KI REPORTS
KIReports.org

The Enigma of Clinical Heterogeneity Among Autosomal Recessive Polycystic Kidney Disease Siblings: *PKHD1* Genotype Versus Other Genomic or Environmental Modifier

Priti Meena[1] and Katharina Hopp[2]

[1]Department of Nephrology, All India Institute Medical Sciences, Bhubaneswar, India; and [2]Division of Renal Diseases and Hypertension, Department of Medicine, University of Colorado Anschutz Medical Campus, Aurora, Colorado, USA

Kidney Int Rep (2022) **7,** 1453–1455; https://doi.org/10.1016/j.ekir.2022.04.092

See Clinical Research on Page 1643

Autosomal recessive polycystic kidney disease (ARPKD) is a rare form of polycystic kidney disease characterized by fibrocystic changes in the kidney and liver during early childhood. It is one of the major causes of dialysis dependency and combined liver-kidney transplantation in the pediatric age group.[1] *PKHD1* has been identified to be the predominant causative gene.

The ARPKD clinical spectrum is highly variable; although 30% to 50% of patients die as neonates, adult patients with only mild-to-moderate symptoms have been reported on. The liver manifestations usually include bile duct dilatation, periportal fibrosis, and portal hypertension. Perinatal death or death shortly after birth is caused by respiratory insufficiency/pulmonary hypoplasia and thoracic compression due to massively enlarged polycystic kidneys.[2]

ARPKD is marked by extensive allelic heterogeneity, and *PKHD1* genotype has been correlated with distinct clinical outcomes. Patients with 2 truncating/loss-of-function mutations typically display perinatal or neonatal mortality, whereas patients with at least 1 missense mutation, not predicted to abolish protein function, display less severe symptoms and are likely to survive the neonatal period.[3,4] Furthermore, a recent observational study suggests that missense mutations to specific regions of the PKHD1 protein can modulate severity of kidney or liver disease outcome.[4]

Mutations to genes beyond the *PKHD1* locus or epigenetic/environmental modifiers affecting ARPKD severity have been suggested to be of importance through ARPKD sibling analyses. This notion was initially fueled by a case report by Barth *et al.*,[5] where the author described a pedigree with varying clinical outcomes in 3 affected fetuses from 1 family. In an additional study of 42 children of 20 sibships with ARPKD, Deget *et al.*[6] evaluated intrafamilial variability in terms of age at diagnosis, liver and kidney affection, and use of antihypertensive therapy. Although the study observed gross variation in age of death in 8 sibships (40% of families studied), only small intrafamilial variability in the overall clinical course was noted in most of the remaining families (11 of 20, 55% of families). In this study, the mean follow-up period was 3.7 years, and no *PKHD1* genotyping was performed.[6] In another study involving 107 patients with ARPKD from 48 ARPKD pedigrees, Bergmann *et al.*[7] noted widely discordant phenotypes in 20 sibships (perinatal/neonatal demise in 1 vs. survival into childhood in the other affected sibling, 42% of families). No discordance in *PKHD1* genotype was found among siblings. Interestingly, none of the sibships with significant phenotypic heterogeneity had 2 *PKHD1* truncating/loss-of-function mutations, suggesting that the impact of other modifying factors affecting clinical outcome is likely most prominent in the setting of missense mutations, which may be hypomorphic in nature. Of note, clinical information beyond perinatal/neonatal demise was absent in a significant portion of pedigrees analyzed (15 of 48 families).

On the basis of these publications, clinical heterogeneity, typically regarding perinatal/neonatal mortality, among ARPKD siblings has been recognized as a clinical

Correspondence: Katharina Hopp, Division of Renal Diseases and Hypertension, Department of Medicine, University of Colorado Anschutz Medical Campus, Aurora, Colorado, USA. E-mail: katharina.hopp@cuanschutz.edu

feature of the disease; however, the characterization of longitudinal clinical course among ARPKD sibships is scarce.

In this context, Ajiri *et al.*[8] add to these records. Uniquely, most patients in this study survived childhood, and detailed clinical evaluations were available for outcome comparison. Ajiri *et al.*[8] analyzed 70 ARPKD siblings from 35 families registered in the ARPKD registry study. The participants were from 20 different centers from 9 different countries. The author only included patients with ARPKD diagnosed based on histology, molecular or clinical findings as per criteria by Zerres *et al.*,[9] whereas patients with genetic, histologic, or clinical proof of another cystic kidney disease were excluded. The study presented a longitudinal clinical course of sibling pairs with a median follow-up time of 3.5 (0.2–6.2) years. The median age of all patients was 0.7 (interquartile range 0.1–6.0) years at initial diagnosis.

In 39 patients from 22 different families, genetic sequencing of *PKHD1* was performed; the detection rate of biallelic pathogenic, likely pathogenic, or variants of unknown clinical significance was 82% (18 of 22 families). In 5 families, only 1 sibling was genotyped, and in 3 families, only 1 pathogenic, likely pathogenic, or variant of unknown clinical significance *PKHD1* variant was identified. The percentage of patients who had severe perinatal disease was 21%, and they were admitted to neonatal intensive care with 15% of patients requiring respiratory support. However, only 1 child died in the neonatal period (a patient with 2 truncating *PKHD1* variants); 8 patients from 7 families required kidney replacement therapy at a median age of 7 years. Differences in the clinical course among siblings were based on perinatal respiratory symptoms; kidney disease severity as measured by chronic kidney disease (G) stage, kidney sonography, and requirement for kidney replacement therapy, and liver disease severity as measured by thrombocytopenia, sonographic splenomegaly, or hepatic complications (e.g., variceal bleeding, liver transplantation). Importantly, for 20 of 35 sibships, the authors had clinical data available that were obtained when the siblings were of similar age, allowing for more ideal direct comparison of clinical disease course.

Unexpectedly, the clinical course among siblings where none of them needed replacement therapy was very consistent (28 families), which parallels the findings of Deget *et al.*[6] In the 7 families affected by kidney replacement therapy, the clinical course among siblings in 4 of the families was also comparable. Hence, only 3 sibling pairs had a pronounced clinical difference during their disease course. In 2 pairs, at comparable age, 1 sibling was classified as chronic kidney disease (G) 5, whereas the other was classified as chronic kidney disease (G) 1. In the third, 1 sibling required renal replacement therapy at 1.9 years of age, whereas the other sibling was classified as chronic kidney disease (G) 2 at 26.8 years of age. Biallelic *PKHD1* missense variants were present in 2 families, but the third was not genotyped. Consanguinity was not documented in any of the 3 families.

The minimal clinical variability among ARPKD siblings as found by Ajiri *et al.*[8] suggests that the underlying *PKHD1* genotype has a substantial influence on the clinical course of the disease in childhood and adolescence. However, with being a registry study of predominantly tertiary care nephrology centers, there could be an underrepresentation of the more severe cases with perinatal death, the milder cases not requiring kidney replacement therapy, or cases with predominant hepatic phenotype. Lacking these populations could explain why only very few sibships with dissimilar clinical course were identified.

It is interesting to note that 2 of the 3 families with significant clinical differences between siblings had biallelic *PKHD1* missense changes. This, in line with the findings of Bergmann *et al.*,[7] would suggest that in the setting of not fully penetrant *PKHD1* mutations, where the ARPKD phenotype is milder, genetic, epigenetic, or environmental modifiers may have a greater impact to drive clinical heterogeneity. In such cases, systematic analyses of other genes, in particular, other PKD genes, are essential, which has not been performed in any of the published studies to date and should become an important goal for future studies.

Overall, the data presented by Ajiri *et al.*[8] provide a valuable longitudinal follow-up for both concordant and discordant courses in ARPKD families. It seems that survival of the neonatal period remains the key determinant of ARPKD severity and that differences in disease course are less likely to be found in families with biallelic *PKHD1* truncating/loss-of-function changes associated with severe ARPKD leading to perinatal/neonatal mortality. In addition, the data from Ajiri *et al.*[8] suggest substantial consistency in the clinical course among ARPKD sibships surviving the neonatal period. However, in light of all published ARPKD sibling cohorts, to date, it remains that vigilant care is needed when counseling families with 1 affected child who are planning to conceive or are expecting a second child. This is particularly true if the underlying *PKHD1* genotype is

unknown, unresolved, or includes non-loss-of-function variants, that is, missense variants.

With the better and advanced quality of intensive care facilities, the chances of neonatal survival are progressively improving making estimation of long-term clinical courses in ARPKD more informative. Longer-term follow-up studies, a continuing collection of ARPKD sibships with detailed clinical records, and global genetic analyses will inform more personalized clinical care for ARPKD families and advance the understanding of the disease.

DISCLOSURE

All the authors declared no competing interests.

REFERENCES

1. Burgmaier K, Kilian S, Bammens B, et al. Clinical courses and complications of young adults with autosomal recessive polycystic kidney disease (ARPKD). *Sci Rep*. 2019;9:7919. https://doi.org/10.1038/s41598-019-43488-w
2. Hartung EA, Guay-Woodford LM. Autosomal recessive polycystic kidney disease: a hepatorenal fibrocystic disorder with pleiotropic effects. *Pediatrics*. 2014;134:e833–e845. https://doi.org/10.1542/peds.2013-3646
3. Bergmann C. Genetics of autosomal recessive polycystic kidney disease and its differential diagnoses. *Front Pediatr*. 2017;5:221. https://doi.org/10.3389/fped.2017.00221
4. Burgmaier K, Brinker L, Erger F, et al. Refining genotype-phenotype correlations in 304 patients with autosomal recessive polycystic kidney disease and PKHD1 gene variants. *Kidney Int*. 2021;100:650–659. https://doi.org/10.1016/j.kint.2021.04.019
5. Barth RA, Guillot AP, Capeless EL, Clemmons JJ. Prenatal diagnosis of autosomal recessive polycystic kidney disease: variable outcome within one family. *Am J Obstet Gynecol*. 1992;166:560–561. https://doi.org/10.1016/0002-9378(92)91672-w
6. Deget F, Rudnik-Schoneborn S, Zerres K. Course of autosomal recessive polycystic kidney disease (ARPKD) in siblings: a clinical comparison of 20 sibships. *Clin Genet*. 1995;47:248–253. https://doi.org/10.1111/j.1399-0004.1995.tb04305.x
7. Bergmann C, Senderek J, Windelen E, et al. Clinical consequences of PKHD1 mutations in 164 patients with autosomal-recessive polycystic kidney disease (ARPKD). *Kidney Int*. 2005;67:829–848. https://doi.org/10.1111/j.1523-1755.2005.00148.x
8. Ajiri R, Burgmaier K, Akinci N, et al. Phenotypic variability in siblings with autosomal recessive polycystic kidney disease. *Kidney Int Rep*. 2022;7:1643–1652. https://doi.org/10.1016/j.ekir.2022.04.095
9. Zerres K, Rudnik-Schoneborn S, Deget F, et al. Autosomal recessive polycystic kidney disease in 115 children: clinical presentation, course and influence of gender. *Acta Paediatrica*. 1996;85:437–445. https://doi.org/10.1111/j.1651-2227.1996.tb14056.x