CLINICAL RESEARCH www.jasn.org

Imaging-Based Diagnosis of Autosomal Dominant Polycystic Kidney Disease

York Pei,* Young-Hwan Hwang,*† John Conklin,‡ Jamie L. Sundsbak,§ Christina M. Heyer,§ Winnie Chan,* Kairong Wang,* Ning He,* Anand Rattansingh,‡ Mostafa Atri,‡ Peter C. Harris,§ and Masoom A. Haider‡

*Division of Nephrology, Department of Medicine and ‡Department of Medical Imaging, University Health Network and University of Toronto, Toronto, Ontario, Canada; †Department of Medicine, Eulji General Hospital, Seoul, South Korea; and §Division of Nephrology and Hypertension, Mayo Clinic, Rochester, Minnesota

ABSTRACT

The clinical use of conventional ultrasonography (US) in autosomal dominant polycystic kidney disease (ADPKD) is currently limited by reduced diagnostic sensitivity, especially in at-risk subjects younger than 30 years of age. In this single-center prospective study, we compared the diagnostic performance of MRI with that of high-resolution (HR) US in 126 subjects ages 16–40 years born with a 50% risk of ADPKD who underwent both these renal imaging studies and comprehensive *PKD1* and *PKD2* mutation screening. Concurrently, 45 healthy control subjects without a family history of ADPKD completed the same imaging protocol. We analyzed 110 at-risk subjects whose disease status was unequivocally defined by molecular testing and 45 unaffected healthy control subjects. Using a total of >10 cysts as a test criterion in subjects younger than 30 years of age, we found that MRI provided both a sensitivity and specificity of 100%. Comparison of our results from HR US with those from a previous study of conventional US using the test criterion of a total of three or more cysts found a higher diagnostic sensitivity (approximately 97% versus approximately 82%) with a slightly decreased specificity (approximately 98% versus 100%) in this study. Similar results were obtained in test subjects between the ages of 30 and 40 years old. These results suggest that MRI is highly sensitive and specific for diagnosis of ADPKD. HR US has the potential to rival the diagnostic performance of MRI but is both center- and operator-dependent.

J Am Soc Nephrol 26: 746–753, 2015. doi: 10.1681/ASN.2014030297

Autosomal dominant polycystic kidney disease (ADPKD) is the most common hereditary kidney disease worldwide and accounts for approximately 5%–7% of ESRD in North America.[1,2] It is characterized by development of renal cysts with increasing age, leading to distortion of normal kidney architecture and ultimately, ESRD in a majority of patients. Mutations of two genes, *PKD1* and *PKD2*, have been implicated for the disease in 85% and 15%, respectively, of linkage-characterized European families.[3] However, a higher prevalence of PKD2 of 26% has been reported by a more recent population-based study.[4] Disease progression of ADPKD is highly variable and in part, because of a strong gene locus effect.[5–8] Adjusted for age and sex, patients with PKD1 have larger kidneys and earlier onset of ESRD than patients with PKD2 (mean age at ESRD=53.4 versus 72.7 years, respectively).[5,8] More recent studies have also shown a significant allelic effect in PKD1, with mild disease associated with nontruncating mutations and severe disease associated with truncating mutations.[9–11] Marked within-family renal disease variability has been well documented in ADPKD and suggests a modifier effect from genetic and environmental factors.[12–14]

Received March 24, 2014. Accepted June 22, 2014.

Y.-H.H. and J.C. contributed equally to this work.

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

Correspondence: Dr. York Pei, Division of Nephrology, Toronto General Hospital, 8N838, 585 University Avenue, Toronto, ON M5G 2N2, Canada. Email: york.pei@uhn.ca

Presymptomatic diagnosis of subjects born with a 50% risk of ADPKD is most commonly performed by ultrasonography (US), which is inexpensive and widely available. Because simple cysts occur with increasing age in the general population,[15–17] age-dependent US diagnostic criteria have been established for PKD1[18] and subsequently refined and extended for evaluation of at-risk subjects of unknown gene type (also known as the unified diagnostic criteria).[19] In general, the performance of these diagnostic criteria is excellent for at-risk subjects older than 40 years of age but suboptimal for those younger than 30 years old.[19] Specifically, the presence of three or more renal cysts in the latter cohort has a positive predictive value (PPV) of 100% but a sensitivity (SEN) of 81.7%. Conversely, the absence of any renal cyst has a negative predictive value (NPV) of 98% but a specificity (SPEC) of 84.5%. Because younger subjects at risk of ADPKD are increasingly being evaluated as living kidney donors to their affected relatives, disease exclusion with high certainty is of utmost importance but not possible by conventional US.[19] Although molecular diagnostics may be used for disease exclusion, it is expensive and time-consuming, and it may not provide a definitive diagnosis in up to one third of cases.[20] With increased resolution for detecting very small cysts by magnetic resonance imaging (MRI) and contrast-enhanced computed tomography (CT), many transplant centers have routinely included one of these imaging modalities in their work-up of subjects at risk of ADPKD; however, validated diagnostic criteria for these modalities are currently lacking.[20] Here, we report the findings of the Toronto Radiological Imaging Study of Polycystic Kidney Disease (TRISP), which compared the diagnostic performance of high-resolution (HR) US with MRI in subjects at risk of ADPKD younger than 40 years of age.

RESULTS

Study Subjects

From June of 2010 to May of 2013, we recruited in TRISP 126 subjects ages 16–40 years born with a 50% risk of ADPKD from 86 families (Figure 1). We excluded 16 of them from 10 families, because no pathogenic mutations were identified in their affected relatives. Concurrently, 45 healthy subjects in the same age range completed the imaging studies only. All of them had no chronic medical illness, had a negative personal and family history of renal disease, including ADPKD, and were not on any medications at the time of the testing. Five of our control subjects each had a total of one to three renal cysts on HR US or a total of one to two renal cysts on MRI. Review of their imaging studies showed normal kidney morphology and cortical echogenicity by US and normal kidney volumes by MRI. All of them also had normal BP reading, serum creatinine, and urinalysis (Supplemental Table 1). In total, 110 at-risk subjects from 76 families whose disease status was genetically defined and 45 control subjects who were considered as unaffected were analyzed. The median (interquartile

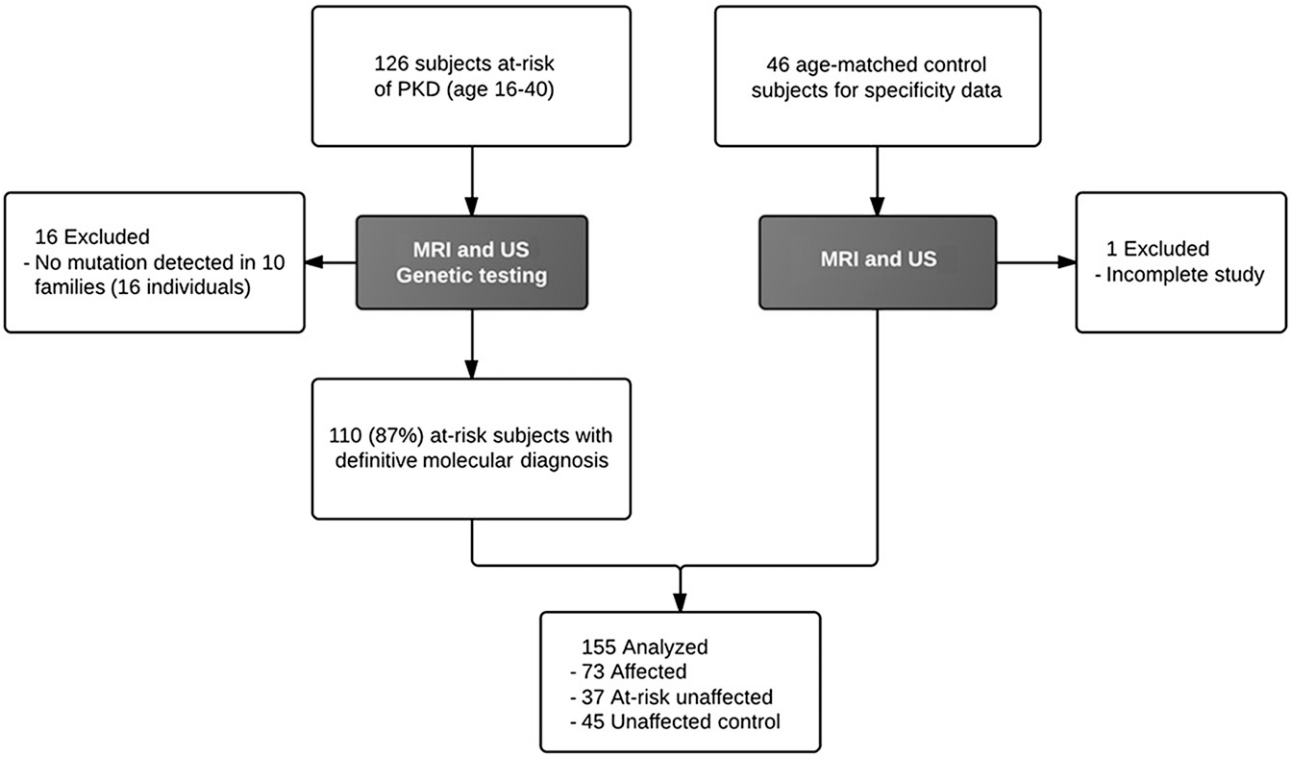

Figure 1. Study subject recruitment and exclusion. Flow diagram detailing the number of at-risk and age-matched control subjects recruited, excluded, and analyzed in the study.

range) age of our study cohort was 27.2 (22.0–33.8) years, 45.2% of subjects were men, 78% of subjects were European, and 47.1% of subjects were genetically affected. Table 1 shows the clinical characteristics of our study subjects. Overall, 54.8% (*i.e.*, 40 of 73) of our affected subjects have *PKD2* and nontruncating *PKD1* mutations, which are associated with smaller total kidney volume (TKV) and mild disease compared with those with truncating *PKD1* mutations (*i.e.*, median TKVs of 424 and 499 versus 806 ml, respectively; P=0.002 by Kruskal–Wallis test).

Comparison of Renal Cyst Counts by US and MRI

We found that only one unaffected subject (*i.e.*, 1 of 82) had more than three cysts, and all except for one affected subjects (*i.e.*, 72 of 73) had >20 cysts in both kidneys by MRI (Figure 2, left panel). Thus, the presence of a total of >10 renal cysts by MRI provides a clear separation of the unaffected from affected subjects. By comparison, complete separation of the unaffected from affected subjects by US was not possible. Specifically, using the widely used unified diagnostic criterion of a total of three or more renal cysts[19] in our study cohort would yield one false negative and three false positive cases (Figure 2, right panel, Table 2). TOR190.1 is a 25-year-old subject with a nontruncating *PKD1* mutation and >20 renal cysts by MRI but none by US; he had a suboptimal US and a high body mass index of 35.6 kg/m^2. TOR31.2 is a 30-year-old at-risk subject from a PKD2 family. He had 6 renal cysts on US and 10 renal cysts on MRI but tested negative for his familial *PKD2* mutation. To exclude sample mix up or a *de novo* mutation, we rescreened him with a new DNA sample for both *PKD1* and *PKD2* but failed to identify any pathogenic mutation. We also repeated his MRI 18 months after his initial scan but did not detect any additional renal cysts. We, therefore, concluded that he had multiple simple cysts and was unaffected. Together with TOR31.2, TOR208.5 and TOR404.1, each with three renal cysts by US, were considered as false positive cases. Excluding these discordant cases, there was a high concordance of renal cyst counts between the two imaging modalities in our healthy controls and at-risk subjects (Figure 3).

Diagnostic Performance by US and MRI

We compared the US diagnostic performance of our cohort with a previous study that we had conducted to derive the unified criteria (regardless of underlying gene type).[19] Overall, we found a significant increase in SEN and NPV with a small decrease in SPEC and PPV in this study across all of the criteria tested and for both age strata (Table 3). For example, using the unified criterion of a total of three or more renal cysts in at-risk subjects of 16–29 years of age would yield an increased SEN (*i.e.*, 97.3% from 81.7%) and a decreased PPV (*i.e.*, 97.3% from 100%). In this study, the presence of two or more cysts in each kidney (with PPV of 100%) can be considered as sufficient for diagnosis for at-risk subjects ages 16–40 years old. Conversely, the absence of any renal cyst (with NPV of 100%) can be considered sufficient for disease exclusion in at-risk subjects ages 30–40 years but not younger.

We also evaluated the diagnostic performance of MRI in our study cohort (Table 4). Interobserver agreement for MRI renal cyst counts was excellent with κ-values of 0.96–0.97 for the three reader pairs (Supplemental Material). Because simple renal cysts were rare in our at-risk unaffected subjects and healthy controls, the presence of a total of >10 renal cysts can be considered as sufficient (SEN and PPV of 100%) for diagnosis of at-risk subjects between 16 and 40 years of age. However, genetically affected subjects from the same age group typically will have >20 renal cysts on MRI. Thus, a total of <10 renal cysts can be regarded as sufficient for exclusion of ADPKD (NPV and SPEC of 100%).

Table 1. Clinical characteristics of study subjects

Clinical Characteristics	At-Risk Subjects from Families with			Control
	Truncating *PKD1* Mutations	Nontruncating *PKD1* Mutations	*PKD2* Mutations	
Age (yr), *n* (%)				
16–29	35 (64)	14 (56)	14 (48)	32 (71)
30–40	20 (36)	12 (44)	15 (52)	13 (29)
Sex, *n* (%)				
Men	24 (44)	14 (54)	9 (31)	23 (51)
Women	31 (56)	12 (46)	20 (69)	22 (49)
Disease status[a], *n* (%)				
Affected	33 (60)	22 (85)	18 (62)	
Unaffected	22 (40)	4 (15)	11 (38)	45
Serum Cr[b] (mg/dl)				
Affected	0.88 (0.81 to 0.96)	0.90 (0.80 to 1.00)	0.74 (0.65 to 0.83)	
TKV[c] (ml)				
Affected	806 (524–1069)	499 (323–842)	424 (286–659)	
Unaffected	304 (275–344)	279 (239–372)	310 (281–339)	307 (272–357)

[a]Defined by molecular genetic testing.
[b]Serum creatinine (Cr) expressed as mean (95% confidence interval).
[c]TKV measured by MRI expressed as median and interquartile range.

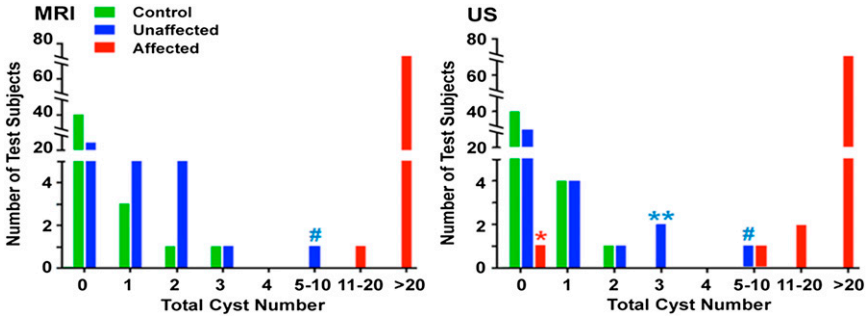

Figure 2. Distribution of total cyst counts by disease status and imaging modality. *TOR190.1 is a genetically affected subject with a body mass index of 35.6 kg/m^2 who had >20 renal cysts by MRI but no cyst detectable by a suboptimal US. **TOR404.1 and TOR208.5 were both unaffected but had three renal cysts by US. #TOR31.2 is a subject with 6 renal cysts on US and 10 renal cysts on MRI; he did not carry the familial *PKD2* mutation and was considered as unaffected.

DISCUSSION

Despite increased SEN for detecting very small cysts by MRI, we only found 1 of 82 unaffected subjects ages 16–40 years who had more than three renal cysts. By contrast, all but one (*i.e.*, 72 of 73) of our genetically affected subjects had a total of >20 renal cysts. These two features together enable MRI to provide highly discriminant diagnostics for ADPKD. Thus, the presence of a total of >10 renal cysts (with both PPV and SEN of 100%) can be considered as sufficient for diagnosis in a subject at risk of ADPKD. Conversely, a total of <10 renal cysts (with both NPV and SPEC of 100%) can be considered as sufficient for disease exclusion. For evaluation of living kidney donors, among whom the clinical agenda is disease exclusion with high certainty, we recommend using a total of less than five renal cysts (with NPV of 100% and SPEC of 98.3%) as a more stringent criterion. In at-risk subjects younger than 40 years of age with equivocal MRI findings (*e.g.*, total renal cyst count of 5–19), molecular testing may be useful to clarify the diagnosis. Currently, most transplant centers use MRI or contrast-enhanced CT for evaluation of their living kidney donors. Pending future studies showing diagnostic equivalence between these modalities, we do not recommend extrapolating the above criteria to contrast-enhanced CT.

Overall, the diagnostic performance of HR US in this study is better than expected compared with previous results with conventional US.[19] We found a significant increase in SEN with a small decrease in SPEC across all of the criteria tested, likely because of increased imaging resolution in detecting cysts as small as 2–3 mm with modern scanners as well as experienced operators attuned to detection of small cysts. By contrast, most of the cysts detected by US in our previous study were approximately 1 cm or more in size.[19] Using the unified criterion of a total of three or more renal cysts in at-risk subjects under 30 years of age, we found a significant increase in SEN (*i.e.*, 97.3% from 81.7%) with a small decrease in PPV (*i.e.*, 100% to 97.3%). To minimize false positive cases with HR US, a more stringent criterion, such as two or more cysts in each kidney (with PPV of 100%), should be used for diagnosis. Conversely, the absence of any renal cyst by HR US may be considered sufficient for disease exclusion in at-risk subjects ages 30–40 years old but not younger. An important caveat is that a suboptimal US scan (*e.g.*, because of increased body habitus) should be interpreted as indeterminate, and this point was well illustrated by TOR190.1 (Table 2). Another limitation of US is that its diagnostic performance is both operator- and center-dependent, reflecting differences, such as imaging resolution of the scanners and experience of the technicians/radiologists. Thus, current availability of US scanners with different imaging resolution has important implications for diagnostic testing. Specifically, the diagnostic criteria that we derived here should be applicable to experienced centers using HR US; otherwise, the unified criteria[19] should be used for centers that use conventional US.

The diagnostic criteria derived here for MRI and US are applicable only for test subjects with a definitive family history of ADPKD who are born with a 50% risk of disease. By contrast, the pretest probability of subjects without a positive family history is that of the population risk (*i.e.*, 1 in 500–1000); thus, the above criteria may not be valid. Moreover, the possibility of other genetic and nongenetic causes of PKD needs to be

Table 2. Clinical findings of discordant patients

Subject	Age (yr)	Disease Status	Mutation	MRI Cyst Count		US Cyst Count		Maximal Cyst Size (mm)
				Right Kidney	Left Kidney	Right Kidney	Left Kidney	
TOR190.1[a]	25	Affected	PKD1: p.A2752D	15	18	0	0	6 on MRI
TOR31.2[b]	30	Unaffected	PKD2: IVS5+1G>A	6	4	6	0	10 on MRI
TOR404.1[c]	40	Unaffected	PKD1: p.P3551fs111x	1	1	2	1	6 on MRI
TOR208.5[c]	36	Unaffected	PKD2: p.V569fs3x	0	0	3	0	5 on US

[a]False negative case by US with a high body mass index of 35.6 kg/m^2.
[b]False positive by US[d] and equivocal by MRI.
[c]False positive by US.[d]
[d]According to the unified US criteria of a total of three of more renal cysts.

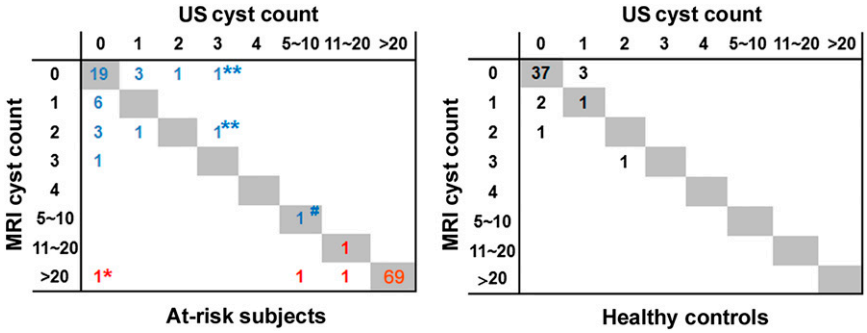

Figure 3. Comparison of total cyst counts by US and MRI. There was a high degree of concordance of renal cyst counts by US and MRI in both at-risk subjects and healthy controls. *TOR190.1 is a genetically affected subject with >20 renal cysts by MRI but no cyst detectable by a suboptimal US. **TOR404.1 and TOR208.5 both were genetically unaffected but had three renal cysts by US. #TOR31.2 is genetically unaffected with 6 cysts on US and 10 cysts on MRI.

considered in the latter setting.[20] In subjects without a positive family history, it is useful to screen their parents and older first-degree relatives with US, because mild disease associated with a *PKD2* or nontruncating *PKD1* may not be apparent, especially in small families.[20] If one or both parents are deceased, reviewing their medical record for prior renal imaging results may also be helpful. The documentation of at least one affected first-degree relative who has bilaterally enlarged kidneys with numerous cysts is sufficient evidence to support the use of the above diagnostic criteria. However, multiple renal cysts without kidney enlargement in an elderly first-degree relative may be caused by simple cysts and should not be considered as sufficient evidence for establishing a positive family history. With a significant level of *de novo* mutations in ADPKD, in the cases when a definitive family of ADPKD cannot be ascertained, molecular genetic testing may be indicated.

Renal disease severity is highly variable in ADPKD and in part, caused by a strong gene locus effect.[4–8] Specifically, the mean age of ESRD in patients with PKD2 is almost 20 years older than those with PKD1. Adjusted for age, patients with PKD2 have fewer renal cysts than those with PKD1.[8] This genic effect has been shown to negatively affect the US diagnostic performance, resulting in decreased SEN and NPV in subjects at risk of PKD2 compared with those at risk of PKD1.[19] More recent studies have shown a significant allelic effect in PKD1 with markedly attenuated renal disease severity in patients affected with nontruncating mutations compared with truncating mutations.[9–11] Indeed, in a large family with bilineal ADPKD, the renal disease was uniformly mild and indistinguishable between subjects affected with a *PKD2* or a nontruncating *PKD1* mutation.[10] Approximately 30% of *PKD1* mutations are nontruncating,[21] but it has not been well defined how many of these mutations are hypomorphic alleles associated with mild disease,[10,11] which can pose a challenge for imaging-based diagnosis similar to PKD2. In this regard, over one half (*i.e.*, 40 of 73; 54.5%) of our affected subjects have either *PKD2* or nontruncating *PKD1* mutations. Thus, the findings of our study should be generalizable to these more challenging cases.

In conclusion, conventional US will continue to be the first test used for presymptomatic screening of subjects at risk for ADPKD at most centers. However, for those subjects with equivocal results or who require disease exclusion with high certainty

Table 3. Diagnostic performance of US

Diagnostic Criterion/Study Cohort	Affected	Unaffected	SEN	SPEC	PPV	NPV
16–29 yr	37	58				
≥1 renal cyst[a]						
Present	36	9	0.973	0.845	0.800	0.980
ref. 19			0.893	0.971	0.966	0.908
≥2 renal cysts[a]						
Present	36	3	0.973	0.948	0.923	0.982
ref. 19			0.848	0.994	0.992	0.877
≥3 renal cysts[a,b]						
Present	36	1	0.973	0.983	0.973	0.983
ref. 19			0.817	1.000	1.000	0.855
≥4 renal cysts[a]						
Present	36	1	0.973	0.983	0.973	0.983
≥2 cysts in each kidney						
Present	36	0	0.973	1.000	1.000	0.983
30–40 yr	36	24				
≥1 renal cyst[a]						
Present	36	4	1.000	0.833	0.900	1.000
ref. 19			0.980	0.948	0.940	0.983
≥2 renal cysts[a]						
Present	36	2	1.000	0.917	0.947	1.000
ref. 19			0.964	0.983	0.979	0.970
≥3 renal cysts[a,b]						
Present	36	2	1.000	0.917	0.947	1.000
ref. 19			0.955	1.000	1.000	0.964
≥4 renal cysts[a]						
Present	36	0	1.000	1.000	1.000	1.000
≥2 cysts in each kidney						
Present	36	0	1.000	1.000	1.000	1.000
ref. 19			0.828	1.000	1.000	0.875

[a]Total number of cysts in both kidneys.
[b]Commonly used US diagnostic criterion for at-risk subjects of unknown gene type.

Table 4. Diagnostic performance of MRI

Diagnostic Criterion	Affected	Unaffected	SEN	SPEC	PPV	NPV
16–29 yr	37	58				
≥1 renal cyst[a]	37	11	1.000	0.810	0.771	1.000
≥2 renal cysts[a]	37	4	1.000	0.931	0.902	1.000
≥3 renal cysts[a]	37	2	1.000	0.966	0.949	1.000
≥5 renal cysts[a]	37	1	1.000	0.983	0.974	1.000
>10 renal cysts[a]	37	0	1.000	1.000	1.000	1.000
≥2 cysts in each kidney	37	1	1.000	0.983	0.974	1.000
30–40 yr	36	24				
≥1 renal cyst[a]	36	7	1.000	0.708	0.837	1.000
≥2 renal cysts[a]	36	5	1.000	0.792	0.878	1.000
≥3 renal cysts[a]	36	1	1.000	0.958	0.973	1.000
≥5 renal cysts[a]	36	0	1.000	1.000	1.000	1.000
>10 renal cysts[a]	36	0	1.000	1.000	1.000	1.000
≥2 cysts in each kidney	36	0	1.000	1.000	1.000	1.000

[a]Total number of cysts in both kidneys.

(*i.e.*, at-risk living donors), MRI will be useful for both obtaining a positive diagnosis and disease exclusion. Specifically, among subjects who are at risk of ADPKD ages 16–40 years old, the presence of a total of >10 renal cysts can be considered as sufficient for diagnosis. Conversely, for evaluation of at-risk subjects as living kidney donors, the finding of a total of less than five renal cysts can be considered sufficient for disease exclusion. HR US using modern scanners has the potential to rival the diagnostic performance of MRI but is both center- and operator-dependent. For optimal use of US-based diagnostic in ADPKD, it is important to standardize the reporting by different centers to provide uniform information on the overall quality and imaging resolution of the scan so that clinicians can apply the appropriate diagnostic criteria accordingly.

CONCISE METHODS

Research Design and Study Conduct

The research protocol of this single-center prospective study was approved by the Research Ethics Board at University Health Network. Consecutive subjects ages 16–40 years old born with a 50% risk of ADPKD having no contraindication to MRI were recruited through the PKD Clinic at the Toronto General Hospital. All study subjects provided written informed consent and underwent an HR clinical US and a research MRI as well as molecular genetic testing to define their disease status. Concurrently, healthy control subjects in the same age range without a family history of ADPKD were recruited to undergo the same imaging protocol to augment SPEC data. All readers of the US (A.R. and M.A.) and MRI (J.C. and M.A.H.) studies and the research teams (K.W. and N.H. from Toronto and J.L.S. and C.M.H. from Mayo Clinic) performing the mutation screen were blinded to the identity and disease status of the study subjects.

Imaging Protocols

All US scans were performed by A.R. under the supervision of M.A. using a Toshiba Aplio (Tustin, CA; with L6- and C3.5-MHz probes) or Philips IU22 (Bothwell, WA; with C1–5- and L4–8-MHz probes) scanner (both with similar imaging capability). A cyst was diagnosed as an anechoic lesion with smooth back wall and through transmission of at least 2–3 mm in diameter. MRI was performed using a standardized respiratory-triggered, T2-weighted, axial, fat-suppressed fast-spin echo sequence without gadolinium on a 1.5-T scanner. All MRI scans were read by J.C., who was trained with a mock sample set under the supervision of M.A.H. before undertaking the actual scoring of the study subjects. A cyst was diagnosed as a sharply demarcated lesion from the surrounding parenchyma with a smooth margin of at least two voxels (or 2.6 mm in width on a single-image plane) and homogeneous internal signal intensity similar to that of spinal fluid. Examples of small subcentimeter cysts detected by HR US and MRI are shown in Figure 4. For each kidney, the exact cyst number was enumerated when <10; otherwise, a count of ≥10 cysts was reported. For MRI cyst counts, an interobserver variability study was conducted with three

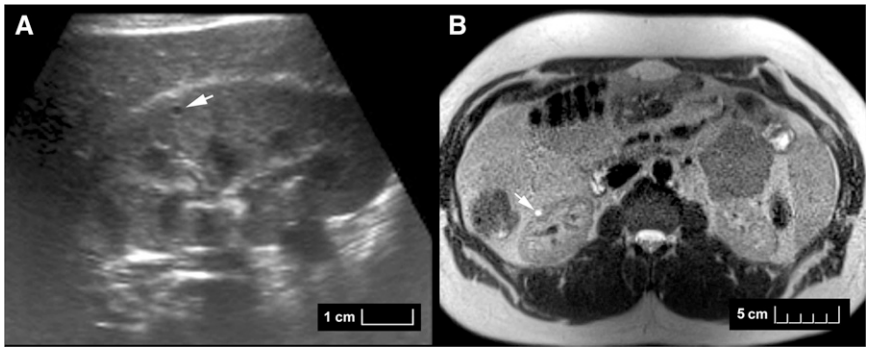

Figure 4. Examples of small renal cysts identified by HR US and MRI. (A and B) Detection of a small (approximately 2.5 mm) cortical renal cyst by HR US and MRI in two different test subjects (denoted by arrows in A and B).

readers: one radiologist with 15 years of experience reading abdominal MRI and two radiology trainees, including J.C., who also performed all of the renal cyst counts for this study. TKV was determined from 3-mm axial T2 magnetic resonance images with renal volumetrics performed using manual segmentation[22] (ImageSetViewer Software, version 1.5.6; University Health Network, Toronto, ON, Canada).

Molecular Genetic Testing

Molecular testing was performed to define the disease status of all at-risk study subjects. If the pathogenic mutation was not already known, we first screened an affected family member of the study subject by bidirectional sequencing of all of the coding regions and splice junctions of both *PKD1* and *PKD2*.[21,23] *PKD1* is a large complex gene, with its first 33 exons duplicated in six pseudogenes (*i.e.*, *PKD1P1–PKD1P6*) with high sequence identity.[1,2] To overcome this complication, we used a PCR protocol to generate locus-specific long-range templates and smaller nested fragments for our screen of this *PKD1* region.[22] All missense, atypical splice site, and small in-frame (<5 amino acids) insertion/deletion variants identified were evaluated for their potential pathogenicity using prediction algorithms (*i.e.*, PolyPhen-2,[24] SIFT,[25] Align GVGD,[22] and PROVEAN[26]) by review of the ADPKD mutation database (http://pkdb.mayo.edu) and segregation analysis with additional affected family members whenever possible. All mutation-negative patients were rescreened by multiplex ligation-dependent probe amplification to detect large gene rearrangements.[23] Using the pathogenic mutation identified in an affected family member, we then tested each study subject to determine his/her disease status (*i.e.*, affected or unaffected). Y.P. and P.C.H. reviewed and approved the results of genetic testing.

Statistical Analyses

Continuous variables are expressed as means and 95% confidence intervals or medians and interquartile ranges (if data are not normally distributed), and discrete variables are expressed as percentages. To allow for direct comparison of our data with the unified US diagnostic criteria,[19] we divided the study subjects into two age groups (16–29 and 30–40 years). For each age group, we constructed 2×2 tables detailing the disease status (affected or unaffected) of the study subjects and specific imaging-based test criteria (on the basis of renal cyst number with or without bilateral involvement). From these tables, we derived SEN, SPEC, PPV, and NPV for the different test criteria.[19]

ACKNOWLEDGMENTS

We thank all of the study subjects and their family members for participation and Drs. Sebastian T. Schindera and Diego Mercer for their help in evaluating interobserver agreement in magnetic resonance imaging renal cyst counts.

This work was supported by grants from the Physicians Services Incorporated Foundation (to Y.P. and M.A.H.) and National Institutes of Health for the Genetics Core of the Mayo Polycystic Kidney Disease Center Grant DK090728 (to P.C.H.).

Part of this study was presented at American Society of Nephrology Kidney Week (November 2–4, 2012) in San Diego, CA.

DISCLOSURES

Y.P. has served as a consultant to Otsuka Pharmaceutical.

REFERENCES

1. Harris PC, Torres VE: Polycystic kidney disease. *Annu Rev Med* 60: 321–337, 2009
2. Igarashi P, Somlo S: Genetics and pathogenesis of polycystic kidney disease. *J Am Soc Nephrol* 13: 2384–2398, 2002
3. Peters DJ, Sandkuijl LA: Genetic heterogeneity of polycystic kidney disease in Europe. *Contrib Nephrol* 97: 128–139, 1992
4. Barua M, Cil O, Paterson AD, Wang K, He N, Dicks E, Parfrey P, Pei Y: Family history of renal disease severity predicts the mutated gene in ADPKD. *J Am Soc Nephrol* 20: 1833–1838, 2009
5. Hateboer N, v Dijk MA, Bogdanova N, Coto E, Saggar-Malik AK, San Millan JL, Torra R, Breuning M, Ravine D: Comparison of phenotypes of polycystic kidney disease types 1 and 2. European PKD1-PKD2 Study Group. *Lancet* 353: 103–107, 1999
6. Dicks E, Ravani P, Langman D, Davidson WS, Pei Y, Parfrey PS: Incident renal events and risk factors in autosomal dominant polycystic kidney disease: A population and family-based cohort followed for 22 years. *Clin J Am Soc Nephrol* 1: 710–717, 2006
7. Magistroni R, He N, Wang K, Andrew R, Johnson A, Gabow P, Dicks E, Parfrey P, Torra R, San-Millan JL, Coto E, Van Dijk M, Breuning M, Peters D, Bogdanova N, Ligabue G, Albertazzi A, Hateboer N, Demetriou K, Pierides A, Deltas C, St. George-Hyslop P, Ravine D, Pei Y: Genotype-renal function correlation in type 2 autosomal dominant polycystic kidney disease. *J Am Soc Nephrol* 14: 1164–1174, 2003
8. Harris PC, Bae KT, Rossetti S, Torres VE, Grantham JJ, Chapman AB, Guay-Woodford LM, King BF, Wetzel LH, Baumgarten DA, Kenney PJ, Consugar M, Klahr S, Bennett WM, Meyers CM, Zhang QJ, Thompson PA, Zhu F, Miller JP; CRISP Consortium: Cyst number but not the rate of cystic growth is associated with the mutated gene in autosomal dominant polycystic kidney disease. *J Am Soc Nephrol* 17: 3013–3019, 2006
9. Rossetti S, Kubly VJ, Consugar MB, Hopp K, Roy S, Horsley SW, Chauveau D, Rees L, Barratt TM, van't Hoff WG, Niaudet P, Torres VE, Harris PC: Incompletely penetrant PKD1 alleles suggest a role for gene dosage in cyst initiation in polycystic kidney disease. *Kidney Int* 75: 848–855, 2009
10. Pei Y, Lan Z, Wang KR, Garcia-Gonzalez M, He N, Dicks E, Parfrey P, Germino G, Watnick T: A missense mutation in PKD1 attenuates the severity of renal disease. *Kidney Int* 81: 412–417, 2012
11. Cornec-Le Gall E, Audrézet M-P, Chen JM, Hourmant M, Morin MP, Perrichot R, Charasse C, Whebe B, Renaudineau E, Jousset P, Guillodo MP, Grall-Jezequel A, Saliou P, Férec C, Le Meur Y: Type of PKD1 mutation influences renal outcome in ADPKD. *J Am Soc Nephrol* 24: 1006–1013, 2013
12. Paterson AD, Magistroni R, He N, Wang K, Johnson A, Fain PR, Dicks E, Parfrey P, St. George-Hyslop P, Pei Y: Progressive loss of renal function is an age-dependent heritable trait in type 1 autosomal dominant polycystic kidney disease. *J Am Soc Nephrol* 16: 755–762, 2005
13. Fain PR, McFann KK, Taylor MR, Tison M, Johnson AM, Reed B, Schrier RW: Modifier genes play a significant role in the phenotypic expression of PKD1. *Kidney Int* 67: 1256–1267, 2005
14. Liu M, Shi S, Senthilnathan S, Yu J, Wu E, Bergmann C, Zerres K, Bogdanova N, Coto E, Deltas C, Pierides A, Demetriou K, Devuyst O, Gitomer B, Laakso M, Lumiaho A, Lamnissou K, Magistroni R, Parfrey P, Breuning M, Peters DJ, Torra R, Winearls CG, Torres VE, Harris PC, Paterson AD, Pei Y: Genetic variation of DKK3 may modify renal disease severity in ADPKD. *J Am Soc Nephrol* 21: 1510–1520, 2010
15. Ravine D, Gibson RN, Donlan J, Sheffield LJ: An ultrasound renal cyst prevalence survey: Specificity data for inherited renal cystic diseases. *Am J Kidney Dis* 22: 803–807, 1993

16. Nascimento AB, Mitchell DG, Zhang XM, Kamishima T, Parker L, Holland GA: Rapid MR imaging detection of renal cysts: Age-based standards. *Radiology* 221: 628–632, 2001
17. Carrim ZI, Murchison JT: The prevalence of simple renal and hepatic cysts detected by spiral computed tomography. *Clin Radiol* 58: 626–629, 2003
18. Ravine D, Gibson RN, Walker RG, Sheffield LJ, Kincaid-Smith P, Danks DM: Evaluation of ultrasonographic diagnostic criteria for autosomal dominant polycystic kidney disease 1. *Lancet* 343: 824–827, 1994
19. Pei Y, Obaji J, Dupuis A, Paterson AD, Magistroni R, Dicks E, Parfrey P, Cramer B, Coto E, Torra R, San Millan JL, Gibson R, Breuning M, Peters D, Ravine D: Unified criteria for ultrasonographic diagnosis of ADPKD. *J Am Soc Nephrol* 20: 205–212, 2009
20. Pei Y, Watnick T: Diagnosis and screening of autosomal dominant polycystic kidney disease. *Adv Chronic Kidney Dis* 17: 140–152, 2010
21. Rossetti S, Consugar MB, Chapman AB, Torres VE, Guay-Woodford LM, Grantham JJ, Bennett WM, Meyers CM, Walker DL, Bae K, Zhang QJ, Thompson PA, Miller JP, Harris PC; CRISP Consortium: Comprehensive molecular diagnostics in autosomal dominant polycystic kidney disease. *J Am Soc Nephrol* 18: 2143–2160, 2007
22. Kistler AD, Poster D, Krauer F, Weishaupt D, Raina S, Senn O, Binet I, Spanaus K, Wüthrich RP, Serra AL: Increases in kidney volume in autosomal dominant polycystic kidney disease can be detected within 6 months. *Kidney Int* 75: 235–241, 2009
23. Consugar MB, Wong WC, Lundquist PA, Rossetti S, Kubly VJ, Walker DL, Rangel LJ, Aspinwall R, Niaudet WP, Ozen S, David A, Velinov M, Bergstralh EJ, Bae KT, Chapman AB, Guay-Woodford LM, Grantham JJ, Torres VE, Sampson JR, Dawson BD, Harris PC; CRISP Consortium: Characterization of large rearrangements in autosomal dominant polycystic kidney disease and the PKD1/TSC2 contiguous gene syndrome. *Kidney Int* 74: 1468–1479, 2008
24. Adzhubei IA, Schmidt S, Peshkin L, Ramensky VE, Gerasimova A, Bork P, Kondrashov AS, Sunyaev SR: A method and server for predicting damaging missense mutations. *Nat Methods* 7: 248–249, 2010
25. Ng PC, Henikoff S: Predicting deleterious amino acid substitutions. *Genome Res* 11: 863–874, 2001
26. Choi Y, Sims GE, Murphy S, Miller JR, Chan AP: Predicting the functional effect of amino acid substitutions and indels. *PLoS ONE* 7: e46688, 2012

This article contains supplemental material online at http://jasn.asnjournals.org/lookup/suppl/doi:10.1681/ASN.2014030297/-/DCSupplemental.