ESRD earlier than patients with PKD2. The median age of ESRD onset in PKD1 patients is ∼20 years earlier than PKD2 (58.1 years and 79.9 years respectively). Additionally, PKD1 patients present with more severe cysts than PKD2; however, this is likely due to the development of cysts at an earlier age rather than an increase in cyst growth [37]. Analysis of over 500 families with ADPKD revealed that patients with truncating PKD1 mutations develop ESRD an average of 12 years earlier than those with non-truncating mutations in this gene (55.6 vs. 67.9 years) [38].

ADPKD is a systemic disorder and can potentially affect a number of other organs beyond the kidneys including liver, pancreas, arachnoid membrane and heart. In ADPKD patients, polycystic liver disease is common. Increasing evidence suggests a dosage-sensitive network with genetic and functional overlap between PKD and polycystic liver disease [39–42]. A range of cardiovascular comorbidities can occur. Approximately 8% of ADPKD patients develop ICAs. Other disease manifestations such as cardiac valve defects that occur in 25% of individuals remain usually subclinical.

With the vasopressin receptor 2 antagonist tolvaptan, the first treatment specifically for ADPKD has been recently approved in many parts of the world. Other treatments (possibly as combination treatments) targeting downstream signalling, such as others inhibiting cAMP generation, more effective mTOR inhibition, addressing metabolic abnormalities and other therapies (such as some already known from tumour treatments) shown effective in rodent studies seem promising. The prospects for better outcome predictions and treatments look good, but an incomplete understanding of the function of PKD proteins is still a major impediment to understanding pathogenesis and the development of rational therapies.

Early and Severe PKD Due to Tuberous Sclerosis

2-PKD1 Microdeletion

Patients with a gross deletion on chromosome 16p that encompass the 2 adjacent genes PKD1 and tuberous sclerosis (TSC2) do usually display an early and severe PKD phenotype. TSC2 is the main gene for TSC, an autosomal dominant disorder that can affect a broad range of organs and has an incidence of 1:6,000 [43]. Epilepsy and cutaneous manifestations are common. Mainly non-cancerous tumours, principally in the kidney, heart and brain, may develop. Cystic kidney disease occurs in 50% and angio-myolipomas are diagnosed in 80% of patients. Overall, renal manifestations are the leading cause of death in adult patients [44].

The clinical overlap between PKD and TSC can be explained by their close physiologic interrelationships. The TSC2 protein tuberin traffics polycystin-1 to its major site of subcellular localization, the plasma membrane [45]. Polycystin-1 and the TSC1/TSC2 tumour suppressor complex do act in concert by suppressing mTOR activity, which leads to G1-cell cycle arrest with apoptosis.

HNF1β-Related Disease Is an Important Differential Diagnosis for ARPKD and ADPKD

ARPKD and ADPKD are subject to a number of phenocopies (Fig. 4). A major entity that needs to be considered for differential diagnosis is HNF1β with autosomal dominant mutations in the HNF1β/TCF2 gene. Overall, HNF1β mutations are thought to constitute the main...
cause of prenatally diagnosed bilateral hyperechogenic kidneys [46]. While many HNF1β foetuses display normal-sized kidneys often with bilateral cortical cysts and normal amniotic fluid volume, patients may show Potter’s sequence with oligo-/anhydramnios and massively enlarged polycystic kidneys (> + 3 SD) that mimic ARPKD. In accordance, mice with an Hnf1β mutation demonstrated a PKD-like phenotype with diminished Pkhδ1 expression [47]. Given the role of HNF1β as a master regulator of a number of cystic kidney disease genes including PKHD1 and PKD2, there is a credible genetic cause that might explain the resemblance between HNF1β and ARPKD/ADPKD patients.

In addition, mutations in HNF1β can result in a broad range of other phenotypes. HNF1β-related disease is commonly designated as renal cyst and diabetes syndrome [48]. However, other characteristics include abnormalities of the genital tract, endocrine/exocrine insufficiency, hypomagnesemia and an increase in liver enzymes (elevated transaminases, which is very uncommon for the typical PKDs). Disease manifestations can be explained by the function of genes that are regulated by the transcription factor HNF1β.

HNF1β is inherited in an autosomal dominant fashion with 50% recurrence risk for affected individuals. As true for most “transcription factor diseases”, mutations in HNF1β result in huge variability in terms of penetrance and expressivity (most probably due to complex spatio-temporal expression patterning and cellular interplay) as well as a high frequency of spontaneous mutations that need to be taken into consideration when evaluating the individual’s family history. Almost 50% of HNF1β patients possess de novo mutations (i.e., do have a negative family history). Additionally, approximately 50% of patients bear large deletions that remove around 1.4 Mb of genomic DNA, which includes HNF1β and several other genes on 17q12. Patients with a large genomic rearrangement in 17q12 are much more frequently affected by cognitive impairment, seizures and other neurodevelopmental disorders (e.g., schizophrenia and autism spectrum disorders) [49, 50]. However, many patients who harbour this microdeletion are not more severely affected than patients with an HNF1β point mutation.

**Nephronophthisis**

NPHP comprises a heterogeneous collection of autosomal recessive cystic kidney diseases that are characterised by tubulointerstitial cysts and small or normal size kidneys. However, in some cases, NPHP patients can show ARPKD-like enlarged kidneys or even Potter-like characteristics. NPHP proteins do form functional networks among each other and with related ciliopathy proteins. Characterisation of the NPHP proteins has yielded considerable gains in the fundamental mechanisms involved in cystogenesis and other cilia-associated disorders. Recently, we identified ANKS6 as a core component of the cystoprotein module, which links NEK8 (NPHP9) to INVS (NPHP2) and NPHP3 [51].

NPHP mutations are a significant cause of ESRD in patients under 25. The most common form of NPHP is juvenile NPHP, which is characterised initially by defects in urinary concentration as well as anaemia, polyuria and polydipsia [52, 53]. NPHP1 mutations, in particular a large deletion encompassing the entire gene, make up about 20–40% of all juvenile NPHP cases. NPHP patients usually develop cysts at the cortico-medullary boundary. However, patients do not normally display cysts until they have already developed advanced chronic kidney disease. Similarly arterial hypertension does not become clinically relevant until late in the disease course. Significant tubulointerstitial fibrosis as well as the disintegration and thickening of the basement membrane are seen by histology [54]. Similar to many cystic kidney diseases and ciliopathies, NPHP genes are largely pleiotropic and can result in a number of extra-renal manifestations [55].

Medullary cystic kidney disease is often called the autosomal dominant “brother” of NPHP and mainly caused by mutations in MUC1 and UMOD. Typically, it has a later onset of ESRD than the recessive forms [56].

**Mutations in Other Ciliary Genes may Mimic Early and Severe PKD**

In rare instances, especially in the prenatal setting and during early childhood, PKD may be mimicked by mutations in genes that typically cause other, usually more complex ciliopathies (e.g., Bardet-Biedl, Joubert or Meckel syndrome). Neurological features are the clinical hallmarks in Meckel (MKS) and Joubert syndrome (JBTS). Both are severe, early-onset developmental disorders that affect multiple organs besides the CNS and kidneys. Most patients with MKS die in utero or shortly after birth due to complications related to occipital meningoencephalocele, The “molar tooth sign” results from the malformation of the mid- and hindbrain and is typical for JBTS [57].

Bardet-Biedl syndrome (BBS) is characterized by obesity, hypogonadism, retinal degeneration, polydactyly,
mental retardation and renal malformations. A range of further features might be present such as hearing loss or metabolic defects. Renal disease is a major cause of morbidity and mortality in BBS and phenotypically heterogeneous; however, it often does impress with PKD-like enlarged, hyperechogenic kidneys. More than 2 dozens of BBS genes are known. ALMS1 mutations in Alstrom syndrome do phenotypically overlap with BBS. However, Alstrom syndrome patients typically have normal intelligence and do not develop polydactyly, whereas they tend to have much more severe sensorineural hearing loss as well as the development of early-onset type 2 diabetes mellitus. Additionally, Alstrom syndrome patients often develop a number of cardiac, pulmonary and hepatic complications that require ongoing clinical management.

**Genetic Testing**

In the past, strategies for genetic testing were mainly based on time- and cost-intensive single-gene testing. The advances in NGS now allow the simultaneous analysis of all genes in a single test at relatively low cost. Single-gene testing is nowadays the exception, especially for genetically heterogeneous disorders with a broad phenotypic spectrum such as cystic kidney disease. NGS improves throughput and quality of genetic testing. For the time being, targeted NGS panel testing is considered to be the most efficient diagnostic approach. Whatever primary strategy is chosen for PKD, the testing approach should be able to detect copy-number variations (e.g., deletions in HNF1β make up about 50% of all mutations) and to cover complex genomic regions such as PKD1.

While genetic testing evolves rapidly, there are still some limitations to consider. A significant problem many physicians in different parts of the world face is cost. Although costs are decreasing, they are still comparably high and the reason why genetics is still not used in many healthcare systems on a broader level for children with kidney diseases. Nevertheless, despite all obstacles, it is widely recommended to offer genetic testing to every family facing early-onset bilateral cystic kidney disease and to discuss the medical and ethical implications in an interdisciplinary manner. For instance, genetic testing may:

- Lead to earlier diagnosis and avoid a “diagnostic odyssey” and unnecessary diagnostic measures such as renal or liver biopsy in patients with hyperechogenic kidneys.
- Establish a definite diagnosis (“relevance to finally give the disease a name”), which represents an underesti-
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26 Bergmann C: Genetics of autosomal recessive polycystic kidney disease and its differential diagnoses. Front Pediatr 2018;5:221.


