A Perspective on Inherited Kidney Disease
Lessons for Practicing Nephrologists

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Genetic studies focused on rare kidney diseases have informed our knowledge and understanding of key kidney structures, such as glomeruli and tubules, while also identifying novel druggable targets (e.g., SGLT2 inhibitors). Recent advances in genomics have highlighted the complexity of Mendelian conditions (1). This complexity is due to allelic heterogeneity (distinct mutations on one gene produce distinct phenotypes), locus heterogeneity (mutations on distinct genes result in similar phenotypes), reduced penetrance, variable expressivity, modifier genes, and/or environmental factors.

Nephronophthisis is one of these complex diseases. There are 20 genes that cause kidney lesions within the nephronophthisis spectrum. Patients typically present with polyuria and normal-sized kidneys harboring corticomedullary cysts; most develop ESRD over time. Extrarenal abnormalities are often uncovered in the context of specific syndromes and cannot be predicted on genotype information alone. Additionally, a subset of Joubert and related syndromes, all with the same structural cerebellar lesion, present with kidney abnormalities that resemble nephronophthisis. Although there are now 27 genes associated with Joubert syndrome, only six have been formally linked to nephronophthisis. Two articles in this issue of the Clinical Journal of the American Society of Nephrology (2,3) provide complimentary data that illustrate the complexity of genotype to phenotype landscapes for patients with nephronophthisis (2) or Joubert syndrome (3). The unique feature of these contributions is in their opposite starting points (kidney or brain involvement) and target outcomes (associated neurologic or kidney phenotypes) in the context of well defined molecular diagnoses. Both papers highlight the wide spectrum of affected organs in both conditions (2,3).

What is clear from these two studies is that the “diagnostic odyssey” (4) experienced by patients does not end with the identification of a disease-causing genotype. Systematic investigations may lead to the discovery of nonobvious phenotypes (Figure 1), suggesting that nephrologists undertake a more detailed “phenomic” approach. Data from these studies may help avoid unnecessary delays to institution of therapies by highlighting unexpected but robust genotype-phenotype associations. More importantly, these studies raise awareness about the unique attributes of a disease in range and severity. The traditional approach using textbook signs and symptoms to guide diagnosis and management is no longer sufficient (5).

König et al. (2) report on the phenotype of 152 patients diagnosed with nephronophthisis. Disease-causing mutations were identified in 97 patients, 60% of whom were carrying NPHP1 mutations. Despite the large study, no pathogenic genotypes were found in 14 of 20 known NPHP genes. The other five genes tested were represented by a median of three patients (range, 1–6). A significant proportion of disease subtypes remains undefined in all molecular diagnosis (30% of patients). In contrast, the study by Fleming et al. (3) included 97 patients who met diagnostic criteria for Joubert syndrome and identified a pathogenic genotype in 95% of patients, implicating 20 of 27 genes associated with this condition. Routine mutation testing of new patients for all 41 distinct genes associated with either nephronophthisis or Joubert syndrome may help reduce the number of undiagnosed patients and further define the range of possible phenotypes.

König et al. (2) found that 23% of patients with NPHP1 genotypes had extrarenal phenotypes (mostly neurologic and/or ocular) compared with 66% in all other genes (mostly neurologic, ocular, and/or hepatic). Patients meeting diagnostic criteria for Joubert syndrome or related conditions were rare in the context of NPHP1 mutations (three of 60) but very common for other genes, such as NPHP6 (100%) or NPHP11 (67%) genotypes. Interestingly, in eight patients with NPHP1 mutations included in this cohort, the “obvious phenotype” that resulted in the initial referral was neurologic (Joubert syndrome and congenital ocular motor apraxia); the molecular diagnosis presumably triggered investigations, leading to the discovery of the kidney phenotype.

The study by Fleming et al. (3), however, was explicitly designed to determine the frequency of kidney involvement among patients meeting diagnostic criteria for Joubert syndrome or related conditions. This patient population is clearly distinct from that presented by König et al. (2), because only one patient had an NPHP1 mutation. Overall, the authors found significant kidney phenotypes in 30% of patients, 60% of whom had pathogenic mutations in nephronophthisis genes (NPHP1, NPHP6, NPHP8, or NPHP11). This overlap was only discovered by careful phenotyping with imaging, regardless of presenting signs and symptoms. Patients with mutations in NPHP11 were far
more common in this study (25% versus 4% in the other study), which makes prevalence estimates difficult. Penetrance of the kidney phenotype for patients with NPHP11 mutations was only 50%. The spectrum of possible kidney pathologies in Joubert syndrome was likely underestimated in the past. For example, nearly 10% of patients in this cohort had an ARPKD-like phenotype, including 30% of patients with NPHP11 mutations. Whether this ARPKD-like phenotype was truly associated with Joubert syndrome was unclear, because only two kindred were previously identified: one with NPHP11 mutations. Identification of three patients with unilateral multicystic dysplastic kidneys also supports the notion that Joubert syndrome is associated with a broad spectrum of cystic kidney diseases. Importantly, none of these forms of cystic kidney diseases would have met selection criteria for the study by König et al. (2). Clinicians should actively investigate all patients with Joubert syndrome for a kidney phenotype given the high frequency found in patients with mutations in genes rarely associated with kidney disease (e.g., AHI1, INPP5E, or TMEM216).

Both studies have notable limitations. It is unclear if the new phenotypes uncovered lead to a change in clinical management. Reporting novel missense mutations usually require more careful vetting, because identification of rare variants in a gene (variants of unknown significance) does not guarantee pathogenicity, even if the correct gene (6). In addition, it is preferable to avoid including genes that are not yet established as disease causing, such as CE Synopsis 2 and KIAA0753 in Joubert syndrome (each observed in one patient). The phenotype spectrum delineated by König et al. (2) also may not be complete, because patients did not undergo systematic evaluations (e.g., brain magnetic resonance imaging not done in all patients). This has practical implications, because nearly all patients with congenital oculomotor apraxia are reclassified as having Joubert syndrome after magnetic resonance imaging (7).

Molecular diagnostic testing is rapidly changing with whole-genome sequencing on the horizon; hence, it is important for practicing clinicians to understand genetic testing. It is increasingly clear that deep phenotyping, defined as “precise and comprehensive analysis of phenotypic abnormalities” (8), is critical. We believe that physicians should take it one step further by reporting “deep patient characterizations,” a combination of detailed, multisystem phenotyping and careful assessment of genotype pathogenicity. It is also clear that larger sample sizes are necessary to better understand the genotype-phenotype dynamics that drive these heterogeneous conditions. International collaborations will only help in these rare kidney diseases to move knowledge forward. A deeper understanding of conditions with complex phenotypes will require active collaboration between various subspecialists caring for these patients. Because 30%–40% of patients with ARPKD do not have mutations in PKHD1 or DZIP1L (9), it may be informative to include the 41 genes identified in the nephronophthisis/Joubert syndrome continuum in an extended ARPKD diagnostic panel (10). Finally, physicians managing adult patients with a diagnosis of cystic disease should broaden the differential diagnoses to avoid missing a “pediatric” condition when the kidney and/or neurologic phenotypes may be mild enough to escape early diagnosis. Implementation of precision medicine in clinical nephrology, which is expected to improve diagnosis, prevention, and treatment of kidney disease, will require practicing nephrologists to have a good understanding of genetic testing and phenotyping (5).

Disclosures

None.

References


Published online ahead of print. Publication date available at www.cjasn.org.