The Mutation, a Key Determinant of Phenotype in ADPKD

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Autosomal dominant polycystic kidney disease (ADPKD) is one of the most common monogenic diseases (frequency 1:500–1000) and a classic dominant disease with a penetrance of practically 100%, if defined as the development of multiple bilateral cysts in a family member that inherits a defined mutation. However, the severity of disease, even in mutation characterized cases, varies greatly. At one extreme are those that live into old age and develop just a few cysts with no renal insufficiency, whereas at the other end of the spectrum are neonates that die shortly after birth with hugely enlarged cystic kidneys, reflecting the phenotype commonly seen in autosomal recessive polycystic kidney disease (ARPKD).

The typical phenotype is of progressive cyst development and expansion leading to ESRD in late middle age. However, even in this textbook view of ADPKD, the age at first presentation of their manifestations as well as the age at ESRD varies greatly. This is not only true for renal disease; the occurrence and severity of cystic and noncystic extrarenal manifestations that characterize ADPKD are also highly variable. Identification of the disease-causing genes, PKD1 (16p13.3) and PKD2 (4p21), in the 1990s was the first step toward understanding the etiology. However, the location of PKD1 in a complex duplicated region with six pseudogenes elsewhere on chromosome 16 has hindered the screening of large disease populations, at least until recently.

In populations identified in the setting of the renal clinic, PKD1 accounts for the majority of resolved cases (approximately 85%), with PKD2 responsible for the remainder of approximately 15%. However, even in comprehensive studies, approximately 9% of cases remained genetically unresolved. Soon after genetic heterogeneity was identified, divergent renal disease severity was noted between the two loci (average age at ESRD of approximately 54 years for PKD1 versus approximately 74 years for PKD2). As described in the ADPKD Mutation Database, mutation screening shows a high level of allelic heterogeneity with 929 PKD1 mutations accounting for 1266 pedigrees and 167 PKD2 mutations in 322 pedigrees; the most frequent mutation, PKD1: c.5014_5015delAG, accounting for just 2.2% of PKD1 families. In typical populations, mutations predicted to truncate the protein (frameshifting, nonsense, and splicing) account for approximately 70% of PKD1 and approximately 82% of PKD2 families, with nontruncating (missense and in-frame changes) accounts for the remainder.

Up until recently there was rather limited evidence of allelic effects in PKD1 or PKD2, with just a relatively weak influence of mutation position in PKD1 on the severity of renal disease and the occurrence of intracranial aneurysms. However, in the past couple of years, studies of families with unusual presentations of ADPKD have identified key roles for incompletely penetrant (hypermorphic) alleles. For instance, the PKD1 allele p.R3277C has been studied in detail and found in homozygosity to be associated with adult onset ADPKD and in heterozygosity to result in the development of just a few cysts. This variant was also inherited in trans with a truncating PKD1 mutation in an ADPKD family, resulting in early onset ADPKD. In a second family with early onset presentation in siblings and a negative family history, which was mistakenly diagnosed with ARPKD, p.R3277C was found in trans with a second PKD1 variant, p.R2220W, in the severe cases. Generation of a mouse knock-in model of p.R3277C proved its hypermorphic nature, resulting in slowly progressive disease as a homozygote (homozygous mice for a fully inactivating mutation...
die embryonically at approximately E14.5) and in combination with a null allele resulting in rapidly progressive PKD. A number of other likely hypomorphic PKD1 and PKD2 alleles found alone, in homozygosity or as a compound heterozygote have been identified in mild or early onset ADPKD cases.6–11

The study by Audrézet et al.,12 and the related PKD1 genotype/phenotype study of Cornec-Le Gall et al.,13 in this issue of JASN describe the largest ADPKD mutation screening with correlation to phenotype yet described, involving patients from the Brittany region of France. The original screen found definite or likely mutations in 627 of 700 families (approximately 90%), with 83.8% and 16.2% of mutation characterized cases being PKD1 and PKD2, respectively; 388 and 54 different PKD1 and PKD2 mutations were described, respectively.12 The genotype/phenotype study analyzed 741 patients from 519 pedigrees, of which 80.4% of resolved families were PKD1 and 19.6% were PKD2; 6.2% of families had no mutation detected.13

Utilizing Kaplan–Meier renal survival analysis, PKD1 patients had onset of ESRD 21.6 years earlier than PKD2, similar to previous studies.13 However, interestingly, the mean ages at onset of ESRD of PKD1 and PKD2, 58.1 years and 79.9 years, respectively, are 4–5 years older than in most previous studies. It is unclear whether this reflects improved care in recent years, as has been suggested,14,15 or the healthy lifestyle in the Brittany region. Analysis of sex in PKD1 showed onset of ESRD for men (56.1 years) was significantly earlier than for women (59.5 years), whereas there was no difference in PKD2. Up to this time, there has been controversy about the role of sex in PKD1,2,16 and one large study of PKD2 found male participants to have considerably more severe disease.17

The most important conclusion from this study13 is that for PKD1, truncating mutations are associated with much early onset of ESRD than nontruncating mutations, with a 12-year difference (55.6–67.9 years). This difference was particularly pronounced in men. No difference in severity of renal disease was found associated with the position of the mutation. This study is therefore important because it shows that a significant proportion of PKD1 missense and other in-frame changes are hypomorphic; these variant are not just limited to atypical families. So although nearly all PKD1 patients with truncating mutations experienced ESRD by 80 years, approximately 30% of nontruncating cases that reached that age did not have ESRD; this compares to approximately 40% for PKD2. It is difficult to estimate the proportion overall, but it seems likely that 10%–20% of all PKD1 mutations are incompletely penetrant. It should be noted in some families that the listed mutation is known to be a hypomorph (such as p.R3277C) or of unproven pathogenicity (p.R4276W), and knowing the phenotype in these families would be of interest.3

If specific mutations can be identified as hypomorphic, it would be of prognostic value. This information could be important when selecting patients for clinical trials (hypomorphic cases may not be suitable as they will usually be slow progressors), for future treatments, these patients may never develop ESRD so the risks may outweigh the benefits, or for other genetic studies to find factors beyond the disease mutation that modify the phenotype (may be a confounder if a PKD1 cohort is selected for study). It is likely that hypomorphic PKD1 alleles vary greatly in penetrance, with some resulting in just a few cysts whereas others are only a little milder than a truncating PKD1 mutation. What is not clear from the present study13 is the extent to which the hypomorphic allele dictates the phenotype in the individual patient (can immediately be identified as hypomorphic) or if genetic background and the environment often mask the penetrance of the allele. Phenotypic analysis in families with a suspected hypomorphic mutation and of recurrent hypomorphic variants will be interesting to judge the phenotypic variability.

It would be inappropriate to consider all missense changes and other in-frame mutations as hypomorphic. In vitro studies show that some missense mutations completely eliminate cleavage at the GPS site of the PKD1 protein, polycystin-1,8 and so are likely fully inactivating. In addition, previous smaller studies did not find a correlation between PKD1 mutation type and renal disease severity,4 indicating that probably at least 50% are fully penetrant. Identifying hypomorphic alleles without clinical information from families is likely to prove difficult. Tools that judge the significance of a substitution against the background of the conservation of the residue in orthologs, homologs, and in defined domains can be helpful, especially if three-dimensional structural data are available.1 However, considering that presently it is not always possible using bioinformatics tools to differentiate pathogenic and neutral changes (p.R3277C scores as Highly Likely Pathogenic from this type of analysis6), identifying incompletely penetrant mutations will likely be challenging. Protein assays, such as monitoring cleavage at the G protein-coupled receptor proteolytic site (GPS) domain and quantifying the abundance of glycoforms, can be helpful and quantitative but usually require in vitro studies.8 At this time, cataloging likely hypomorphic variants identified from family and population studies in the ADPKD Mutation Database seems the best way to keep track of these mutations.

The recognition that PKD1 hypomorphic alleles are not rare means that the prognostic advice that a PKD1 mutation universally results in a more severe phenotype with earlier ESRD needs to be reconsidered in cases in which a nontruncating change is detected. If hypomorphic alleles could be better recognized, the value of molecular diagnostic in ADPKD, that at present is not widely utilized, would increase as prognostic information could be provided. Overall, the findings from the study by Cornec-LeGall et al. indicate that more of the variability of the ADPKD phenotype rests at the allelic level than previously thought.

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DISCLOSURES

None.

REFERENCES


See related article, “Type of PKD1 Mutation Influences Renal Outcome in ADPKD,” on pages 1006–1013.

A Piece of the Puzzle in the Cardiorenal Conundrum

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Clinical investigations in recent years have established that the presence of even mild or moderate decreases in estimated GFR (eGFR) consistently confers a significantly elevated risk for cardiovascular disease (CVD),1 the leading cause of death in the United States and most industrialized countries. Moreover, in one study of almost 28,000 people followed for 5 years, those with eGFR <90 ml/min per 1.73 m² were more likely to die than to reach dialysis; the authors surmised that most fatal events were from CVD based on the increasing prevalence of cardiac risk factors over the follow-up period.2

A related topic is the growing recognition that CKD alters the predictable ability of traditional CVD risk factors, yet the understanding of why this is remains a puzzle. This puzzle is nested within a larger puzzle of a cardiorenal conundrum, in which kidney and heart dysfunction appear intimately linked in a manner that is incompletely understood.

Although the cardiorenal syndrome typically refers to diuretic-refractory advanced heart failure seen in the setting of decreased eGFR,3 other notable cardiorenal relationships in the realm of acute coronary syndromes and cardiac-related deaths

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