


ARPKD and ADPKD: First Cousins or More Distant Relatives?

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Superficially, autosomal dominant polycystic kidney disease (ADPKD) and autosomal recessive polycystic kidney disease (ARPKD) seem to be more different than alike. ADPKD is common, its cysts arise from any nephron segment, and it is slowly progressive. Hepatic cysts are its primary extrarenal lesion. The disease results from mutation of either of two genes, PKD1 and PKD2, that encode distinct proteins (PC1 and PC2) that form a receptor-channel complex. In sharp contrast, ARPKD is 20-fold less common, presents primarily in infancy and childhood, and is typically more severe. Affected newborns are often born with massively enlarged, cystic kidneys and die in the perinatal period from respiratory failure. Unlike in ADPKD, these cystic kidneys retain their reniform shape and the cysts are fusiform dilations mainly of the collecting ducts. A variety of liver abnormalities that result from ductal plate malformations are universally present. The disease results from mutation of PKHD1, a novel gene that encodes a cell-surface receptor or ligand.

Despite these differences, there are several indirect lines of evidence to suggest that the diseases may be more related than previously suspected. First, there are occasional cases that present with overlapping clinical features. Second, we now know that ADPKD is recessive on a molecular level, with its two-hit mechanism explaining some of the clinical differences between it and ARPKD. In fact, mice homozygous for a hypomorphic missense change of Pkd1 develop severe cystic disease restricted to distal nephron segments that is remarkably like that seen in human ARPKD. Third, the proteins encoded by each locus have been shown, in animal models, to be critically involved in tubular luminal regulation. Despite these differences, there are several indirect lines of evidence to suggest that the diseases may be more related than previously suspected. First, there are occasional cases that present with overlapping clinical features. Second, we now know that ADPKD is recessive on a molecular level, with its two-hit mechanism explaining some of the clinical differences between it and ARPKD. In fact, mice homozygous for a hypomorphic missense change of Pkd1 develop severe cystic disease restricted to distal nephron segments that is remarkably like that seen in human ARPKD. Third, the proteins encoded by each locus have been shown, in animal models, to be critically involved in tubular luminal regulation. Despite these differences, there are several indirect lines of evidence to suggest that the diseases may be more related than previously suspected. First, there are occasional cases that present with overlapping clinical features. Second, we now know that ADPKD is recessive on a molecular level, with its two-hit mechanism explaining some of the clinical differences between it and ARPKD. In fact, mice homozygous for a hypomorphic missense change of Pkd1 develop severe cystic disease restricted to distal nephron segments that is remarkably like that seen in human ARPKD. Third, the proteins encoded by each locus have been shown, in animal models, to be critically involved in tubular luminal regulation.
mediated by subunits of kinesin-2. Both studies also found that FPC was essential for the normal channel properties of PC2, leading both groups to conclude that PC2 is likely a downstream target of both FPC and PC1. A third report by our group described genetic interaction between the Pkd1 and Pkhd1 loci. We developed a line of Pkhd1 mutant mice recapitulating most human ARPKD phenotypes and found that Pkhd1/Pkd1 transmutants had markedly more severe disease.

The most recent contribution is the study by Kim et al. in this issue of JASN. The investigators generated a new line of Pkhd1 mutant mice and found that homozygotes were born at a lower frequency than predicted, suggesting embryonic lethality. Survivors developed variably severe cystic disease of the kidney and pancreas and fibrocytic disease of the liver that culminated in premature death in the majority of mutants. Heterozygotes inexplicably also tended to die prematurely. Unexpectedly, an undefined fraction of the Pkhd1−/− mutants also developed ulcerative and hemorrhagic lesions in the gastrointestinal tract and vacuolar lesions of the brain, abnormalities not typically associated with human ARPKD. Consistent with previous reports, the authors found that the primary cilia of renal epithelial cells of Pkhd1−/− specimens were reduced in number and length.

Given the group’s previous findings that PC2 and FPC form a complex, they examined the relationship between the respective genes and proteins in samples and cultured cells using a combination of biochemical, electrophysiologic, and genetic analyses. They found greatly reduced levels of PC2 in Pkhd1−/− samples despite normal levels of mRNA encoding Pkd2. They also noted that FPC/PC2 complexes were absent from samples genetically lacking either Pkhd1 or Pkd2, and PC2 channel activity was absent from Pkhd1−/− cells. Finally, they reported increased severity of renal cystic disease in transmutant mice.

At first glance, the results of the four studies seem to be consistent with the idea that the three proteins PC1, PC2, and FPC form a functional complex with common downstream signaling pathways. There are, however, important differences that suggest that these relationships are more complicated than anticipated. For example, Wang et al. found no reduction in PC2 levels or in FPC/PC2 interactions in inner medullary collecting duct cells with 90% reduction in FPC levels. This difference may in part be explained by how Pkhd1 was targeted in the different models because another inner medullary collecting duct clone silenced using a different construct resulted in a reduced amount of PC2/FPC complexes. More surprising is the apparent discordance between disease severity and the dramatic effects of Pkhd1 mutation on PC2 levels and activity. The majority of Pkhd1−/− mice survive to birth and many have relatively mild disease. This is very different than what is observed in Pkd2−/− mutants. One possible explanation for this apparent discrepancy may be that PC2 level or channel activity is not reduced in less severely affected animals. This seems to be unlikely, though, given that reduced PC2 levels/activity was apparently a constant finding, whereas the phenotype was highly variable.

The results of the genetic interaction studies also raise perplexing questions. Kim et al. describe a modest increase in the number of spherical cysts observed in transmutants but no other consequences. One might have expected haploinsufficiency for Pkd2 to reduce PC2 levels further, resulting in a marked increase in overall disease severity. In fact, this is what we observed with Pkhd1/Pkd1 transmutants, who had dramatically more severe disease involving most organ systems and greatly increased rates of premature mortality. Our two studies also differ in that Kim et al. describe an increased number of ADPKD-like cysts in transmutants, whereas we found an accentuation of the underlying ARPKD phenotype.

We are concerned that the choice of spherical cysts as a readout could be problematic because we find that ADPKD-like cysts are amply and variably found in Pkhd1 mutant specimens. Of course, there is no absolute a priori reason to expect that the results of Pkhd1/Pkd2 and Pkhd1/Pkd1 crosses should be the same. The threshold levels required for each protein and the effects of haploinsufficiency on complex assembly and function may differ. Given the prevailing models of how these proteins cooperatively function and the profound effects that reduction of FPC levels had on PC2, however, we find these differences somewhat surprising. Finally, in previous unpublished studies, we had found that the level of PC2 in cystic kidneys of Pkhd1 mutants and Pkhd1/Pkd1 transmutants was not reduced (M. Garcia-Gonzalez, Pasteur Institute, personal communication, April 2007, Johns Hopkins). Although differences in how Pkhd1 was targeted could potentially explain these discrepancies, our data suggest that mutation of Pkhd1 can result in renal cystic disease without requiring changes in PC2 levels.

In conclusion, there is increasing evidence that the proteins encoded by the principal cystic disease loci somehow cooperate to ensure normal renal tubular morphology. This latest study by Kim et al. reports new tools to study these processes and provides additional evidence in support of this model. Like any interesting study, it raises more questions than it answers and provides ample testable hypotheses for future discovery.

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DISCLOSURES

None.

REFERENCES

Too Much of a Good Thing: Does Nek8 Link Polycystic Kidney Disease and Nephronophthisis?

Yiqiang Cai and Stefan Somlo

Autosomal dominant polycystic kidney disease (ADPKD) is characterized by age-dependent occurrence of bilateral, multiple renal cysts resulting in kidney enlargement in association with a variable spectrum of extrarenal manifestations, most commonly simple cysts arising from bile ducts in the liver. Nephronophthisis (NPHP) is an autosomal recessive kidney disease characterized by tubular basement membrane disruption, tubular atrophy, and tubulointerstitial nephritis, associated with corticomedullary cysts typically without kidney enlargement. Liver disease, when it occurs in NPHP, is characterized by portal tract fibrosis with little or no bile duct proliferation. ADPKD and NPHP, respectively, are the most common genetic causes of end-stage kidney disease in adults and children or adolescents. Cysts are considered the initiating pathogenetic event in ADPKD to the point where recent studies suggest that serial measurements of cyst and kidney volumes can be used as determinants of disease progression. Cysts in NPHP do not have a similar central role in pathogenesis of the disease. Nonetheless, a growing body of cellular and molecular evidence has come to suggest an interrelationship among these diseases and a number of others, such as autosomal recessive polycystic kidney disease (ARPKD), Bardet-Biedl syndrome (BBS), and Meckel-Gruber syndrome. These relationships are based on the association of many of the causative disease gene protein products with the cilia/basal body complex.

There is little doubt that the primary cilium plays a central role in both establishing and maintaining the complex yet reproducible three-dimensional structure of the kidney. In addition to “guilt by association” arising from the finding that many gene products that are mutated in fibrocystic kidney diseases in humans and mice localize to cilia, there are several prospective studies confirming this association. For example, kidney cysts develop when Kif3a, a component of the anterograde transport machinery required for structural integrity of cilia but not otherwise known to be associated with cystic diseases, is inactivated in the kidney. Similarly, a forward genetic screening in zebrafish using pronephric kidney tubule dilation as the phenotype identified 10 mutant genes among which there was a marked overrepresentation of cilia-associated protein products. This convergence on the importance of the cilium/basal body complex in fibrocystic diseases has fostered a reductionist approach to mechanism based on the premise that at

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