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Polycystic Kidney Disease: An Examination and Review of Disease Type, Presentation, Treatment, and Prognosis

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Title: Polycystic Kidney Disease: An examination and review of disease type, presentation, treatment, and prognosis

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One Sentence Summary:

Polycystic Kidney Disease is a ciliopathy with a broad spectrum of presentations that calls for continued research into disease function and treatment.

Contents

Abstract

Polycystic Kidney Disease (PKD) is a ciliopathy that primarily presents as renal cysts. Inherited as either a dominant (ADPKD) or recessive (ARPKD) mutation, PKD is one of the most commonly inherited kidney diseases. ADPKD is caused by the inheritance of a mutation in either *PKD1* or *PKD2*, which code for the polycystin-1 and -2 proteins, respectively. The less severe form of PKD, ADPKD is typically adult-onset, with the possibility of extremely late-stage presentation. In addition to renal cysts, hepatic and pancreatic cysts are common, as well as other non-cystic symptoms including headache and hypertension. ARPKD is caused by the inheritance of a *PKHD1* or *DZIP1L,* which encode fibrocystin and DZIP1L, respectively. ARPKD is typically onset in either fetal development or during the perinatal stage. ARPKD is the more severe form of PKD, with a 30% mortality rate of neonatal diagnoses. Additional presentations of ARPKD include enlarged kidneys visible in utero by sonogram, liver fibrosis, pulmonary hypoplasia, and abnormalities of the limbs and spine. Multiple treatments exist to manage this condition including drug therapies such as Tolvaptan, as well as renal replacement in the form of dialysis and eventual kidney transplant.

Polycystic Kidney Disease: An Overview

Polycystic Kidney Disease (PKD) is a hereditary disease of the kidneys that has plagued humanity for centuries. First documented following the death of Polish King Stefen Bathory in 1586, PKD is one of the most commonly inherited kidney diseases affecting millions worldwide (Balat, 2016; Goksu & Khattar, 2020; Torres & Watson, 1998). Since the first use of the term polycystic kidney by Flix Lejars in 1888, PKD has been identifiable by the growing bilateral cysts within the kidneys (Balat, 2016). Due to the improper functioning of the cilia on the surface of kidney epithelium, PKD was labelled a ciliopathy. Today, it is understood that PKD arises from defective proteins that colocalize to the ciliary membrane and render the cilia non-functional.

Cilia and Their Pathologies

Cilia are thin, cytoplasmic projections that extend from many eukaryotic and prokaryotic cells, including cells found within the kidneys. Historically, cilia were first identified around 1675 by Anton van Leewenhoek and are the oldest recorded organelle (Satir, 2017). Evolutionarily, the conservation of cilia from the last eukaryotic common ancestor, over 800 million years ago, is indicative of their necessity to cell and organismal survival (Piasecki et al., 2010).

Classified as either motile or primary, cilia are composed of a 9+2 or 9+0 arrangement of microtubules, respectively surrounded by cytoplasm and a cell membrane (See Figure 1). Motile cilia, similar to the singular flagella, are used for cellular movement and motion. The 9+2 formation of the microtubules consists of 9 doublet pairs surrounding a pair of singlet microtubules in the center of the cilia. The doublet pairs are connected to the inner singlets by radial protein spokes. These spokes work in conjunction with the arms of the doublets, composed

of the motor protein dynein, causing directed movement of cilia. Cells of the human respiratory

tract are lined with motile cilia that beat together, working to move mucus and keep the airway

clear (Bergmann et al., 2018; Jenkins et al., 2009; Mann, 2020).

In contrast, primary cilia work to send signals from the exterior of the cell to the interior

in order to better understand the external environment of the cell. Similar to motile cilia, primary

cilia have 9 doublet microtubule pairs on the outside of the cilia. However, primary cilia lack the

2 additional singlet microtubules in the middle, as well as the radial spokes and dynein arms, as

they are not specialized for movement. Within the kidney, cilia function to transfer signals of

fluid flow to track the urine output of the kidney, thereby monitoring hydration levels of the

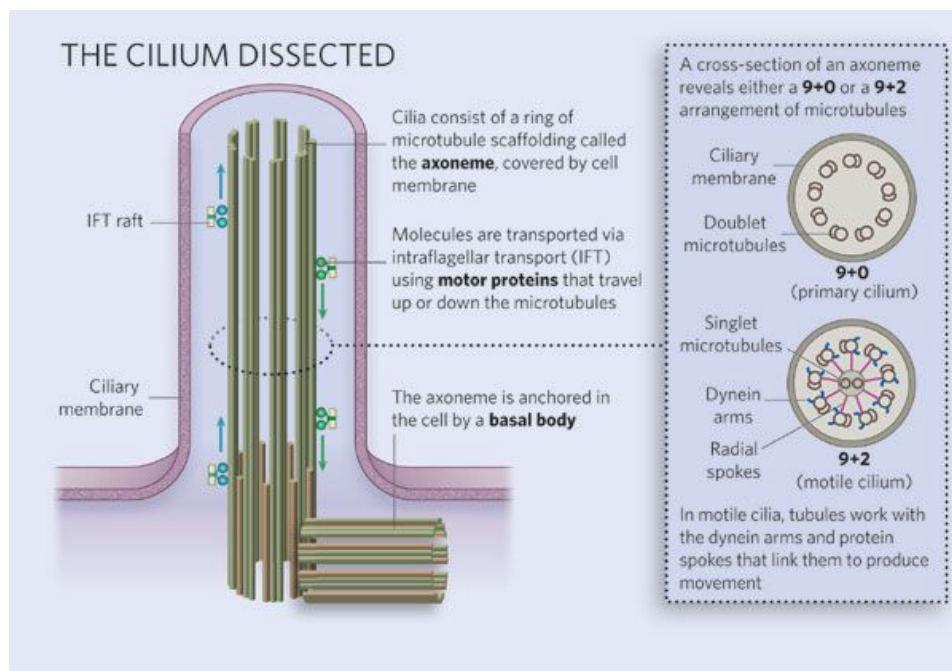organism (Bergmann et al., 2018; Jenkins et al., 2009; Mann, 2020).

Figure 1. The Cilium Dissected. The lateral image depicts the construction of the cilium and the ability to move cargo up and down the cilia via intraflagellar transport. The cross section depicts the 9+0 and the 9+2 arrangement of microtubules of sensory and motile cilia, respectively. Image adopted from Ainsworth, 2007. Legend adopted from Mann, 2020.

Ciliopathies are conditions that are distinguished as either the malformation or improper functioning of cilia due to defective proteins. More than 30 different ciliopathies have been identified and are thought to affect 1 in 2,000 individuals (Reiter & Leroux, 2017; Schmidts & Mitchison, 2018). The variety of genes responsible for cilia development makes them one of the more commonly presented genetic disorders.

The genes that control cilia formation and function are highly evolutionarily conserved, and their proteins often interact directly with one another. Ciliopathies are inherited, with few exceptions, in an autosomal recessive manner (Braun & Hildebrandt, 2017). Therefore, the individual requires two copies of the affected gene to present with the mutant phenotype. If only one copy is present, in most cases, the individual will have normally functioning cilia and may remain asymptomatic throughout their lifetime. Ciliopathies vary widely in their symptomatic presentation, including eye movement and visual impairment, polydactyly, and kidney dysfunction. Many genes have been identified to cause ciliopathies when mutated by affecting a wide range of proteins within the cilia. These proteins appear to cluster in their cellular location based on the disease group to which they belong, such that the proteins of one particular ciliopathy will colocalize together, suggesting a connection between the different genes and their relationships to the cilia formation and function (Braun & Hildebrandt, 2017). The expression of these different genes and their protein end products demonstrate the complexity of these thin, hair-like projections (Mann, 2020). The PKD proteins affected by mutation will localize together as transmembrane proteins, with some forming complexes together to better transduce the signal of fluid flow.

Genetics and Associated Physiology

PKD can be classified by its inheritance pattern as either autosomal dominant (ADPKD) or autosomal recessive (ARPKD). Both forms are caused by mutations in genes that code for ciliary transmembrane proteins, each of which are responsible for different components of cilia function/development.

ADPKD

ADPKD is the more prevalent of the two types, affecting between 1 in 400 and 1 in 1,000 people worldwide. This form of the disease is typically noted to be the less severe form and typically presents in older adults. Of those affected with ADPKD, 85% present with a mutation in the *PKD1* gene. Found on the 16th chromosome, *PKD1* codes for the polycystin-1 protein. The other 15% of ADPKD patients have a mutated *PKD2* gene; *PKD2* codes for the polycystin-2 protein and is found on the 4th chromosome (Loftus & Ong, 2013).

Polycystin-1 and polycystin-2 are transmembrane proteins that together form a receptor-channel complex that is responsible for ion flow, specifically calcium ions. This complex is found in the primary cilium of epithelial and endothelial renal cells (See Figure 2). When colocalized to these locations, this receptor-channel complex works to convert shear-stress signals into a calcium signal; polycystin-1 receives the mechanical signal and acts as a regulator of the ion channel created by polycystin-2, allowing for the influx of calcium (Mekahli et al., 2012; Nauli et al., 2003; Sharif-Naeini et al., 2009). When either of these proteins become nonfunctional due to mutation, the regulation of this pathway ceases, causing the buildup of fluid and the creation of cysts.

Inheritance patterns of ADPKD appear to play a role in disease severity. Some data suggest that those with milder forms may have incompletely penetrant *PKD1* alleles, which

indicates that cyst formation/severity may depend on the level of functional PKD1 protein (Halvorson et al., 2010; Rossetti et al., 2009). This can also be connected to individuals with mosaic PKD, a non-inherited form of the disease that results from post-zygotic *de novo* mutations. Individuals with mosaic PKD have both normal and diseased cells, and their phenotypes vary depending on which tissues are affected (Hopp et al., 2020). Additionally, individuals who present with mutations in both *PKD1* and *PKD2* experience worse outcomes than those with only a single mutation; a homozygous mutation presentation of the PKD1 protein is suggested to be lethal to the affected fetus (Halvorson et al., 2010; Paterson et al., 2002; Pei et al., 2001) Notably, a family history is not entirely necessary for ADPKD presentation, as around 2-5% are thought to be *de novo* in origin; both ADPKD genes can also be inherited recessively (Bergmann, 2012; Bergmann, 2015).
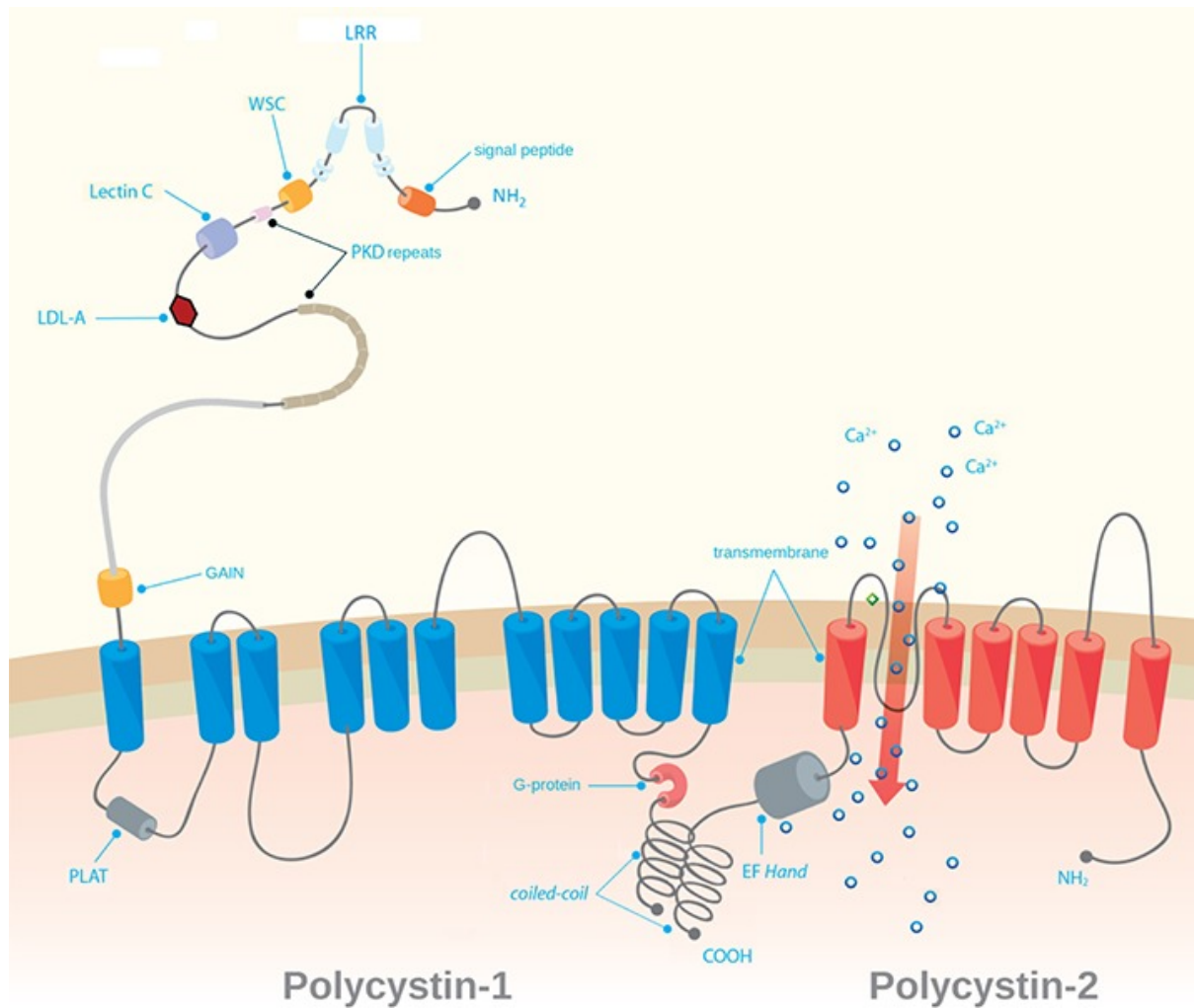
Figure 2: Polycystin-1 and Polycystin-2. Both proteins localize together on the ciliary membrane to translate mechanical stress signals into calcium influx. Image adopted from (Ferreira et al., 2015).

ARPKD

ARPKD is the lesser common, more severe form of PKD, affecting between 1 in 20,000 and 1 in 200,000 people worldwide. Traditionally ARPKD presents itself either during neonatal development or early childhood. This presents challenges for finding causes and examining the molecular mechanisms at play. Until recently, ARPKD has been shown to be caused by mutations only in the PKHD1 (Polycystic Kidney Disease and Hepatic Disease 1) gene.

However, recent studies have found that a second gene DZIP1L, also plays a role in the pathogenesis of ARPKD (See Figure 3) (Lu et al., 2017).

PKHD1 encodes for the fibrocystin protein (also known as polyductin), a large protein with a length of 4,074 amino acids (Onuchic et al., 2002). Fibrocystin, like polycystin-1 & -2, localizes to the membrane of the cilia within renal epithelial cells (Bergmann et al., 2018). Additionally, PKHD1 can be found in low amounts within the pancreas and the liver, which causes additional symptom presentations. Fibrocystin is a receptor-like protein that is believed to play a role in maintaining lumen structures/tubulogenesis within epithelial cells (Kim et al., 2008). It appears to work in tandem with polycystin-2 in a common pathway; the COOH terminus of fibrocystin will interact with the NH2 terminus of polycystin-2, and a lack of fibrocystin will affect the expression of polycystin-2. However, the reverse is not true, which suggests that fibrocystin may function upstream of polycystin-2. This supports experimental findings that fibrocystin can serve as a regulator/modifier in controlling disease severity in patients with ADPKD that stems from mutations within the *PKD2* gene (Kim et al., 2008).

Recently, a recessive mutation in the *DZIP1L* (DAZ (Deleted in Azoospermia) Interacting Protein 1 Like) gene was found to produce renal cysts similar to that of ARPKD, but without the occurrence of hepatic cysts (Lu et al., 2017). DZIP1L is a 767 amino acid protein that has been found to localize in both centrioles as well as the distal end of the basal body (Adamiok-Ostrowska & Piekiełko-Witkowska, 2020; Lu et al., 2017). A mutation in *DZIP1L* was confirmed as a secondary ARPKD locus after mice with chemically created *DZIP1L* mutations presented with renal cysts that were found to be consistent with those typically displayed in ARPKD (Adamiok-Ostrowska & Piekiełko-Witkowska, 2020; Lu et al., 2017; Ma, 2020).

Mutations of *DZIP1L* have been detected both prenatally and in early childhood, though it has not been noted in death of either fetuses or newborns (Lu et al., 2017). This differs from *PKHD1* presentation, as those afflicted with the more common mutation typically face perinatal death at a rate of 30%, primarily caused by respiratory insufficiency (Harris & Torres, 2009; Lu et al., 2017). Mutations affecting the presentation of the DZIP1L protein account for only 2-5% of the ARPKD cases, while mutations influencing PKHD1 are responsible for the remaining cases. The difference in cases affected by each gene may be attributed to the difference in size; less than 800 amino acids comprise DZIP1L while over 4,000 make up PKHD1.
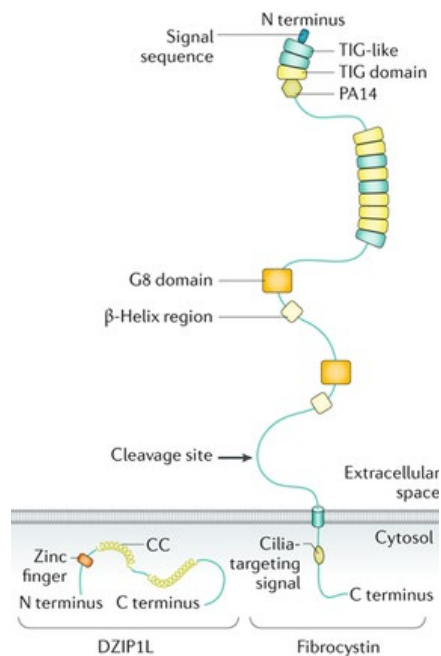

Figure 3. Proteins involved in ARPKD presentation: DZIP1L and Fibrocystin. Fibrocystin is thought to interact with ADPKD effector Polycystin-2 on the ciliary cell membrane, while DZIP1L localizes to the distal end of the basal body. Image adopted from (Bergmann et al., 2018).

Clinical Presentation

PKD earns its name from the fluid-filled cysts that form within the kidneys, causing loss of kidney function and eventually kidney failure in the patient. However, renal cysts are not always the initial indicator of PKD. Additional symptoms can be noted prior to a diagnosis, including hypertension, cardiovascular anomalies, and headaches.

ADPKD

In presentations of ADPKD, over 70% of cases first present with arterial hypertension before the associated renal failure is noted; hypertension correlates with renal cystic mass volume (Noël & Rieu, 2015). The presentation of renal cysts will lead to a decrease in renal flow as their growth impacts kidney function due to their continued progression of bilateral cystic growth.

It should be noted that there is a wide range of presentation of renal cysts with ADPKD. It can present in early stages of fetal development with notably enlarged kidneys depicted in an ultrasound, as well as first indicators not being present at high enough levels to cause concern (i.e. semi-functional kidney presentation) until well into the latter half and end stages of life. It is this wide range of presentations that can make ADPKD difficult to determine as the cause of illness unless imaging is conducted. The imaging results will determine the need for additional testing in the form of genetic screening. Other presentations, including hematuria, urinary tract infections, flank pain, and renal colic are also noted, though the variety in which these phenotypes are seen can make them difficult to relate to ADPKD (Harris & Torres, 2009).

However, ADPKD is not limited to the kidneys, as ADPKD is a noted systemic disorder. In addition to renal cysts, it can also cause cysts of both the pancreas and liver, as well as the arachnoid and seminal vesicles. In the case of liver cysts, it can cause cystic growth of such severity that it can lead to polycystic liver disease (PLD) that can require surgical intervention, though this presentation is much less common (Harris & Torres, 2009).

Additionally, non-cystic phenotypes of ADPKD are also present within the affected population and have been shown to involve the body's vasculature. Intracranial aneurysms are shown to be present in those with ADPKD at a rate five times greater than the general

population; mortality and morbidity shows greater association with aneurysmal rupture in this population as well (Harris & Torres, 2009).

ARPKD

Unlike ADPKD, those with ARPKD will typically begin to present symptoms during fetal development or just after birth. The classical presentation of considerably larger and echogenic kidneys can allow for visual diagnosis using imaging before birth. The Potter's phenotype is the most extreme of the ARPKD cases, which consists of characteristic facies and pulmonary hypoplasia, as well as notable abnormalities of the limbs and spine (Harris & Torres, 2009).

Those that survive past the neonatal period typically present with hypertension and renal insufficiency, with up to one third of children requiring a form of renal replacement therapy (dialysis or transplant) (Harris & Torres, 2009). An additional sign of disease is biliary dysgenesis resulting in congenital hepatic fibrosis, as well as intrahepatic bile duct dilatation (Caroli disease); this disease presentation can be diagnosed throughout all stages of life, not just neonatally (Harris & Torres, 2009). Notably, those that are able to live longer without receiving a diagnosis typically have less severe presentations of kidney disease; those with the later diagnosis of ARPKD are typically diagnosed after presentation of liver disease complications instead (Harris & Torres, 2009).

Additionally, distinctions can be made between the renal cystic presentation of ADPKD and ARPKD. Renal cysts of ADPKD can present as smaller fluid cysts that are surrounded by a more extensive fibroid tissue. These cysts can form in various locations throughout the kidney, but typically present within the distal regions (Bergmann et al., 2018; Halvorson et al., 2010; Noël & Rieu, 2015). ARPKD renal cyst presentation demonstrates cystic formation in the distal

renal tubules, as well as the collecting ducts. On the microscopic level, cysts are fusiform

dilatations of the distal portions of the nephron. These portions are lined by a ciliated columnar

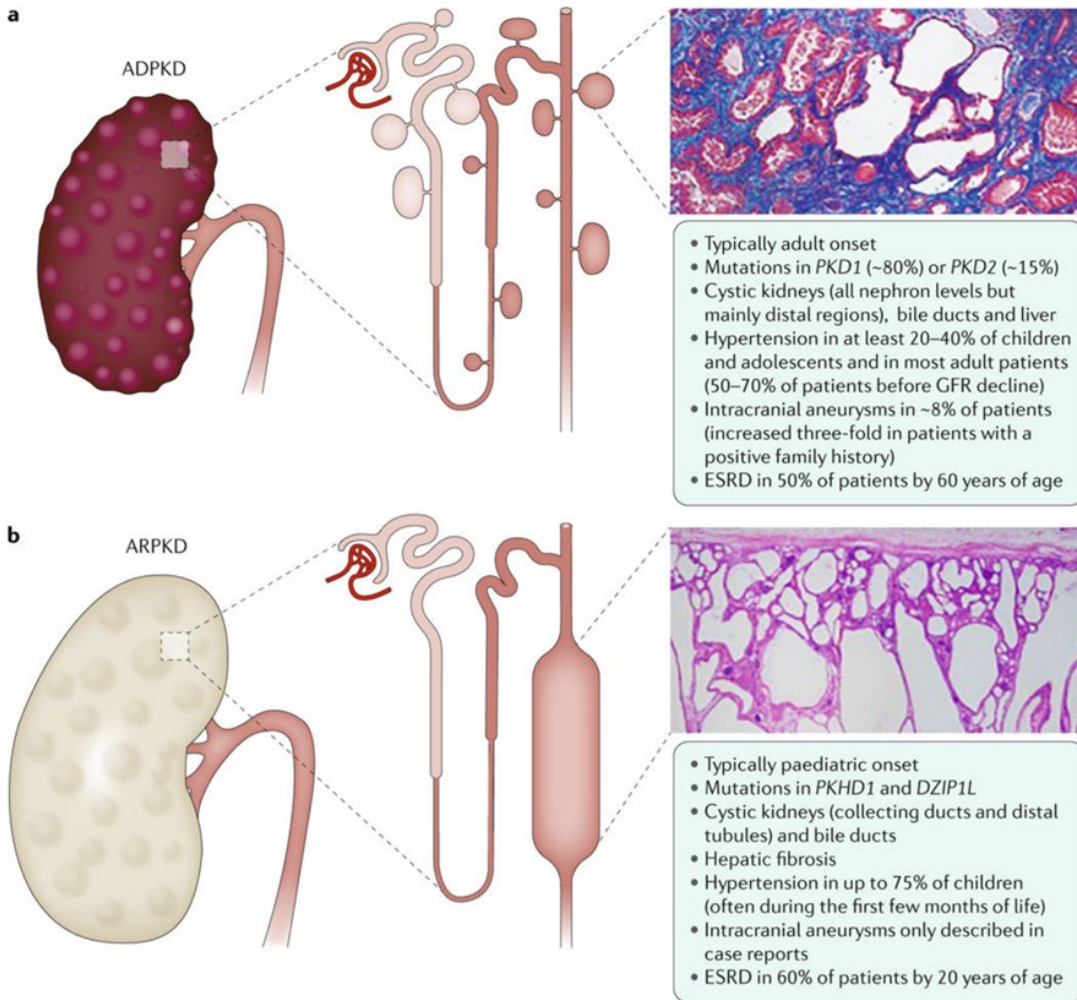or cuboidal epithelium. (See Figure 4) (Bergmann et al., 2018).

Figure 4. Differentiations of Clinical Presentations of ADPKD and ARPKD. A) ADPKD is typically adult onset and presents cystic kidneys mainly in the distal regions of, though presentation in all renal tissues have been noted. Accompanying renal cysts, hypertension is noted in patients of varying life stages. Additional increased risk for intracranial aneurysms (this increase will increase by an additional 3 times in patients that present with a family history of intracranial aneurysms. B) ARPKD is typically pediatric onset, though it can be detected in a developing fetus. Cystic presentation is noted in all portions of the kidneys will typical presentation found in the collecting ducts and distal tubules. Hypertension is presented in a majority of the pediatric patients. GFR-Glomerular Filtration Rate. ESRD-End Stage Renal Disease. Image adopted from (Bergmann et al., 2018)

Diagnostics

Diagnosis of PKD is essential for proper treatment and management of the disorder, as well as continued monitoring of genetic risk factors when family planning. Additionally, the almost inevitable development of end stage renal disease (ESRD) means that effective disease management from the earliest possible diagnosis is essential for ensuring the best possible outcomes for patients. Diagnostics of PKD include measurements of kidney function to determine cystic impact and visualization of the affected kidneys, which can be performed both in utero and adult development.

ADPKD Diagnosis Based on Clinical Presentation

ADPKD is capable of presenting in utero, however the cysts will continue to grow and develop throughout the patient's lifetime as the disease progresses. As the cystic growth continues, the volume of the kidney will expand and its efficiency will decrease; this decrease can be accompanied or preceded by the onset of clinical symptoms that include early-onset hypertension, abdominal pain/fullness, hematuria, and urinary tract infections (Bergmann et al., 2018) Though cyst formation begins in utero, ADPKD is an adult-onset disease that typically does not manifest itself until the latter half of the lifespan.

Use of imaging technologies such as a CAT-scan, MRI, and ultrasound can allow for visualization and subsequent diagnosis of the disease prior to the onset of clinical symptoms. Visualization is the typical initial form of investigation and diagnostics performed in ADPKD due to both its cost effectiveness and widespread availability, as well as its non-invasive aspect (Cornec-Le Gall et al., 2019). However, this is typically only conducted in patients that present with a genetic/familial risk factor that indicates they could have ADPKD. This is used in conjunction with guidelines put forth to determine the number of cysts that need to be visualized

to make a positive diagnosis of ADPKD that also accounts for age, as development of cysts within the kidneys can occur with age without the need for a defective PKD gene.

ARPKD Diagnosis Based on Clinical Presentation

The aggressive nature of ARPKD gives it the potential to be diagnosed in utero or shortly after birth due to its advanced rate of cyst formation, though later diagnosis is not unheard of. Diagnostics through infancy would include visualization of kidneys that present as echogenic and are bilaterally enlarged, as well as small, localized cystic growth within the collection ducts and distal tubules (Bergmann et al., 2018). Diagnosis of an older child or young adult can include the presentation of portal hypertension or cholangitis; rarely does a patient live to adulthood without a diagnosis, and this typically signifies a less aggressive and slower progressing form of the disorder (Bergmann et al., 2018; Cornec-Le Gall et al., 2019).

Infants who are diagnosed early with ARPKD and survive are also at risk for early onset ESRD, resulting in the need for dialysis and eventual kidney replacement therapy at a young age. Notably, those that present earlier in childhood display less evidence of renal enlargement, while those that present later are more likely to have additional portal hypertension complications. As the disease progresses, it can alter in presentation to resemble ADPKD, suggesting that early diagnosis is not only vital for proper treatment and therapy, but also necessary to ensure time is not wasted with a misdiagnosis. Notably, those that do experience the altered, ADPKD-like presentation of ARPKD will lose kidney volume as the interstitial fibrosis increases (in ADPKD, the kidney volume will increase with this change) (Bergmann, 2015; Bergmann et al., 2018).

Diagnosis Based on Genetic Screening

Genetic screening allows for a clearer picture and better understanding of the phenotype that a patient presents based upon which gene carries the mutation, even though ADPKD and

ARPKD vary widely in their presentation. The knowledge obtained by genetic screening can create insights into additional symptoms that the patient may need to address, as well as providing more information about the severity and progression of the patient's case. In cases when cysts are present but familial history is negative for any renal disorders, particularly any variation of PKD, genetic screening can be utilized to identify if the cystic growths that have been visualized are caused by a gene mutation in the PKD genes. Additional genetic testing can also determine if the cysts are of PKD origin, but are instead a presentation of a different disorder, such as Nephronophthisis-Medullary Cystic Disease or Medullary Sponge Kidney Disease, as these diseases can present similarly in the patient, but treatment can be conducted more effectively if the cause is properly understood. Genetic screening is the standard for diagnosis if a definitive diagnosis is requested/required for additional medical procedures (Cornec-Le Gall et al., 2019).

Treatment
Drug Therapies

Treatment of PKD is a new and continuingly evolving system of clinical trials and trial expansions constantly being created and evaluated. However, the differences between the dominant and recessive forms of PKD play a major role in the types of treatments available, as well as whether the focus of the treatment is for the disease itself, or to rectify the symptoms the patient is experiencing.

One of the most promising treatments for those who suffer with ADPKD is the use of Tolvaptan. Functioning as a vasopressin V2 antagonist, Tolvaptan works to block the antidiuretic vasopressin pathway to limit its impact on cystic growth and development, as well as disease progression. Functionally, vasopressin works to up-regulate the production of cAMP, which in

turn affects both kidney cell proliferation as well as fluid secretion, thereby promoting cystic development and growth (Edwards et al., 2018; van Gastel & Torres, 2017). Based upon the success of V2 antagonists within rodent models, a clinical trial was conducted in 2004 to determine the efficacy of Tolvaptan use in patients with ADPKD. Treatment with Tolvaptan was found to be efficacious when administered twice daily to suppress urine osmolality to <300 mOsm/kg (Edwards et al., 2018). However, changes in glomerular filtration rate (GFR) reversed rapidly after discontinuation of Tolvaptan, indicating the necessity for continual treatment (Edwards et al., 2018). Additionally, Tolvaptan-induced hepatotoxicity and the possible loss of drug efficacy over longs periods of use limit its broad prescription for PKD therapy, thereby suggesting that new and more functional treatment methods are still a necessary and timely issue (Sans-Atxer & Joly, 2018).

Additional research is being conducted on other drug therapies that may potentially be used both in conjunction and exclusively for the treatment of PKD. A prospect that has recently come to light is the use of melatonin for cyst reduction. Conducted in a Drosophila model, melatonin has been shown to reduce the cysts within the renal tubules, thereby demonstrating a regional specificity that creates a differential response similar to that in humans.

The Drosophila model was found to present similar phenotypes to that of ADPKD, though the affected gene differs from the *PKD1* gene that over 80% of ADPKD patients typically present with (Gamberi et al., 2017; Loftus & Ong, 2013; Millet-Boureima et al., 2020). In place of the *PKD1* gene, *BICAUDAL C* (*BICC1* in humans and *BicC* in Drosophila) acts as the mutated gene within the model organism. This system remains functional for evaluation of treatments even without the main target gene as *BICC1* has been found to be affected downstream of the *PKD1* gene, and in turn is responsible for the regulation of TOR and MYC

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expression. The effect that the BicC protein has on its downstream effectors displays similar phenotypes to that of ADPKD, thereby making the gene and its subsequent mutation in a model organism acceptable for study of drug treatments and their effects on the symptoms traditionally associated with the *PKD1* mutation (Gamberi et al., 2017).

Melatonin has been shown to functionally reduce the growth of cancer cells through a variety of growth-factor pathways, including the TOR pathway. This makes melatonin a potential candidate for reducing cyst growth caused by proliferation and fluid buildup within the renal tubules. When tested within the *BicC* mutant Drosophila, melatonin was found to significantly reduce the cysts found in the renal tubules while simultaneously displaying regional specificity for affecting different regions of the tubules at different rates. This suggests that melatonin may have the ability to decrease the amount of cystic activity within the renal tubules of ADPKD patients, as they also tend to experience cystic renal tubules (Millet-Boureima et al., 2020). Therefore, melatonin has the potential to change the way ADPKD is treated in terms of pharmaceuticals. Its functionality yields positive results in the model, suggesting that it will be useful in humans due to its ability to target the same downstream pathway from the PKD1 protein. Additionally, its low toxicity makes it a potentially more viable candidate for long term use than some current treatments.

Non-drug Therapies

Non-drug therapies, including kidney transplantation, are another important form of treatment. The outcomes of kidney transplantation in ADPKD patients are better than the average ESRD patient (Bergmann et al., 2018). In ARPKD, the patients typically face more restriction for renal replacement therapy; this is caused by the small size of the patient due to the typically young age of diagnosis (Bergmann et al., 2018).

Other treatment regimens are also necessary to manage the additional effects of PKD that affects portions of the body other than the kidneys. This is traditionally completed on an individual basis as patient presentation can vary case to case. However, some non-renal symptoms that typically present themselves include growth failure, liver disease, respiratory problems, and high blood pressure. Growth failure can be treated with nutritional changes and monitoring, though in severe cases use of human growth hormone may be needed. Liver disease can result in the need for medications or the need for a liver transplant. Artificial ventilation can be utilized for respiratory problems, and high blood pressure can typically be sufficiently managed with the use of blood pressure medications; treating high blood pressure may be able to slow the progression of PKD toward renal failure (Guay-Woodford & Desmond, 2003).

Prognosis

Prognoses for PKD patients vary widely based on phenotypic presentation. Those with rapidly-developing cysts may be diagnosed in utero and typically have worse prognoses than those with slower-developing cysts that survive to adulthood without a diagnosis. This difference in prognosis can be attributed to the type of PKD a patient experiences, being either autosomal dominant or recessive, as well as the individual genes that are affected within each disease type and the age of diagnosis. ADPKD patients with *PKD1* mutations typically have the more aggressive form of ADPKD and, by extension, the less favorable prognosis. Typically, they experience hypertension and ESRD at earlier rates than those with the *PKD2* mutation, thereby leading those affected with the *PKD2* mutation to better prognoses. Additional factors including gross hematuria and an increased mass of the left ventricle have been shown to correlate negatively with an ADPKD patient's prognosis (Bergmann et al., 2018 & Gabow PA, Johnson AM, Kaehny WD, et al., 1992 as cited in Halvorson et al., 2010). ARPKD patients also

experience differences in prognosis. One such significant factor thought to be correlated with disease prognosis is the necessity of neonatal ventilation, as better respiratory conditions are positively associated with disease outcomes (Halvorson et al., 2010).

Additionally, disease prognosis for both ADPKD and ARPKD are associated with the age at which diagnosis occurs. This factor can be attributed to a less severe disease, and by extension a better prognosis, based on the time needed for diagnosis. Disease that is aggressive and demands earlier diagnosis is more likely going to correlate with a worse prognosis, while the milder disease forms will not demand diagnosis as early in the manifestation. Therefore, the longer an individual can live comfortably with mild to no symptoms without the need to seek a diagnosis is indicative of better outcomes (Bergmann et al., 2018; Halvorson et al., 2010).

Conclusion

PKD is one of the most commonly inherited kidney diseases that affects millions of people worldwide. The large spectrum of disease presentation makes PKD difficult to diagnose and provide accurate prognoses for. The high variability of PKD presentations and prognoses demonstrates the need for more effective pharmaceutical interventions with low toxicity that can be used for long-term disease management, thereby allowing for better patient outcomes on a larger scale. Further research into the function of the PKD proteins will allow for greater understanding of their mechanisms as well as additional routes of management and possible pharmaceutical treatments. With an increasing knowledge base of how PKD functions, millions of people will have the potential to reach better outcomes and increase their quality of life.

Acknowledgements

Notes

Author declares no competing interests.

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