Molecular Diagnostics of ADPKD Coming of Age

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Ever since the first autosomal dominant polycystic kidney disease (ADPKD) gene was localized to a chromosomal interval (*PKD1*: 16p13.3) in 1985, brave souls have been performing molecular-based diagnostics (1). The enthusiasm was tempered by the discovery of a second gene (*PKD2*: 4q21) and suggestions of a third, with the realization that reliable linkage-based diagnostics required families large enough to determine unequivocally the gene involved (2). Identification of the *PKD1* and *PKD2* genes in the mid 1990s revived interest, although the large coding region of *PKD1* (approximately 13 kb) and reiteration of the genomic region several times elsewhere on chromosome 16 greatly complicated mutation screening (3,4). Consequently, the initial focus was mutations to the single-copy, 3′ region (approximately 20%) of *PKD1*, and *PKD2* (5,6). It was not until the dawning of the new millennium, after the development of methods for locus-specific amplification of the duplicated part of *PKD1*, that comprehensive analysis of both genes was possible (7,8). Even then, indirect methods were used to screen for bp changes—methods that because of the level of precision were not well suited to clinical diagnostics.

In the past year, larger studies that screened *PKD1* and *PKD2* by direct sequencing have shown that molecular diagnostics of ADPKD is finally coming of age (9,10). These genes offer unique challenges, including a high level of allelic heterogeneity (many different mutations cause ADPKD, the majority unique to a single family); that only approximately two thirds of mutations are predicted to truncate the protein and hence are definitely pathogenic, with the other third consisting mainly of missense changes (single base-pair substitutions); and a high level of amino acid substitutions that do not seem disease related (neutral polymorphisms). Nevertheless, with careful analysis, a likely mutation can now be assigned in up to 90% of patients (10), although, at this stage, diagnostic decisions in the approximately 25% of cases with nondefinite mutations are more risky. This can be overcome to some extent by using a family-based study that also allows segregation to be tested, as illustrated by Zhao *et al.* in this issue of the *Clinical Journal of the American Society of Nephrology* (11).

Equally important as the difficulties of mutation analysis to limiting the use of molecular diagnostics in ADPKD has been demand. The majority of patients' disease can be reliably diagnosed using imaging moieties such as ultrasound, computed tomography, or magnetic resonance imaging with multiple cysts typically detected in all but the youngest affected individuals. Specific age-related criteria for a positive diagnosis by ultrasound have been defined by Ravine *et al.* (12) to distinguish ADPKD from occasional simple renal cysts found in unaffected individuals as they age. However, in certain situations, imaging analysis can be equivocal, especially in younger adults and those with milder disease (PKD2), for which molecular testing can be critical for determining management decisions (11). The two situations analyzed by Zhao *et al.* (11) are evaluating younger, at-risk family members as potential living-related donors and understanding the significance of renal cystic disease without a family history. In families in which a definite mutation was identified (truncating or nonsense), PKD1 or PKD2 disease was confirmed, individuals without the mutation were cleared as potential donors, and the status of family members with a few cysts was clarified as unaffected. The one caveat is that not finding the mutation in a parent with a few cysts does not rule out that individual being a mosaic and other siblings being at risk. The two families in which nondefinite mutations were identified were less clear-cut, but the addition of linkage/segregation analysis in one family enabled an unaffected at-risk individual to be cleared as a transplant donor. Therefore, in four of five families, molecular diagnostics provided a clear result when there was some uncertainty from imaging and family history alone.

At present, the utility of a molecular diagnostic test in ADPKD is limited to a small but important fraction of patients, especially living-related donors. The prospects could change dramatically, however, once treatments that significantly slow the progression of disease become available (13). Because it is likely that treatments will be started in young adulthood or earlier, when renal damage from cyst development is limited but imaging data are less reliable, the demand for molecular diagnostics is likely to increase significantly. The challenge now for the molecular geneticist is to obtain molecular data that are reliable for diagnostic purposes in a greater number of patients. Present efforts to develop a database containing all described mutations will aid the identification of recurrent changes (ADPKD Mutation DataBase; PKDB; http://pkdb.mayo.edu) (14). The larger data set will also allow a more systematic analysis of changes to assess their significance, and the context in which they are found within families. Ultimately, a functional test for mutant alleles would be ideal, but even if this was available, it is not

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clear that it will be practical to use in a diagnostic setting. Another challenge is to reduce the cost of the analysis, and variant array approaches may help here in the next few years, at least as a prescreen. The nephrology community also needs a clear report and analysis of the molecular data that is readily interpreted by the nephrologist. Despite the challenges, molecular diagnostics is likely to become more important in management of patients with ADPKD, moving from its present niches to become more mainstream.

Disclosures

None.

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See related article, "Molecular Diagnostics in Autosomal Dominant Polycystic Kidney Disease: Utility and Limitations," on pages 146–152.