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The importance of quantifying genetic heterogeneity in ADPKD

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Abstract

ADPKD is the most common hereditary renal disease. New data provided in this edition of Kidney International suggests that mutations in the PKD1 and PKD2 genes may account for all cases of ADPKD. Further improvements in mutation detection methodologies are needed to determine the true relative frequency of PKD1 vs. PKD2 as well as to establish the value of mutation type and location to predict disease severity in this disorder.

In this edition of Kidney International, Harris and colleagues[1], painstakingly review five independent ADPKD families reported not to be linked to mutations in either the PKD1 or PKD2 gene. The initial assignment of non-PKD1 and non-PKD2 status creates the potential for at least a third gene potentially responsible for ADPKD. The re-reviewing of the original pedigrees and phenotypes, evaluation of original and recollection of DNA for analysis and direct sequencing of the PKD1 and PKD2 genes, where methodologies were not available at the time of the original publication, have now identified mutations in the PKD1 or PKD2 gene with no evidence for a third unidentified locus. Harris and colleagues now clarify that the five previously reported unlinked ADPKD families are not actually unlinked, but either misdiagnosed and not ADPKD with a presentation inconsistent with this disease, or reported as unlinked due to biological sample or pedigree mix-ups. All are now identified as PKD1 or PKD2 affected families. This work strengthens the views by many that there are only two genes responsible for the development of ADPKD. Consistent with our understanding of the natural history of PKD1 vs. PKD2, those with PKD2 mutations described in this paper appear to have a milder phenotype[2].

Despite these findings, concern for other genetic loci causing ADPKD continues. Although direct gene sequencing is the current gold standard for a molecular diagnosis of ADPKD, a significant portion of ADPKD individuals (approximately 10–13% in the best of hands), fail to demonstrate a mutation in either the PKD1 or PKD2 gene. Large direct sequencing studies including the Consortium for Radiologic Imaging Studies in Polycystic Kidney Disease (CRISP) have an approximately 86% mutation detection rate[3]. Those with no mutations detected in this well characterized cohort have a range of disease severity, but with a significant proportion having a mild phenotype, similar to PKD2 CRISP individuals,

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and similar to other previously reported unlinked PKD families. The absence of mutation identification in these individuals has been ascribed to the level of difficulty with complete sequencing the PKD1 gene, potential disease causing sequence changes in non-coding regions in both PKD1 and PKD2, mosaicism, or combined hypomorphic alleles.

Even after considering these possibilities, genes other than PKD1 or PKD2 may cause ADPKD and clarification of this issue is needed. A full understanding of the genetic epidemiology of ADPKD is necessary to develop an accurate natural history of ADPKD, provide accurate prognostic information to patients, develop novel targets for therapeutic intervention, and accurately quantify the financial and personal cost of inheriting a PKD mutation. Only when direct sequencing of the PKD1 and PKD2 genes can be done with 100% reliability in population based surveys can we move forward in the areas outlined above and completely assess the genetic contributions to disease severity in ADPKD. We have come a long way, but have more to go.

The genetic epidemiology of ADPKD remains to be accurately measured and quantified. The reported cases of unlinked PKD families available for study are a much smaller subset of a larger number of unreported families. Given the apparent milder disease severity seen in a significant proportion of families in the report by Harris et al, we may be overestimating the severity of disease due to ADPKD. The vast majority of reviews and book chapters written on the topic of the natural history of ADPKD begin with statements that need to be carefully assessed. With regard to the prevalence of ADPKD, estimates vary from a frequency of 600,000 to less than 300,000 individuals diagnosed with ADPKD in the United States.

The second statement that relates to the first is that PKD1 accounts for approximately 85% and PKD2 accounts for approximately 15% of all affected PKD individuals. The frequency of PKD mutations reported vary from 1:400 to 1:1000 in ADPKD and estimates of PKD2 mutations are often calculated from the relative frequency of mutations reported in PKD2 vs. PKD1 genes. The contribution of PKD2 affected individuals to the total number of PKD individuals differs from approximately 15% in clinical studies of affected individuals to more than 27% when autopsy studies are included[4]. It is most likely that there is a larger number of PKD2 affected individuals than we are aware of. Given that PKD2 is a milder disease and potentially undiagnosed during life, a complete screening for PKD1 and PKD2 mutations at the population level would help to clarify these issues.

The prognostic information related to both genetic heterogeneity with PKD1 and PKD2 and mutation heterogeneity within both PKD1 and PKD2 is increasing and demonstrating significant predictive power. Large direct sequencing studies including the CRISP[3], the HALT PKD Consortium[4] and most informatively by Pei et al[5], suggest that identification of both genotype and mutation type contribute to the prediction of renal disease severity. Once mutation detection rates in the PKD1 gene approaches 100% we will have even more insight into the prognostic value of the location and nature of the PKD mutations. Clinically we still rely on age of onset of ESRD to predict PKD1 or PKD2 status[6] and systematic mutation detection has not become part of our medical assessment in this most common hereditary kidney disease. Our understanding of the scope of severity of disease in ADPKD and

providing focused medical supervision of those individuals and their families who should be monitored more closely could be further developed by including this type of screening and genetic information in clinical practice. Until recently, the importance of mutation type in disease severity was not detectable due to reduced mutation detection rates and relatively small sample sizes to inform outcomes. With the reduced cost of gene sequencing, the increasing number of well phenotyped ADPKD populations bringing PKD mutation types in clinical practice will most likely reduce the economic cost of disease and reduce monitoring in those destined to be symptom free while increasing preventive monitoring proactively for those at high risk for progressive renal disease.

The final area for consideration with regard to the number of genetic loci responsible lies with the exponential progress in translational research in ADPKD. The cellular and extracellular signaling pathways and biological processes altered due to abnormal polycystin 1 and 2 function have provided a number of potential pathways for intervention. Should there be a polycystin 3 or beyond, additional pathways would also be identified and characterized. In addition to important supportive therapies for blood pressure, chronic kidney disease, hyperparathyroidism, anemia and metabolic acidosis, molecularly targeted approaches to slowing cyst formation and growth are now being developed and tested in patients with ADPKD. Many of these are specific to the kidney and others more systemic in nature, and some relate specifically to polycystin 1 or 2 function or to the functional polycystin complex. By defining the genetic heterogeneity in ADPKD, we will better refine the appropriate patient population for study in randomized clinical trials and develop new rationales for treatments using the molecular information obtained from loci and mutation detection. Therefore, 100% reliability in genetic screening and establishing the number of genetic loci responsible for ADPKD and the mutations within all PKD genes will inform the results of these provocative studies.

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