Unified Criteria for Ultrasonographic Diagnosis of ADPKD

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Abstract

Individuals who are at risk for autosomal dominant polycystic kidney disease are often screened by ultrasound using diagnostic criteria derived from individuals with mutations in *PKD1*. Families with mutations in *PKD2* typically have less severe disease, suggesting a potential need for different diagnostic criteria. In this study, 577 and 371 at-risk individuals from 58 *PKD1* and 39 *PKD2* families, respectively, were assessed by renal ultrasound and molecular genotyping. Using sensitivity data derived from genetically affected individuals and specificity data derived from genetically unaffected individuals, various diagnostic criteria were compared. In addition, data sets were created to simulate the *PKD1* and *PKD2* case mix expected in practice to evaluate the performance of diagnostic criteria for families of unknown genotype. The diagnostic criteria currently in use performed suboptimally for individuals with mutations in *PKD2* as a result of reduced test sensitivity. In families of unknown genotype, the presence of three or more (unilateral or bilateral) renal cysts is sufficient for establishing the diagnosis in individuals aged 15 to 39 y, two or more cysts in each kidney is sufficient for individuals aged 40 to 59 y, and four or more cysts in each kidney is required for individuals ≥60 yr. Conversely, fewer than two renal cysts in at-risk individuals aged ≥40 yr is sufficient to exclude the disease. These unified diagnostic criteria will be useful for testing individuals who are at risk for autosomal dominant polycystic kidney disease in the usual clinical setting in which molecular genotyping is seldom performed.

Autosomal dominant polycystic kidney disease (ADPKD) is the most common hereditary kidney disorder, affecting approximately one in 500 births. It is characterized by focal development and progressive enlargement of renal cysts, typically leading to chronic renal failure by late-middle age. It is a systemic disorder affecting multiple organs, resulting in extrarenal cysts and complications such as cardiac valvular defects, colonic diverticulosis, inguinal hernias, and intracranial arterial aneurysms.[1] Overall, it accounts for approximately 5% of ESRD in developed countries.[1–3] ADPKD is genetically heterogeneous: Mutations of *PKD1* (MIM 601313) and *PKD2* (MIM 173910), respectively, accounted for approximately 85% and approximately 15% of cases in a linkage-characterized European population.[1–8] The existence of at least one rare additional disease gene has been suggested by several families reported to be unlinked to either known gene locus[9,10]; however, recent confirmation of these findings is lacking, and one previously reported family has proved to be compound heterozygous for *PKD1* and *PKD2* mutations.[11]

Polycystins 1 and 2, the gene products of *PKD1* and *PKD2*, are transmembrane proteins that are components of a novel multifunctional signaling pathway.[1] Polycystin 1 may function as a receptor involved in cell–cell and/or cell–matrix interaction.[12] By contrast, polycystin 2 functions as a subunit of a cation channel with nonselective permeability.[13] Both proteins interact through their cytoplasmic region[12] and transmit fluid flow–mediated mechanosensation, which is detected by the primary cilium of renal epithelium.[14] Disruption of normal polycystin function by mutations predispose to cyst formation through loss of mechanical cues in tubular epithelial cells that regulate tissue morphogenesis.[1,14]

Although the phenotypes of PKD1 and PKD2 overlap completely, PKD1 is associated with more severe renal disease with an earlier clinical presentation and an excess of premature mortality.[8] Age-dependent ultrasound diagnostic criteria are established only for PKD1.[15] Specifically, the presence of at least two (unilateral or bilateral) renal cysts and two cysts in each kidney are considered sufficient for diagnosis in at-risk individuals aged 15 to 29 and 30 to 59 yr, respectively. By contrast, at least four cysts in each kidney are required for diagnosis of at-risk individuals aged ≥60 yr. Conversely, the finding of fewer than two cysts in each kidney is considered sufficient for disease exclusion in at-risk individuals aged ≥30 yr. Although these test criteria are widely used for genetic counseling and for evaluation of at-risk individuals as living-related kidney donors for their affected relatives, the validity of their application to families of undefined genotype is uncertain. We report here a comparative study to evaluate the performance of ultrasound diagnostic criteria for both PKD1 and PKD2. In addition, because molecular genotyping is seldom performed in the clinic, we derived by simulation studies diagnostic criteria with high sensitivity and specificity for evaluating at-risk individuals from ADPKD families of unknown gene type.

RESULTS

At the time of their ultrasound scan, 31.5% (299 of 948), 55.3% (524 of 948), and 13.2% (125 of 948) of the study participants were of age 15 to 29 yr, 30 to 59 yr, and ≥60 yr, respectively. Overall, the agreement on renal cyst counts on the basis of a standardized set of 40 images among the six study radiologists was excellent (intraclass correlation 0.949; 95% confidence interval 0.921 to 0.969; also see Supplemental Table 1). On the basis of their genotype, 52.3% (496 of 948) of the study participants were considered affected. In the two younger cohorts aged 15 to 29 and 30 to 59 yr, those shown by molecular genotyping to have PKD2 had a milder renal cystic burden than those with PKD1 ($P < 0.0001$; Figure 1). We found that the diagnostic criteria currently used for PKD1 did not perform as well when applied to PKD2, primarily because of a higher risk for false-negative results, which reduced test sensitivity (Tables 1 and 2). For at-risk participants aged 15 to 29 yr, the current diagnostic criterion of at least two (unilateral or bilateral) renal cysts yielded a sensitivity of 71.9% and a specificity of 100% in the PKD2 cohort (compared with 98.1% sensitivity and 98.8% specificity in the PKD1 cohort). Similarly, for at-risk participants aged 30 to 59 yr, the current diagnostic criterion of at least two cysts in each kidney yielded a sensitivity of 75.8% and a specificity of 100% in the PKD2 cohort (compared with 93.1% sensitivity and 100% specificity in the PKD1 cohort; data not shown). In the latter PKD2 cohort, the loss of diagnostic sensitivity was most marked in participants aged 30 to 39 yr (Table 2). For at-risk participants aged ≥60 yr, the current criterion of four cysts in each kidney provides sensitivity and specificity values of 100% in both PKD1 and PKD2 cohorts.

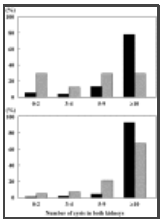


Figure 1.

Comparison of renal cyst number between affected individuals with PKD1 (■) and PKD2 (▨); diagnosed by molecular genotyping. (Top) Percentage of affected individuals who had different number of total renal cysts and were between 15 and 29 yr of ...

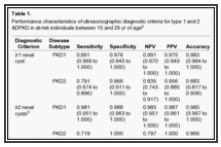


Table 1.

Performance characteristics of ultrasonographic diagnostic criteria for type 1 and 2 ADPKD in at-risk individuals between 15 and 29 yr of age[a]

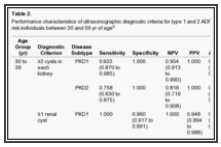


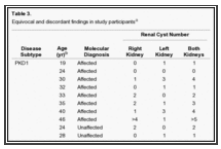
Table 2.

Performance characteristics of ultrasonographic diagnostic criteria for type 1 and 2 ADPKD in at-risk individuals between 30 and 59 yr of age[a]

We examined all participants with equivocal or discordant findings (Table 3). In general, it was rare to detect simple cyst(s) in genetically unaffected participants aged 15 to 29 yr: Only 1.4% (three of 144) had a single renal cyst, whereas 0.7% (one of 144) had two renal cysts. By comparison, 3.9% (nine of 232) and 1.7% (four of 232) of genetically unaffected participants aged 30 to 59 yr had one renal cyst and two or more renal cysts, respectively. Among genetically affected participants aged 15 to 29 yr, 26.8% (11 of 41) of those with PKD2 compared with 1.8% (two of 113) of those with PKD1 had fewer than two renal cysts ($P < 0.0001$). Similarly, among genetically affected participants aged 30 to 59 yr, 14.6% (18 of 123) of those with PKD2 compared with 3.5% (six of 170) of those with PKD1 had fewer than two cysts in each kidney ($P < 0.0009$).

Table 3.

Equivocal and discordant findings in study participants[a]



Through simulation studies, we evaluated the performance of different test criteria for at-risk participants with unknown genotype (Table 4; Supplemental Information). Two test criteria are particularly useful for establishing diagnosis: First, for those aged 15 to 39 yr, the presence of three or more (unilateral or bilateral) renal cysts provides a positive predictive value of 100%. Second, for those aged 30 to 59 yr, the presence of two or more cysts in each kidney also provides the same degree of diagnostic certainty; however, these criteria yield a false-negative rate in excess of 14% and cannot be used for disease exclusion. Instead, the finding of fewer than two renal cysts provides a negative predictive value of 100% and can be regarded as sufficient for ruling out disease in at-risk individuals aged ≥40 yr.

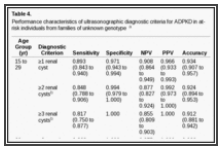


Table 4.
Performance characteristics of ultrasonographic diagnostic criteria for ADPKD in at-risk individuals from families of unknown genotype[a]

DISCUSSION

Previous studies have shown that the gene locus for ADPKD exerts a major effect on renal disease severity.[2,3,16,17] Specifically, the median age of ESRD in patients from PKD1 families occurs 16 yr earlier than those from PKD2 families.[16] In addition, adjusted for both age and gender, patients with PKD2 have fewer renal cysts than those with PKD1.[18] Consistent with these observations, we found in our study that renal cysts in PKD2-affected individuals become detectable by renal ultrasound at an older age and, when detected, were fewer in number than in PKD1-affected individuals. The milder renal cystic involvement in PKD2 has an adverse impact on the sensitivity of ultrasound diagnostic criteria that apply to those with PKD1.

Simple renal cysts were rare in genetically unaffected participants who were younger than 30 yr, which underpins the high specificity of renal ultrasonography among young adults. This finding is consistent with previous data for at-risk PKD1 individuals[15] or for individuals who underwent ultrasonography for nonrenal indications.[19,20] Nonetheless, 2.1% (three of 144) and 0.7% (one of 144) of the genetically unaffected cohort younger than 30 yr had one and two renal cysts, respectively. These data highlight the need for using more stringent criteria such as three or more (unilateral or bilateral) renal cysts to minimize false-positive diagnoses in this age group. Similarly, 1.7% (four of 232) of the genetically unaffected individuals aged 30 to 59 yr had at least two (unilateral or bilateral) renal cysts; however, these latter individuals will not adversely affect the performance of the test criterion based on two or more cysts in each kidney.

Recent studies suggested that biallelic *PKD1* or *PKD2* inactivation from germline and somatic mutations within individual epithelial cells is a major mechanism for focal cyst formation in ADPKD.[21–25] Accordingly, the frequency of somatic PKD mutations is predicted to influence the total cyst number in ADPKD.[25] Because of its large size and complexity, *PKD1* is thought to be four to five times more prone to mutations than *PKD2*,[26] which may account for the difference in renal disease severity between the two gene types.[16,18] Nevertheless, in our PKD1 and PKD2 cohorts, we observed several affected individuals with very mild renal cystic disease, suggesting a modifier gene effect.[27] For example, three affected individuals who had PKD1 and six affected individuals who had PKD2 and were aged ≥30 yr had fewer than four (unilateral or bilateral) renal cysts (Table 3). These mildly affected individuals will continue to be a source of diagnostic uncertainty by renal ultrasonography.

Although gene-based diagnosis of ADPKD is now feasible, it is expensive and detects definitive mutations in approximately 41 to 63% of cases and both definitive and likely disease-associated mutations in 78 to 89% of cases.[28,29] Magnetic resonance imaging (MRI), with its enhanced sensitivity for detecting small renal cysts, is also a promising modality[30]; however, MRI may also detect a greater number of

simple cysts as well as small cysts arising from ADPKD. Until the diagnostic utility of MRI in ADPKD is formally evaluated, the high diagnostic accuracy of ultrasonography, as well as its safety, accessibility, and comparatively low cost, will ensure its ongoing widespread use in ADPKD. On the basis of the results of our simulation studies, we recommend the following approach for evaluating at-risk individuals from ADPKD families of unknown genotype (Table 4). The presence of at least three (unilateral or bilateral) renal cysts and two cysts in each kidney can be regarded as sufficient for diagnosis of at-risk individuals aged 15 to 39 and 40 to 59 yr, respectively. For at-risk individuals aged ≥60 yr, in whom renal cysts are numerous in both PKD1 and PKD2 and among whom simple cysts are frequently found, the stringent criterion of four or more cysts in each kidney is required for diagnosis.

For evaluating potential kidney donors, among whom the clinical agenda is disease exclusion rather than diagnosis, a modification to the current criterion for PKD1 is required. Specifically, consistent with our observation that all affected individuals who had PKD1 and PKD2 and were aged ≥40 yr had at least two renal cysts, an ultrasound scan finding of normal kidneys or one renal cyst has a negative predictive value of 100%, which provides strong reassurance for those wishing to rule out the disease. For at-risk individuals aged 30 to 39 yr, the absence of any renal cyst provides almost certainty for disease exclusion (with a false-negative rate of 0.7%). In latter scenario, a negative MRI or computed tomography scan could provide further assurance that the at-risk individuals are not affected, bearing in mind the associated risk of detecting additional simple cysts, a scenario that is yet to be addressed by any systematic study.

The utility of ultrasonography for disease exclusion may be limited in at-risk individuals who are younger than 30 yr and have a negative or indeterminate scan. In these individuals, repeat ultrasound scanning every 6 to 12 mo may be helpful to detect new cysts; however, if these individuals are being evaluated as living-related kidney donors, then molecular genetic testing is justifiable. This can be done by linkage analysis using polymorphic *PKD1* and *PKD2* markers if multiple affected and unaffected family members are available. Alternatively, mutation screening of *PKD1* and *PKD2* can be performed.[28,29] Because the sensitivity for *PKD2* mutation detection is at least 80% and most affected individuals with equivocal ultrasound results will have the milder PKD2 disease, gene-based testing is expected to provide reasonable diagnostic utility in this special target group.

CONCISE METHODS

Study Participants

We recruited study participants from eight international PKD research centers in Australia, Europe, and North America. They comprised 577 individuals from 58 PKD1 families and 371 individuals from 39 PKD2 families, all born with 50% risk for ADPKD. We excluded the ascertainment proband from each family from the evaluation of ultrasound diagnostic performance. Most families had already been well characterized clinically, because they had been previous participants in studies to define the clinical phenotypes, natural history, and genotype–phenotype correlations of the two subtypes of ADPKD.[2,3,16,17] We obtained informed consent from all study participants, and the research protocols used in the study were approved by the institutional review board of each participating center.

Study Protocols

Renal ultrasound scan with a 3- or 5-MHz mechanical sector probe was performed for all study participants. Scan images were read at each center by a radiologist who was experienced in ultrasonography and had no knowledge of the underlying genotype. A cyst was defined as a hypoechogenic structure with a distinct posterior wall and posterior enhancement, and a cyst with septation would be counted only as one cyst. In general, most cysts detected by ultrasonography were >1 cm in diameter. To evaluate the agreement of renal cyst counts between different centers, six radiologists from six of the eight study centers were available to rate a standardized set of 40 renal ultrasound images (containing from zero to four or more cysts) selected from the study patients in a “single-blind” study (see Supplemental Table 1). We used intraclass correlation coefficient (ICC) to assess the agreement between the individual raters. We performed molecular studies to define the genotype of each participant. We tested all families for *PKD1* and *PKD2* linkage using polymorphic markers flanking these loci.[16,17] We calculated logarithm of odds scores by pairwise analysis using the MLINK program. We combined data available from the linked markers for *PKD1* and *PKD2* used in each family using a Bayesian weighting formula[15] to estimate the likelihood of PKD1 and PKD2 disease, before

calculating the posttest probability of each study participant in inheriting a disease-causing mutation. In addition, we screened the genomic DNA of an affected subject from each *PKD2*-linked family for mutations in all exons and splice junctions of *PKD2* by single-stranded conformational polymorphism, heteroduplex analysis, or direct sequencing.[17] We found *PKD2* protein-truncating mutations in 80% (31 of 39) of the *PKD2*-linked families (data not shown). In these families, we also examined the segregation of *PKD2* mutations with ADPKD in all study participants.[17] Only participants who had a posttest probability of ADPKD <1 or ≥99% or were shown to have a *PKD2* mutation were included in the assessment of ultrasound diagnostic performance. Those who had a posttest probability of >99% or were shown to have a *PKD2* mutation were designated affected regardless of the renal ultrasound findings. We confirmed the genotype findings of all discordant cases by re-typing multiple polymorphic microsatellite markers at *PKD1* and *PKD2*[11] and by segregation analysis of the disease haplotype and/or pathogenic mutation.

Statistical Analysis

Continuous variables are expressed as means and 95% confidence intervals, and discrete variables are expressed as percentages. We used ICC to assess the reliability of individual rating.[31] ICC is the ratio of within-participant variability of ratings to the variability across all ratings and participants, whereby raters are a random sample of all possible raters and each rater rates each participant. The resulting ICC can be generalized to other samples of raters. To allow for direct comparison of our data with the commonly used PKD1 diagnostic criteria, we divided study participants into three age groups (15 to 29, 30 to 59, and ≥60 yr).[15] To derive diagnostic criteria for evaluating at-risk PKD1 subjects, we first performed bootstrap sampling to create replicate data sets that simulated the ratio of affected to unaffected individuals seen in clinic. To create each replicate, a participant was randomly drawn one at a time from the pool of individuals with PKD1. After each draw, the selected individual was replaced in the same pool and the draw was repeated until a designated sample size was reached. We assigned weights to each participant to control for increasing probability of previous diagnosis with increasing age. Because the pretest likelihood of PKD1 is the age-specific prevalence of previously undetected cases among individuals born at 50% risk, we calculated this estimate from age-specific cumulative probability of diagnosis resulting from investigation of symptomatic affected individuals with PKD1.[8] We made a further assumption that only genetically affected indiiduals who met the ultrasound diagnostic criterion being examined could carry a previous clinical diagnosis, and we adjusted weights accordingly. For each age group in the PKD1 cohort, we created 1000 replicates each with a sample size of 143 to 222, depending on the age stratum. We repeated this process for the participants with PKD2, except that we used PKD2 age-specific cumulative probability of diagnosis to calculate the pretest likelihood of disease.[8] For each age group in the PKD2 cohort, we created 1000 replicates each with a sample size of 100 to 108, depending on the age stratum. For each bootstrap sample by genotype and age group, we constructed two-by-two tables detailing the disease status (affected or unaffected) of the study participants as defined by the molecular genotype and the specific ultrasound test criteria (based on renal cyst number, with or without bilateral involvement). From these tables, we estimated the means and 95% confidence intervals of sensitivity, specificity, positive and negative predictive values, and accuracy for different test criteria.[32] To derive diagnostic criteria for evaluating at-risk individuals from families with unknown genotype, we combined bootstrap samples from both PKD1 and PKD2 families using additional weights to reflect the case mix seen in the clinic by maintaining a constant ratio for unaffected PKD1 to unaffected PKD2 individuals of 85:15 across all age groups (also see Supplemental Information). For each age group in this combined cohort, we created 1000 replicates each with a sample size of 243 to 330, depending on the age stratum. To identify test criteria with optimal performance in study participants aged 30 to 59 yr, we repeated these analyses by each decade of age.

DISCLOSURES

None.

Supplementary Material

[Supplemental Data]

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Notes

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See related editorial, “Unified Ultrasonographic Diagnostic Criteria for Polycystic Kidney Disease,” on pages 6–8.

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See "Unified ultrasonographic diagnostic criteria for polycystic kidney disease." on page 6.

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