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The genetics of Autosomal Recessive Polycystic Kidney Disease (ARPKD)

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ABSTRACT

ARPKD is a genetically inherited kidney disease that manifests by bilateral enlargement of cystic kidneys and liver fibrosis. It shows a range of severity, with 30% of individuals dying early on and the majority having good prognosis if they survive the first year of life. The reasons for this variability remain unclear. Two genes have been shown to cause ARPKD when mutated, *PKHD1*, mutations in which lead to most of ARPKD cases and *DZIP1L*, which is associated with moderate ARPKD. This mini review will explore the genetics of ARPKD and discuss potential genetic modifiers and phenocopies that could affect diagnosis.

1. Introduction

Autosomal Recessive Polycystic Kidney Disease (ARPKD) is a rare form of chronic kidney disease (CKD) characterised by the presence of cystic kidneys. The reported prevalence of ARPKD is generally accepted as being ~1:20,000 in Europe [1]. ARPKD usually manifests early on in life and is typically diagnosed in the neonatal/perinatal period or early childhood [1–10]. However, individuals with adult-onset ARPKD have also been reported, highlighting a significant amount of variation in disease presentation [2,8–10]. The first year is critical for those diagnosed early in life, with an observed mortality rate of ~30–40% [1]. However, for those surviving this initial period, 1-year and 10-year survival rates were estimated at 85% and 82%, respectively [1]. No ethnicity or gender bias has been reported in the development or progression of ARPKD [1–6,8–10].

The phenotypic presentation of ARPKD is highly variable, with those diagnosed early in life manifesting a more severe kidney phenotype compared to those typically diagnosed at an older age. The kidney phenotype includes the formation of cysts located within the distal tubules and collecting ducts of the nephron [1]. As a consequence of cyst development, individuals develop enlarged, echogenic kidneys that contain poor corticomedullary differentiation, but retain a typical kidney shape [1,11]. Due to the kidney changes that occur because of ARPKD, the kidney is often described as having a "salt and pepper" pattern in ultrasounds [12,13]. Kidney function will progressively worsen due to the formation of macroscopic cysts and interstitial fibrosis and around 50% of the patients will eventually progress to CKD stage 5 by adulthood.

The mechanisms underlying the formation of kidney cysts in ARPKD are poorly understood but they have been associated among other proposed mechanisms with ciliary defects, hence the characterisation of ARPKD as a Ciliopathy [14–18]. Many diseases in which kidney cysts also manifest, such as nephronophthisis, Joubert syndrome and Bardet-Biedl syndrome are caused by mutations in genes whose proteins either localise to or require primary cilia for signalling [15,16]. ARPKD is caused by mutations in *Polycystic Kidney and Hepatic Disease 1* (*PKHD1*) or less commonly in *DAZ interacting zinc finger protein 1* (*DZIP1L*) [17–20]. These genes encode Fibrocystin (FPC) and DZIP1L respectively, both of which localise to cilia [17–19]. The functions of FPC are not fully understood. However, due to its ciliary localisation and structural homology, it may act as a ciliary receptor protein, whereas DZIP1L localises to the ciliary transition zone, where it plays a role in transporting gene products into the ciliary axoneme [17–19]. Like ARPKD, Autosomal Dominant Polycystic Kidney Disease (ADPKD), another polycystic kidney disease but of dominant inheritance, is caused by mutations in *PKD1* and *PKD2* that encode the Polycystin 1 (PC1) and Polycystin 2 (PC2) proteins that form a complex which localises to primary cilia [1,14–16]. PC2 is an ion transporter and interactions between FPC and PC2 have been shown to occur in the cilia, where the two proteins form a complex and drive PC2 channel activity [14,21]. However, the exact importance of this relationship in the manifestation of PKD is unknown as loss of the PC2 binding domain in FPC did not cause PKD in mice [14]. FPC and PC1 do not appear to participate in similar genetic pathways according to RNA-sequencing experiments carried out

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in murine models [22]. However, digenic mice and rats with mutations in both *Pkhd1* and *Pkd1* have a more rapid and severe manifestation of PKD, highlighting a synergistic effect between these two genes [14,22]. Although loss of FPC expression did not affect the expression or localisation of the PC1/PC2 complex, it is still possible that PC1, PC2 and FPC belong to interacting genetic pathways, with the ciliary compartment being highlighted as a common dysregulated target in murine models with mutations in *Pkd1* or *Pkhd1* [14,22]. Loss of DZIP1L is reported to inhibit the localisation of PC1 and PC2 to the ciliary axoneme [17]. In turn, this results in the accumulation of the PC1 and PC2 in the ciliary basal body/transition zone [17]. Interestingly, no interaction between the two ARPKD genes *PKHD1* and *DZIP1L*, has been detected [17]. Thus, although ARPKD shows similarities to ADPKD, with dysregulated ciliary pathways, proliferation, apoptosis and fluid secretion observed in both, they have got distinct histopathological features and cellular characteristics [1,14–16]. An example of these differences is the dysregulated non-canonical Wnt/Planar Cell Polarity (PCP) signalling, reported in ARPKD [23] but not ADPKD, suggesting that although Polycystins, FPC and DZIP1L can interact and have got functions related to cilia, these functions are not necessarily converging.

The kidney damage that can arise from ARPKD is not the sole symptom of the disease, with extra-renal indication of hypertension and liver defects, although the latter may not always result in obvious clinical symptoms [1,8,11,24]. Individuals with a neonatal presentation of ARPKD may present with oligohydramnios, which can give rise to the manifestation of Potter Syndrome [1]. Potter Syndrome is associated with pulmonary hypoplasia, characteristic facial features and spine, limb and foot defects [1]. Death because of pulmonary distress can also arise during the neonatal period [1,24]. The liver phenotype forms due to ductal plate malformations early in development and gives rise to the later appearance of congenital liver fibrosis [1,8,24]. Several potentially lethal co-morbidities are associated with the liver presentation and include portal hypertension, variceal bleeding, oesophageal varices, cholangitis and hypersplenism [1,8,24].

2. *PKHD1* and *DZIP1L*- the two key genes in ARPKD

PKHD1 is a gene located within chromosome 6p12 and it consists of a total of 86 exons [19,20,25]. The gene translates several protein isoforms of variable size, whose functional roles are not entirely understood [26–28]. The longest open reading frame of *PKHD1* is 67 exons long and encodes the protein FPC [18,19]. The expression of *PKHD1* appears not only to be tissue-specific but also cell-type-specific, being most commonly observed in the ductal cells of the kidney (collecting duct), liver (bile duct) and pancreas (pancreatic islets) and their precursors during development [18,27–29]. FPC may play an essential role in the development of other organs as well, such as the lung [26,28]. Isoforms of FPC are expressed in various subcellular compartments, including the primary cilia, plasma membrane, cytoplasm, Endoplasmic Reticulum and Golgi [18,27,29–31].

FPC is a 4074 amino acid long protein, comprising of two core components [19,20] (Fig. 1). The first core component of FPC is a large extracellular domain that encompasses the N-terminal region and contains multiple domains of interest, such as IPT, G8 and Parallel Beta-Helices [18,19,32]. The second core component is a much shorter intracellular C-terminal domain with a cilia localisation sequence, which may drive internal protein-protein interactions such as the one with PC2 and it can be released for a currently unknown purpose following Notch-like proteolytic cleavage [21,30,33–35]. The exact function of the protein is currently unknown. However, due to its shape and localisation, it is hypothesised to play the role of a receptor protein and may be involved in controlling ductal cell formation, proliferation, apoptosis, adhesion and signalling [18–21,23,30,33,35–37].

ARPKD's manifestation caused by mutations in *PKHD1* is highly variable but it is typically associated with both kidney and liver disease. The severity of kidney disease is often related to the age of death/diagnosis, with perinatal death being the most severe disease presentation [3–6,8–10,38–42]. There is currently no known relationship between the presentation of severe kidney disease and severe liver disease [8]. Most individuals who manifest severe kidney disease, assuming

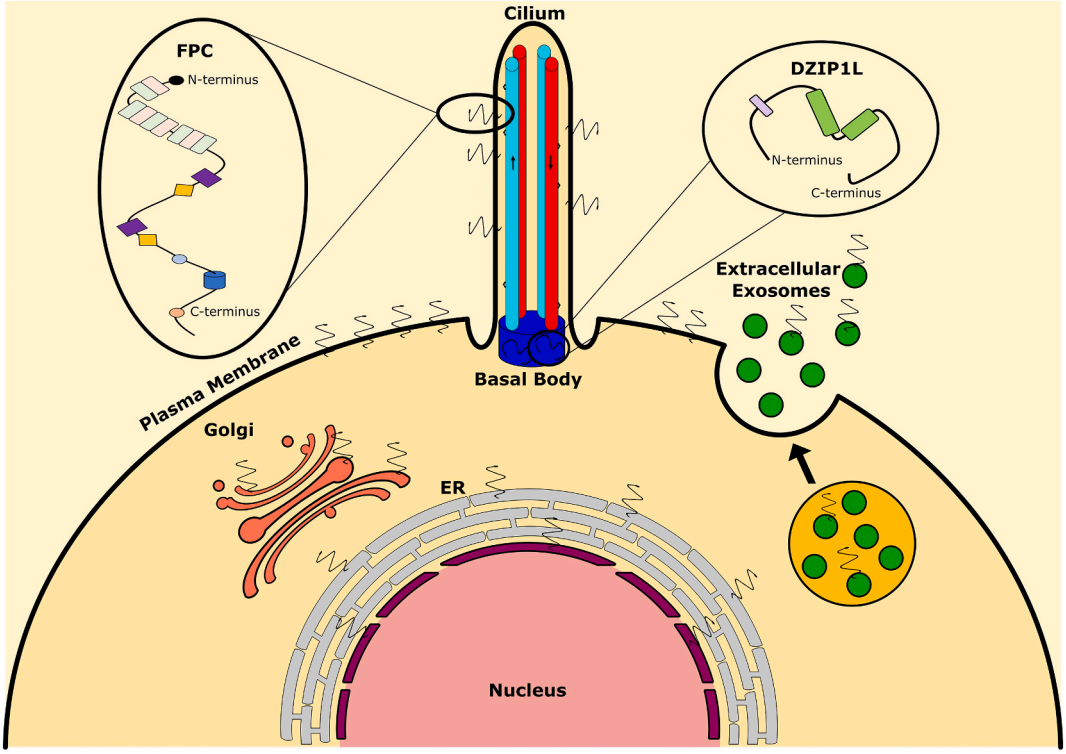

Fig. 1. A schematic diagram of the protein structure of Fibrocystin (FPC) and DZIP1L, including an illustration of their most common expression localisation in the cell. ER, Endoplasmic Reticulum; FPC, Fibrocystin; Golgi, Golgi Apparatus.

perinatal survival, will also develop a severe liver phenotype [8]. However, combinations of severe kidney disease with mild liver disease, mild kidney disease with severe liver disease and both mild kidney and liver disease have been reported [8]. What gives rise to this variance is not entirely understood. Nevertheless, a trend has been identified between disease severity (perinatal demise vs perinatal survival) and the type of mutations carried by an individual [3–6,8,9,38,41]. The presence of two truncating mutations is associated with the most severe phenotype. In contrast, the presence of two missense mutations or a missense mutation inherited alongside a truncation was generally associated with a less severe phenotype [3–6,8,9,38,41]. Some missense mutations have been linked to a predominantly severe phenotype, but there is no concrete association between a mutation's location within *PKHD1* and disease severity [3–6,8,38,42]. There is also no definitive association between mutation type and whether an individual will have a dominant liver phenotype [5].

In ARPKD, most mutations are dispersed throughout the extracellular region of FPC with no clustering within specific regions of FPC relating to a specific phenotype [3–8,40]. Determining a relationship between an individual's mutations and their disease presentation is complicated by the low frequency of most mutations and the recessive nature of inheritance [3,4,6,8]. This is further impeded by the complex nature of *PKHD1* expression, our lack of understanding of the protein structure/functions of FPC and intrafamilial variability [3–5,7,8,26]. Certain mutations have a higher occurrence in the population, some of which are attributed to founder effects [2–7,9,10,38,41–43]. The mutation T36M has the highest known occurrence, accounting for approximately 20% of all ARPKD cases and is typically associated with a severe phenotype [3,5,6,38,40,41,44,45]. The first exon screening algorithm was suggested by Bergmann and colleagues [45] and they found that when screening their top 9 exon fragments, they could detect 50% of all mutations within their cohort. Their detection efficiency could be expanded to an estimated 80% when covering their top 27 exons [45]. A common occurrence within many of these exon profiles is the presence of the top three largest exons (exons 32, 58 and 61) as well as exon 3, where the T36M mutation occurs [9,10,39,44,45]. Similar results have been seen in other publications but with variable exon frequencies and percentage coverages and may suggest a difference in mutation distribution by population, as seen in the Spanish, Dutch, Italian and Oman cohorts [9,10,39,44].

Additionally, although there is so far no known FPC hotspot associated with disease outcome, a few studies have attempted to identify patterns between the position of mutations on *PKHD1* and disease severity [3,6,43,46]. Mutations within the region of 700–2000 amino acids on FPC have been suggested to cause a milder kidney phenotype compared to those with mutations in other regions of FPC [6,46]. Furthermore, individuals with mutations around FPC amino acids 2600–4074 may develop a more prominent liver phenotype [43,46]. However, additional research is currently needed to confirm these relationships. The actual occurrence of chain terminating mutations versus missense mutations is currently unknown, with a wide range of variability recorded between studies [3,4,6–8,38,41]. Studies featuring more severe kidney patients have a more significant proportion of chain terminating mutations [4,7,8]. Despite improvements in the genetic diagnosis of ARPKD patients, not all mutations can be identified. Some ARPKD patients may have mutations within intronic regions, splicing sites or regulatory regions [5,10,39–42,47]. Some individuals may have large-scale changes to the structure of *PKHD1*, such that standard sequencing techniques do not detect them [9,10,39]. The subject becomes further complicated by ARPKD phenocopies, mutations in other modifier genes or misdiagnoses.

Mutations in *DZIP1L* have only been identified in a small number of individuals with moderate ARPKD [17]. Although the kidney manifestation associated with mutations in DZIP1L is better characterised, our understanding of the effect of *DZIP1L* mutations and their ability to cause a liver phenotype is not as clear. Mice carrying mutations in *Dzip1l* show ductal plate malformations but lack more severe liver defects [17]. The absence of such defects has been proposed to be a result of the early demise of the mice [17]. Additionally, only a small cohort of ARPKD patients are reported to have mutations in *DZIP1L* and of the cohort studied in [17], only one patient had reported liver defects at the time of the study.

3. Phenocopies, modifier genes and the complex landscape of disease mechanisms

It thus becomes apparent from the above that a complex landscape is emerging in ARPKD. ARPKD phenocopies have been identified in various model systems, the most prominent of which are associated with early onset ADPKD [48–50]. However, ADPKD is not the only reported instance of ARPKD phenocopying, with Nephronophthisis, *HNF-1β* and more recently *CYS* being reported [48,49,51]. Additionally, it is possible for mutations in *PKHD1* to phenocopy other ciliopathies, most notably, *PKHD1* mutations have been reported in ADPKD patients that lack mutations in *PKD1* and *PKD2*, suggesting a complex relationship between the various genes, mutations in which give rise to Ciliopathies [52,53].

The role of genetic modifiers has also recently emerged, with work from our lab identifying ATMIN as a potential modifier of ARPKD [23]. Atmin is a DNA damage response protein that may also act as a transcription factor [54]. ATMIN has been demonstrated to regulate the expression *of DYNLL1* through a negative feedback loop where ATMIN directly binds to the *DYNLL1* promoter region and when DYNLL1 reaches a set threshold, the binding of DYNLL1 directly to ATMIN inhibits ATMIN's ability to bind to the *DYNLL1* promoter [55–57]. The ATMIN-DYNLL1 relationship has been shown to be important for tissue development and may play a role in cilia formation [58]. Atmin has also been shown to be important for mouse kidney development by modulating Wnt signalling [59]. Atmin modulation impacted Pkhd1 and affected cellular proliferation and adhesion, leading to defective non-canonical Wnt/Planar Cell Polarity (PCP) signalling in ARPKD [23]. The mechanisms of the Atmin-Pkhd1 interaction may involve genetic or other intermediary protein interactions or transcriptional/translational regulation processes, since Atmin does not directly bind to the C-terminus of Fibrocystin [23]. The $Atmin^{Gpg6}$ mouse, which phenocopies ARPKD by displaying a kidney, liver and lung phenotype could prove a useful tool in better understanding disease mechanisms and the role of genetic modifiers in ARPKD [23,58,59]. It should be noted that in animal models the genetic background also appears to affect cystic kidney disease severity [60], thus making the interpretation of results harder. HNF-1β is another candidate modifier gene in ARPKD that can cause early onset diabetes of the young (MODY5) and congenital kidney cyst development and can phenocopy ARPKD [48,49]. Additionally, transgenic mice with mutations in *Hnf1β* develop kidney cysts and *Hnf1β* has been demonstrated to transcriptionally regulate *Pkhd1* [61,62]. Loss of *Hnf1β* or its C-terminus results in downregulation of *Pkhd1* in transgenic mice, highlighting similarities in the molecular pathways of kidney cyst formation in the two diseases [61,62].

Furthermore, several signalling pathways have been identified to be mis-regulated in ARPKD and these have been excellently reviewed in [14,23,63]. Our own work has uncovered an emerging role for non-canonical Wnt/PCP signalling in ARPKD [23]. Significantly increased *WNT5A*, *VANGL2* and *SCRIBBLE* expression was observed in ARPKD kidneys compared to age-matched healthy controls, which together with a striking increase in E-cadherin, point towards an important role of non-canonical Wnt signalling in ARPKD. Additional work is currently undertaken to carefully dissect these functions and determine the hierarchy of events.

4. Conclusion

As ARPKD is a rare disease with complex and diverse causative

mechanisms and a disease incidence that is variable among populations, it is important that well-designed and appropriately controlled longitudinal studies are conducted, to be able to fully dissect disease mechanisms and impact on diagnosis, prognosis, and treatment. ARPKD animal models can significantly help in this direction although for the time being, there is not one animal model that fully recapitulates ARPKD, meaning that these models are invaluable in informing disease mechanisms, but their application needs to be tested in human studies. Although it is believed that there is no significant gender or ethnicity bias in ARPKD, studies with a great number and diversity of participants need to be conducted for this question to be comprehensively answered. The increasing occurrence of national and international registries for rare diseases could help bridge this gap in data collection and it could also assist in the design of longitudinal studies that inform ARPKD prognosis and aid with personalised medicine approaches. Data collected for registries and biobanks should nonetheless be homogeneous and uniformly useful, so that it adheres to standards that can subsequently allow for data sharing and the potential merging of these databases. Great emphasis should be placed on collaborative networks within and across countries and continents, so as to be able to combine all the data on ARPKD and achieve the power in numbers that such a rare disease requires. Knowledge transfer from other similar rare diseases such as Nephronophthisis, could facilitate a better understanding of disease mechanisms and minimise mis-diagnosis. Priority should also be given on predictors of disease progression and the identification of novel biomarkers that could inform not only ARPKD progression but also treatment. There are many challenges associated with working on a rare disease, nevertheless, a sound starting ground has been achieved in ARPKD and with collective action, strides in ARPKD diagnosis, prognosis and treatment may well be in sight.

Declaration of competing interest

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bbadis.2022.166348.

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