Radiology

Pancreatic Cysts in Autosomal Dominant Polycystic Kidney Disease: Prevalence and Association with *PKD2* Gene Mutations[1]

Jin Ah Kim, MD
Jon D. Blumenfeld, MD
Shalini Chhabra, MD
Silvina P. Dutruel, MD
Nanda Deepa Thimmappa, MD
Warren O. Bobb, NP
Stephanie Donahue, NP
Hanna E. Rennert, PhD
Adrian Y. Tan, PhD
Ashley E. Giambrone, PhD
Martin R. Prince, MD, PhD

Purpose: To define the magnetic resonance (MR) imaging prevalence of pancreatic cysts in a cohort of patients with autosomal dominant polycystic kidney disease (ADPKD) compared with a control group without ADPKD that was matched for age, sex, and renal function.

Materials and Methods: In this HIPAA-compliant, institutional review board–approved study, all patients with ADPKD provided informed consent; for control subjects, informed consent was waived. Patients with ADPKD (n = 110) with mutations identified in *PKD1* or *PKD2* and control subjects without ADPKD or known pancreatic disease (n = 110) who were matched for age, sex, estimated glomerular filtration rate, and date of MR imaging examination were evaluated for pancreatic cysts by using axial and coronal single-shot fast spin-echo T2-weighted images obtained at 1.5 T. Total kidney volume and liver volume were measured. Univariate and multivariable logistic regression analyses were conducted to evaluate potential associations between collected variables and presence of pancreatic cysts among patients with ADPKD. The number, size, location, and imaging characteristics of the cysts were recorded.

Results: Patients with ADPKD were significantly more likely than control subjects to have at least one pancreatic cyst (40 of 110 patients [36%] vs 25 of 110 control subjects [23%]; P = .027). In a univariate analysis, pancreatic cysts were more prevalent in patients with ADPKD with mutations in *PKD2* than in *PKD1* (21 of 34 patients [62%] vs 19 of 76 patients [25%]; P = .0002). In a multivariable logistic regression model, *PKD2* mutation locus was significantly associated with the presence of pancreatic cysts (P = .0004) and with liver volume (P = .038). Patients with ADPKD and a pancreatic cyst were 5.9 times more likely to have a *PKD2* mutation than a *PKD1* mutation after adjusting for age, race, sex, estimated glomerular filtration rate, liver volume, and total kidney volume.

Conclusion: Pancreatic cysts were more prevalent in patients with ADPKD with *PKD2* mutation than in control subjects or patients with *PKD1* mutation.

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Online supplemental material is available for this article.

Autosomal dominant polycystic kidney disease (ADPKD) affects up to 12 million patients worldwide and accounts for 10% of patients with end-stage renal disease (1,2). It is caused by mutations in the *PKD1* and *PKD2* genes and is characterized by abnormal proliferation of renal tubular epithelium, leading to massive kidney enlargement and progressive chronic kidney disease (1,2). Extrarenal manifestations involve the cardiovascular (3–5), gastrointestinal (3,6–8), and genitourinary (2,3,9) systems.

Animal models of ADPKD develop pancreatic cysts in the presence of either a *PKD1* or *PKD2* mutation (10–13). Pancreatic cyst prevalence in ADPKD is 5%–9% by using abdominal ultrasonography (US) (7,8). In one US study of patients with ADPKD, investigators found an association of pancreatic cysts with germline *PKD1* mutations (7). However, US of the pancreas has substantial technical limitations, owing to its retroperitoneal location and interference by bowel gas (14). Magnetic resonance (MR) imaging has a higher sensitivity for detecting pancreatic cysts, with a prevalence of 14%–45% in the general population (14–18).

The purpose of this study was to define the MR imaging prevalence of pancreatic cysts in a cohort of patients with ADPKD compared with a control group without ADPKD that was matched for age, sex, and renal function.

Advances in Knowledge

- Pancreatic cysts are present in 36% of patients with autosomal dominant polycystic kidney disease (ADPKD, 40 of 110) compared with 23% of matched control subjects (25 of 110; *P* = .027) on two-dimensional single-shot fast spin-echo MR images.

- Patients with a *PKD2* gene mutation were 4.9 times more likely to have pancreatic cysts than the *PKD1* group and were 5.9 times more likely to have pancreatic cysts after adjusting for potential confounders.

Materials and Methods

Patients

All patients with ADPKD participated in the Rogosin Institute Polycystic Kidney Disease Repository (no. NCT00792155), an ongoing, single-center, longitudinal study initiated in December 2002, designed to evaluate genotype and phenotype data (19). The study was approved by the institutional review board committees at Weill Cornell Medical College and The Rockefeller University (New York, NY), and written informed consent was obtained. Data are collected biennially on these patients with ADPKD. The study is financially supported in part by grant no. UL1RR024143 from the National Center for Advancing Translational Sciences, National Institutes of Health. Patients with ADPKD who underwent MR imaging between December 2002 and November 2013 were eligible for inclusion in this retrospective analysis of those prospectively acquired MR images. After excluding patients without a detectable mutation in *PKD1* or *PKD2* and patients for whom no matching control subject could be found, 110 patients with ADPKD were included in the current study (Fig 1). Pathogenic variants of *PKD1* or *PKD2* were determined by means of mutation analysis, as reported previously (19). Age, sex, race, height, estimated glomerular filtration rate (eGFR) attained by using the serum creatinine level obtained within 3 months of the MR imaging examination, and *PKD* genotype data were obtained from the Rogosin Institute ADPKD repository database.

The control group comprised patients who underwent abdominal MR imaging and were randomly selected from the picture archiving and communication software database at Weill Cornell Medical College. Retrospective collection of data from control subjects was compliant with the Health Insurance Portability and Accountability Act and was institutional review board approved; informed consent was not required. Individuals with ADPKD or those who were known to have or were suspected of having pancreatic disease were excluded from the control group. By using clinical and laboratory data obtained retrospectively from their medical records, control subjects were matched with the ADPKD group for age, sex, eGFR, and date of MR imaging performed during their initial visit in the ADPKD repository study. Only the data needed for matching were obtained from the control subjects. For patients with ADPKD who underwent multiple follow-up MR imaging examinations, only the images from their first MR examination were analyzed for this study. To avoid bias related to changes in MR imaging techniques during the 11-year period of recruitment for the ADPKD repository study, control subjects and patients with ADPKD were also matched so that their MR imaging examinations were performed within 1 year of each other. eGFR was calculated

Implication for Patient Care

- In ADPKD, the presence of pancreatic cysts favors *PKD2* mutation, which tends to have a later onset of renal failure when compared with *PKD1*.

Author contributions:
Guarantor of integrity of entire study, J.K.; study concepts/study design or data acquisition or data analysis/interpretation, all authors; manuscript drafting or manuscript revision for important intellectual content, all authors; approval of final version of submitted manuscript, all authors; agrees to ensure any questions related to the work are appropriately resolved, all authors; literature research, J.K., J.D.B., S.C., S.P.D., N.D.T.; clinical studies, J.D.B., S.C., S.P.D., N.D.T., W.O.B., S.D., H.E.R., M.R.P.; statistical analysis, J.K., S.C., N.D.T., A.Y.T., A.E.G.; and manuscript editing, J.K., J.D.B., S.C., S.P.D., N.D.T., A.E.G., M.R.P.

Conflicts of interest are listed at the end of this article.

Figure 1

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250 PKD patients enrolled between
12/1/2002 and 11/30/2013:
    │
    ├──→ 72 patients: MRI not available due to
    │    administrative issues or lack of SSFSE
    │    images at the outset of the study
    ▼
178 patients had baseline MRI
    │
    ├──→ 40 patients did not have a definite
    │    PKD gene mutation identified
    ▼
138 patients had PKD gene mutations
identified
    │
    ├──→ 28 patients excluded: unable to find
    │    matched controls
    ▼
110 patients had matched controls
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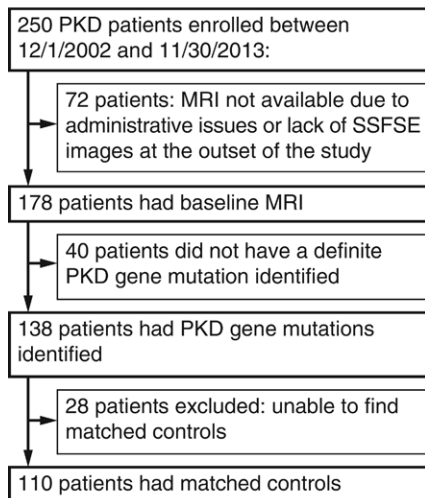
Figure 1: Flowchart shows the accrual flow, demonstrating subject enrollment in the study. *PKD* = polycystic kidney disease, SSFSE = single-shot fast spin-echo.

Table 1

Imaging Parameters

Sequence	Axial SSFSE Imaging	Coronal SSFSE Imaging
Coil	Body array coil	Body array coil
Repetition time	Single shot	Single shot
Echo time (msec)	91–185	89–185
Flip angle (degrees)	90	90
Matrix	256–512 × 192–512 × 40–48	256–512 × 192–512 × 36–48
Section thickness (mm)	8–10	6–10
Spacing (mm)	0–2	0–2
Field of view (cm)	30–38	44–48
Bandwidth (kHz)	21	22
No. of signals acquired	0.54	0.54

Note.—For imaging, a Signa Excite 12.0–15.0 (General Electric) MR imaging unit was used.

with the four-variable Modification of Diet in Renal Disease study formula by using the serum creatinine level obtained within 3 months of the MR imaging examination. The medical records of patients with ADPKD and pancreatic cysts were reviewed for any reports of procedures and pathologic findings.

PKD Gene Sequence Analysis

Genomic DNA was extracted from peripheral blood lymphocytes by using a Gentra Puregene blood kit (Qiagen, Valencia, Calif). *PKD1* (reference sequence NM_000296.2) and *PKD2* (reference sequence NM_000297.2) were analyzed by using Surveyor Nuclease Wave (Transgenomic, Omaha, Neb) denaturing high-performance liquid chromatography screening, followed by confirmatory sequencing (19) or directly by Sanger sequencing (20) by using an ABI 3130 genetic analyzer (Applied Biosystems, Foster City, Calif). Alternatively, long-range polymerase chain reaction products covering the entire exonic regions and most of the 5′ and 3′ untranslated regions of *PKD1* and *PKD2* were sequenced by using next-generation sequencing on an Illumina MiSeq system (San Diego,

Calif), followed by confirmatory Sanger sequencing of the pathogenic mutations (21). To avoid amplification of *PKD1* pseudogenes, *PKD1* was amplified by using primers anchored either in the rare mismatched region with the human homologs or in the single-copy region of *PKD1*. Sanger and next-generation sequencing data were analyzed by using Mutation Surveyor software version 4.0 (Soft Genetics, State College, Pa) (20) and the laboratory-developed pipeline (21), respectively.

Imaging Protocol

All patients underwent imaging at 1.5 T (Signa Excite 12.0–15.0; General Electric, Waukesha, Wis) by using a body phased-array coil. Axial and/or coronal SSFSE images were used to evaluate pancreatic cysts. Coronal and axial SSFSE images were obtained over single or multiple breath holds by using the parameters presented in Table 1.

Image Analysis

Pancreatic cysts were identified on baseline axial and/or coronal SSFSE images in all patients with ADPKD and control subjects. MR images were reviewed independently by three radiologists (M.R.P., J.K., S.C.), one attending physician with 20 years of body MR imaging experience and two 2nd-year MR imaging fellows. Consensus among all readers, with repeat review of images, was used to resolve differences. This was necessary in 12% of the population

(27 of 220 individuals). All viewers were blinded to the clinical, laboratory, and *PKD* mutation data; blinding of ADPKD status was not possible because this diagnosis was apparent on MR images. Pancreatic cyst maximum dimension was measured from inner wall to inner wall (Fig 2); a minimum threshold diameter of 2 mm was used. The number, size, location, and imaging characteristics of pancreatic cysts were recorded. The volumes of both kidneys and the liver of each patient were measured by tracing the outer boundary on a three-dimensional workstation (Advantage Windows workstation 4.1 software; General Electric).

When follow-up studies of patients with ADPKD were available, changes in the imaging characteristics of pancreatic cysts were evaluated.

Statistical Analysis

Continuous variables are presented as means with standard deviations or as medians with interquartile ranges. Log transformations of total kidney volume (TKV) and liver volume were used to establish normal distributions. Differences in demographic variables between patients and control subjects were assessed with the Student t test, Wilcoxon test, or χ^2 test, as appropriate. A χ^2 test was used to evaluate any difference in the prevalence of cysts in patients with a *PKD1* or *PKD2* gene mutation and the presence or absence of cysts in patients with ADPKD. The

Wilcoxon rank sum test was used to evaluate any associations between pancreas cyst properties and characteristics of *PKD* gene mutations. The Fisher exact test was used to evaluate any associations between the presence of cysts in patients with ADPKD and location of mutations in *PKD1* and *PKD2*.

Univariate and multivariable logistic regression analyses helped determine whether variables were associated with presence of pancreatic cysts in patients with ADPKD. Covariates included in the models, selected on the basis of pathophysiological considerations, were age, sex, race, eGFR, log transformation of height-adjusted TKV and liver volume, and *PKD* gene mutation locus. The interaction between age and eGFR was also evaluated. All *P* values were two sided and were evaluated at the .05 α level. Interobserver reliability was evaluated by using the κ statistic for a binary "yes or no" presence of cysts, and an intraclass correlation coefficient for a continuous number of cysts was identified. All analyses were performed with SAS version 9.3 software (SAS Institute, Cary, NC).

Results

This study included 110 patients with ADPKD and 110 control subjects who were matched for age, sex, and eGFR (Table 2). Clinical indications for the MR imaging studies of the control subjects were evaluation for hepatobiliary lesions (*n* = 63), gastrointestinal lesions (*n* = 16), renal lesions (*n* = 8), pelvic lesions (*n* = 5), or other lesions (*n* = 6). Although ADPKD and control groups were of predominantly white race, the prevalence of white subjects was significantly greater in the ADPKD group (97 of 110 vs 82 of 110, respectively; *P* = .009). The ADPKD group had a threefold greater height-adjusted TKV (640 mL vs 197 mL, respectively; *P* < .0001) and significantly greater height-adjusted liver volume (1102 mL vs 896 mL, respectively; *P* < .0001) than did control subjects. In the ADPKD group, 36.4% of patients (40 of 110) had at least one pancreatic cyst, compared with 22.7% of control
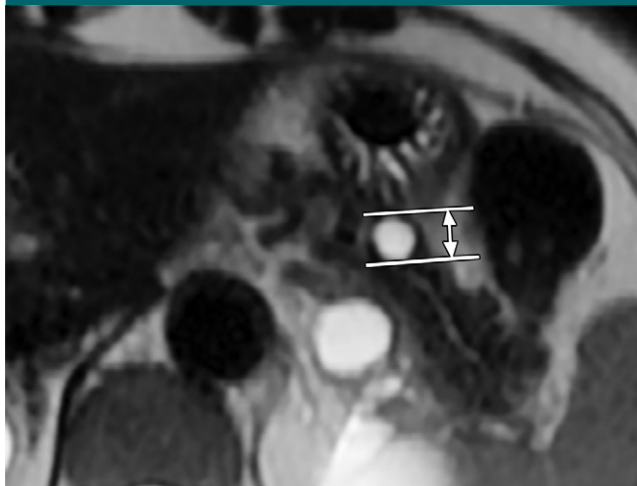

Figure 2: Axial SSFSE MR image shows that cyst size was measured by using an electronic caliper from the inner wall to the inner wall. In this case, it was 11 mm.

Table 2

Comparison of Clinical and Radiologic Features, Including Pancreatic Cyst Prevalence in Patients with ADPKD and Control Subjects

Parameter	Patients with ADPKD (*n* = 110)	Control Subjects (*n* = 110)	*P* Value
Age (y)*	47.4 ± 14.2	47.5 ± 14.2	.97
Patient sex			NA
Men	49 (44.5)	49 (44.5)	
Women	61 (55.5)	61 (55.5)	
Race or ethnicity			.0094
White	97 (88.2)	82 (74.5)	
Non-white	13 (11.8)	28 (25.5)	
eGFR (mL/min/1.73 m²)*	67.1 ± 27.0	69.1 ± 26.6	.58
TKV (mL)†	1074.5 (660–1954)	332 (278–418)	<.0001
Liver volume (mL)†	1791 (1450–2215)	1496.5 (1251–1788)	<.0001
Height-adjusted TKV (mL/m)†	640.0 (374–1151)	196.9 (174–243)‡	<.0001
Height-adjusted liver volume (mL/m)†	1101.6 (863–1250)	895.8 (761–1043)	<.0001
Presence of pancreatic cysts			.0267
Yes	40 (36.4)	25 (22.7)	
No	70 (63.6)	85 (77.3)	
No. of cysts			.01
0 cysts	70 (63.6)	85 (77.3)	
1 cyst	15 (13.6)	16 (14.5)	
2–10 cysts	23 (20.9)	7 (6.4)	
>10 cysts	2 (1.8)	2 (1.8)	

Note.—Numbers in parentheses are percentages, unless indicated otherwise. NA = not applicable.

* Data are means ± standard deviations.

† Data are medians, and numbers in parentheses are interquartile ranges.

‡ Height data were missing in seven control subjects.

subjects (25 of 110; P = .027; Table 2). The distribution and mean size of pancreatic cysts did not differ in the ADPKD and control groups (Table E1 [online]). There was high reader agreement and reliability among the radiologists who evaluated the MR images (κ = 0.84 [P < .0001]; intraclass correlation coefficient = 0.97; 95% confidence interval: 0.96, 0.98).

In the ADPKD group, 69% (76 of 110 patients) had a *PKD1* mutation, and 31% (34 of 110 patients) had a *PKD2* mutation (Table 3). Patients with a *PKD2* mutation were older than those with a *PKD1* mutation (53.0 years vs 44.9 years, respectively; P = .005). Height-adjusted TKV and liver volumes were not significantly different in the *PKD1* and *PKD2* groups. Although

mutations in *PKD1* were more prevalent overall, pancreatic cysts were more than twice as prevalent in the *PKD2* group than in the *PKD1* group (62% [21 of 34 patients] vs 25% [19 of 76 patients], respectively; P = .0002). The number of pancreatic cysts was also greater when a mutation in *PKD2* was present; more than one cyst was found in 47% of the *PKD2* group (16 of 34 patients), compared with only 12% of the *PKD1* group (nine of 76 patients, P = .0004). The size and distribution of pancreatic cysts did not differ significantly in the *PKD1* and *PKD2* groups (Table E2 [online]).

In the univariate regression analysis, age (odds ratio [OR], 1.03; P = .04) and presence of a *PKD2* mutation (OR, 4.85; P < .0001; Table 4) were associated with pancreatic cyst prevalence. In the multivariable model, an association with the presence of a *PKD2* mutation remained (OR, 5.91; P = .0004), but the association with age did not persist after adjustment for confounders. The multivariable model was also used to identify an association of pancreatic cysts with log height-adjusted liver volume (OR, 3.64; P = .038); log height-adjusted TKV was of borderline significance (OR, 0.51; P = .08). There was no

Table 3

Prevalence of Pancreatic Cysts according to *PKD* Gene Mutation

Parameter	*PKD1* (*n* = 76)	*PKD2* (*n* = 34)	*P* Value
Age (y)*	44.9 ± 14.0	53.0 ± 13.2	.0049
Patient sex			.95
Men	34 (44.7)	15 (44.1)	
Women	42 (55.3)	19 (55.9)	
Presence of cysts			.0002
Yes	19 (25.0)	21 (61.8)	
No	57 (75.0)	13 (38.2)	
No. of cysts			.0004
0 cysts	57 (75.0)	13 (38.2)	
1 cyst	10 (13.2)	5 (14.7)	
2–10 cysts	9 (11.8)	14 (41.2)	
>10 cysts	0 (0)	2 (5.9)	
TKV (mL/m)†	632 (375–1118)	677 (336–1300)	.76
Liver volume (mL/m)†	999 (868–1334)	1092 (800–1200)	.87

Note.—Numbers in parentheses are percentages, unless indicated otherwise.

* Data are means ± standard deviations.

† Data are medians, and numbers in parentheses are interquartile ranges.

Table 4

Association of Pancreatic Cysts with Mutations in *PKD2*

Parameter	Unadjusted			Adjusted		
	OR	95% Confidence Interval	*P* Value	OR	95% Confidence Interval	*P* Value
PKD gene						
PKD1	Reference	Reference	Reference	Reference	Reference	Reference
PKD2	4.85	2.04, 11.51	<.0001	5.91	2.22, 15.72	.0004
Log (height-adjusted liver volume)	2.48	0.86, 7.13	.09	3.64	1.08, 12.30	.0379
Log (height-adjusted TKV)	0.97	0.58, 1.63	.90	0.51	0.24, 1.08	.08
eGFR	0.99	0.97, 1.00	.08	0.98	0.95, 1.01	.11
Age	1.03	1.00, 1.06	.0444	1.00	0.95, 1.01	.90
Patient sex						
Men	Reference	Reference	Reference	Reference	Reference	Reference
Women	0.97	0.45, 2.12	.94	0.76	0.30, 1.94	.56
Race						
White	2.06	0.53, 7.96	.30	3.33	0.65, 17.07	.15
Non-white	Reference	Reference	Reference	Reference	Reference	Reference

Note.—"Reference" refers to the reference group selected for analysis.

significant interaction between age and eGFR; thus, the analysis was performed without an age*eGFR interaction variable. There was no association of race or sex with the presence of pancreatic cysts.

Truncating mutations were identified in 57.9% of the *PKD1* group (11 of 19 patients) and 76.2% of the *PKD2* group (16 of 21 patients). However, there was no association of the mutation

type (truncating vs nontruncating) with the size or number of pancreatic cysts (Table E3 [online]). Moreover, there was no association of the presence of a pancreatic cyst with the mutation location in either *PKD1* or *PKD2* (Table E3 [online]).

Among the 40 patients with ADPKD and pancreatic cysts, six of 40 (15%) had cyst diameters that were 1 cm and larger, and five had a *PKD2*

mutation. Of those six patients, four had complex cysts with multilobulated or multiseptated appearance (Figs 3, 4) or internal debris (Fig 5); three had cysts with connection to the main pancreatic duct or uncinate duct, indicating possible side-branch intraductal papillary mucinous neoplasms or dilated side branches (Fig 4). One of these cysts measured 2.6 cm, with characteristics of serous cystadenoma (Fig 3). None of these six patients had symptoms or signs of pancreatic pathologic findings, and none underwent surgical resection. One patient underwent endoscopic US-guided fine-needle aspiration biopsy (Fig 4a). The pathologic findings indicated a possible low-grade, mucinous, cystic lesion.

Follow-up MR images were available for 23 patients with ADPKD and pancreatic cysts, with follow-up intervals ranging from 279 days to 7.5 years. Patients with longer follow-up intervals were more likely to show a change (P = .02; Table E4 [online]). Nine of 23 patients (39%) showed changes in pancreatic cysts (Fig 4): Five of 23 (22%) had interval increases in the number of cysts, and one of 23 (4%) had an interval decrease in the number of cysts. All nine patients with a change
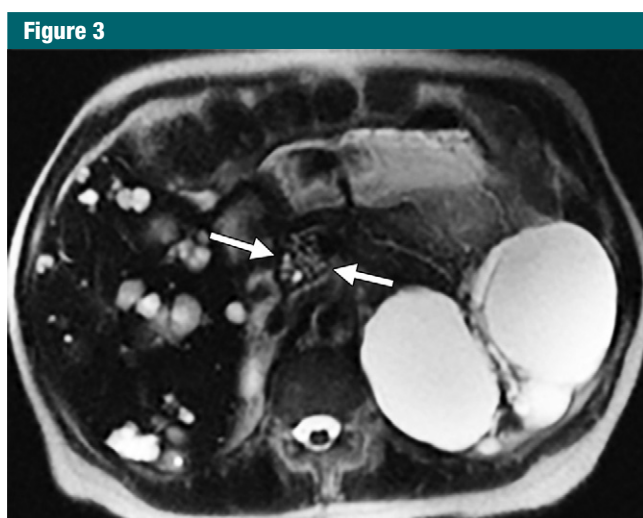

Figure 3: Axial MR image obtained in a 71-year-old woman with *PKD2* mutation. There is a cluster of tiny cysts in the pancreatic head, measuring 26 mm in maximum dimension.
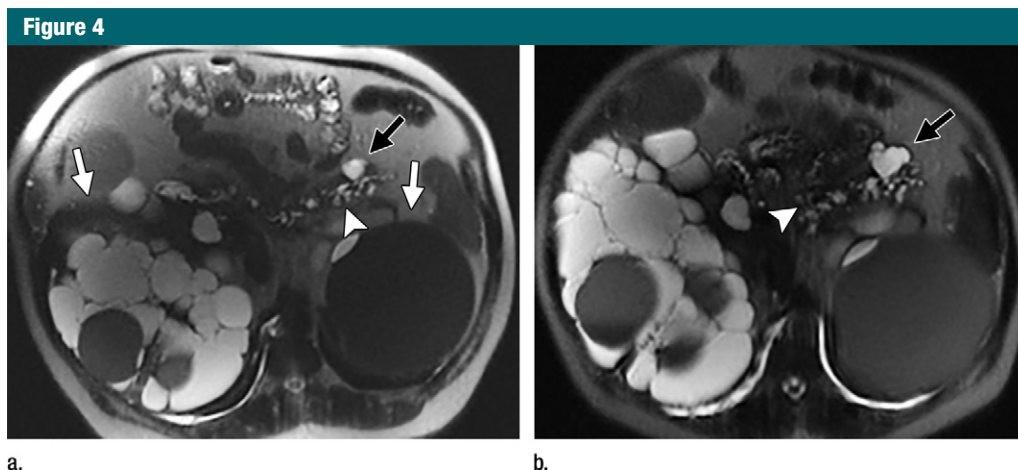

a.   b.

Figure 4: Axial MR images obtained in a 58-year old man with *PKD2* mutation show multiple pancreatic cysts, with the largest in the tail of the pancreas, measuring 25 mm (black arrow). Most of the cysts demonstrate connection to the main pancreatic duct (arrowhead). Note numerous cysts in the right kidney and a large hemorrhagic cyst in the left kidney (white arrows). Endoscopic US–guided fine-needle aspiration biopsy was performed, and the result was benign. The size and the number of cysts increased in the 3 years after the biopsy. **(a)** Initially, there were up to 20 cysts, and the largest cyst size was 25 mm. **(b)** After interval biopsy and 3 years, there were at least 31 cysts, and the largest cyst size was 35 mm.
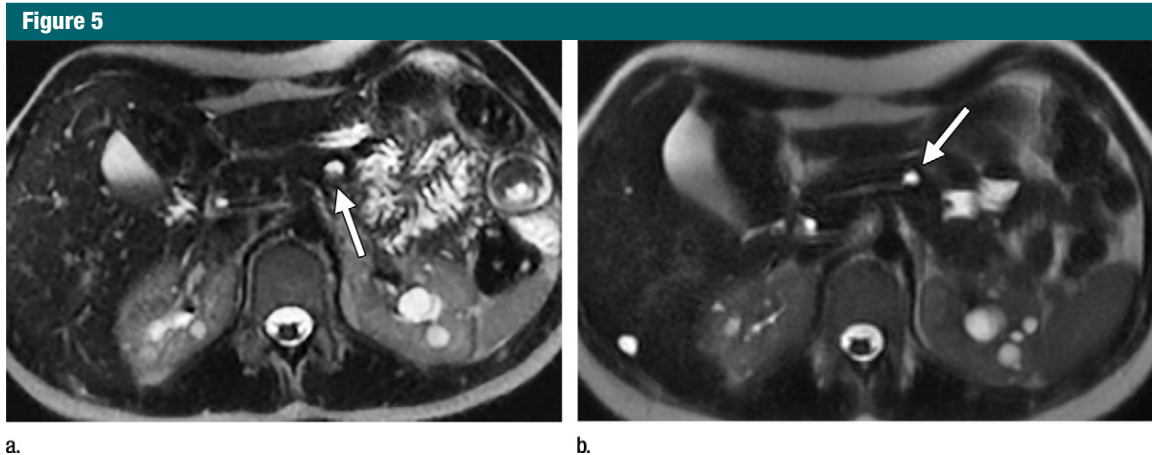
Figure 5

a.   b.

Figure 5:   Axial MR images obtained in a 19-year old woman with *PKD1* mutation. **(a)** A 10-mm pancreatic cyst with internal debris is seen (arrow). **(b)** After 3 years, the debris was cleared (arrow), with no interval size growth of the cyst.

in pancreatic cyst size showed interval growth. Internal cyst debris cleared spontaneously in one patient during follow-up (Fig 5).

Discussion

In this cross-sectional study, we found the prevalence of pancreatic cysts to be significantly higher in an ADPKD cohort compared with a matched control population without ADPKD. Patients with ADPKD and a *PKD2* gene mutation were five times more likely to have pancreatic cysts than patients in the *PKD1* group; this finding persisted after adjusting for potential confounders.

PKD1 has a more aggressive disease course, with an earlier age of symptom onset, end-stage renal disease, and death (1,2). Thus, the potential to discriminate *PKD1* from *PKD2* on MR images has important prognostic implications. MR imaging identification of pancreatic cysts in ADPKD significantly increases the likelihood that a *PKD2* mutation is present.

The mechanism(s) whereby *PKD* gene mutations cause pancreatic cysts has not been established. Homozygous mutations of *PKD1* or *PKD2* genes in animal models are embryonically lethal, causing structural cardiac defects, edema, focal hemorrhage, skeletal deformities, and development of cysts

in the kidneys, liver, and pancreas (10–12,14). One generally accepted view is that ADPKD is recessive at the cellular level and that clonal proliferation of a renal tubular epithelial cell follows an inactivating somatic mutation (1,10,11,13,22,23). Rodent models of ADPKD develop pancreatic cysts when *PKD1* or *PKD2* is either globally or conditionally inactivated (10–12), consistent with this "two-hit" mechanism. Polycystin-2, the product of *PKD2*, also appears to contribute to pancreatic development at or after the point at which common pancreatic progenitor cells are committed to become ductal epithelium (10). Our current finding of an association of *PKD2* mutations with pancreatic cysts supports the conclusion that polycystin-2, the gene product of *PKD2*, is required for the maintenance of the normal pancreatic duct structure in adults. However, causality cannot be determined from the observational data reported in this cross-sectional study.

Overall, we found *PKD2* gene mutations in 30% of the patients with ADPKD in this study, which is approximately twice that reported previously (2,24–26). However, the *PKD2* mutation prevalence in our cohort is similar to that in population-based studies in which *PKD2* mutations were found in 24%–36% of patients (2,24–26). Higher *PKD1* mutation

prevalence in previous studies may have been overrepresented because of ascertainment bias, as clinical manifestations are more severe in patients with *PKD1* mutations, whereas less severely affected patients with *PKD2* mutations likely did not receive diagnoses (25). Torra et al (7) reported linkage to *PKD1* in six patients with ADPKD and pancreatic cysts. However, their conclusions may have been confounded by the small number of patients evaluated.

The position of a *PKD1* mutation (24) and the presence of a truncating mutation (25) contributed to the severity of the ADPKD phenotype in previous studies. In our study, however, neither of these variables was associated with pancreatic cyst prevalence; this may reflect the relatively small sample size.

Pancreatic cysts are more likely to be discovered incidentally at MR imaging than at US in the general population (14%–20% vs 0.21%, respectively) (14,16,17) and even more frequently at MR cholangiopancreatography (45%) (18), reflecting the higher spatial resolution and excellent image contrast of T2-weighted MR imaging. This is consistent with our finding of pancreatic cysts in more than 20% of the control population. Postmortem examinations of patients with ADPKD have yielded a prevalence of approximately 9%

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(27,28). However, autopsy studies can be confounded by selection bias, which limits generalization of the findings.

Few investigators have systematically evaluated pancreatic cysts in ADPKD. In the HALT Progression of Polycystic Kidney Disease, or HALT-PKD, study, a multicenter clinical trial of antihypertensive drug treatment in ADPKD in which MR imaging was limited to the coronal plane, pancreatic cysts were identified at baseline in only 1.8% of 560 patients with ADPKD, with 62% having only one cyst (29). By contrast, in our study, 36% of all patients with ADPKD (40 of 110) had at least one pancreatic cyst; 63% of those patients (25 of 40) had more than one cyst. Our findings suggest that pancreatic cysts are among the most prevalent extrarenal manifestations of ADPKD. The discrepancy between our findings and those of HALT-PKD may reflect the limited imaging plane available in HALT; pancreatic cysts are difficult to detect on coronal images (30). Moreover, the HALT-PKD population was limited to young subjects with early-stage kidney disease; the mean age was approximately 10 years younger than that in the present study. Although kidney cysts develop at a later age in ADPKD with a *PKD2* mutation (31), it is unclear whether pancreatic cyst formation is associated with age. We identified an association of age with pancreatic cysts in a univariate model, but this association did not persist after adjustment for potential confounders.

The natural history and risk of complications of pancreatic cysts in ADPKD have not been established. In our study, no patient with pancreatic cysts had related symptoms or complications. However, only one patient underwent invasive evaluation (ie, cyst aspiration); thus, more complex lesions could have been undetected. In previous reports, investigators have concluded that pancreatic cysts in ADPKD are usually benign and that inflammatory or neoplastic changes that arise from these lesions rarely occur (32,33). In a large cohort from the general population referred with pancreas cysts selected for radiographic

surveillance, Gaujoux et al reported a 1% incidence of pancreatic malignancy (34). However, our study was not designed to evaluate the natural history of pancreatic cysts in ADPKD. A systematic assessment of the natural history of pancreatic cysts in ADPKD is warranted to address these issues.

Strengths of this study include the characterization of clinical, laboratory, genetic, and radiologic features of the ADPKD population. ADPKD diagnosis was confirmed in all subjects by results of *PKD* gene mutation analysis. The control population was matched for several potential clinical and laboratory confounders, including the timing of the MR imaging procedure. Blinding of the investigators to these confounders also limited the potential for bias.

Some aspects of the study design limit the generalization of our findings. The control group was selected retrospectively from a clinical imaging database in a single tertiary care medical center. Both the ADPKD and control groups were predominantly white, and findings may differ in more diverse populations. Although dates of MR imaging testing were matched, we cannot be certain that all methodological confounders were controlled. Although the lower prevalence of pancreatic cysts in the *PKD1* and control groups suggests a specific effect of *PKD2* mutations in the development of pancreatic cysts in ADPKD, our cross-sectional observational study was not designed to assess mechanisms of pancreas cyst formation. Therefore, our findings should be considered hypothesis generating.

In conclusion, pancreatic cysts were found to be more prevalent in patients with ADPKD than in matched subjects without ADPKD in this cross-sectional study and were associated with the presence of a mutation in the *PKD2* gene. Therefore, future studies of the pathogenesis and natural history of pancreatic cysts in ADPKD should be evaluated in the context of the *PKD* genotype.

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