

# Autosomal Dominant Polycystic Kidney Patients May Be Predisposed to Various Cardiomyopathies



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**Introduction:** Mutations in *PKD1* and *PKD2* cause autosomal dominant polycystic kidney disease (ADPKD). Experimental evidence suggests an important role of the polycystins in cardiac development and myocardial function. To determine whether ADPKD may predispose to the development of cardiomyopathy, we have evaluated the coexistence of diagnoses of ADPKD and primary cardiomyopathy in our patients.

**Methods:** Clinical data were retrieved from medical records for patients with a coexisting diagnosis of ADPKD and cardiomyopathies evaluated at the Mayo Clinic (1984–2015).

**Results:** Among the 58 of 667 patients with available echocardiography data, 39 (5.8%) had idiopathic dilated cardiomyopathy (IDCM), 17 (2.5%) had hypertrophic obstructive cardiomyopathy, and 2 (0.3%) had left ventricular noncompaction. Genetic data were available for 19, 8, and 2 cases of IDCM, hypertrophic obstructive cardiomyopathy, and left ventricular noncompaction, respectively. *PKD1* mutations were detected in 42.1%, 62.5%, and 100% of IDCM, hypertrophic obstructive cardiomyopathy, and left ventricular noncompaction cases, respectively. *PKD2* mutations were detected only in IDCM cases and were overrepresented (36.8%) relative to the expected frequency in ADPKD (15%). In at least 1 patient from 3 IDMC families and 1 patient from a hypertrophic obstructive cardiomyopathy family, the cardiomyopathy did not segregate with ADPKD, suggesting that the *PKD* mutations may be predisposing factors rather than solely responsible for the development of cardiomyopathy.

**Discussion:** Coexistence of ADPKD and cardiomyopathy in our tertiary referral center cohort appears to be higher than expected by chance. We suggest that *PKD1* and *PKD2* mutations may predispose to primary cardiomyopathies and that genetic interactions may account for the observed coexistence of ADPKD and cardiomyopathies.

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KEYWORDS: ADPKD; cardiomyopathies; hypertrophic cardiomyopathy; idiopathic dilated cardiomyopathy; left ventricular noncompaction; polycystic kidney

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Autosomal dominant polycystic kidney disease (ADPKD) is characterized by relentless formation of fluid-filled cysts in the kidney, leading eventually to end-stage renal disease. It is caused by mutations to *PKD1* encoding polycystin-1 or *PKD2* encoding polycystin-2 (PC2).<sup>1–5</sup> Polycystin-1 is a transmembrane protein in the cell membrane and primary cilia where it interacts with PC2.<sup>6–13</sup> PC2 is a member of the transient

receptor potential channel family, found in the endoplasmic reticulum and in primary cilia. Polycystins, particularly PC2, contribute to the regulation of calcium release from intracellular stores.<sup>11–14</sup>

Polycystins are expressed in many tissues, including tubular epithelia, endothelial and vascular smooth muscle cells, and cardiomyocytes.<sup>15–20</sup> In fact, ADPKD is a systemic disease associated with several extrarenal manifestations, including multiple cardiovascular complications such as early development of hypertension, left ventricular hypertrophy, and diastolic dysfunction; cardiac valvular disease; aortic root dilatation; arterial aneurysms and dissections; and pericardial effusion.<sup>21</sup> Although the cardiovascular

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manifestations of ADPKD have been thought to be due to compression of the renal vasculature by cysts, leading to hypertension and cardiac dysfunction, increasing evidence suggests that alterations in polycystin expression directly affect the function of the endothelium,<sup>22</sup> vascular smooth muscle,<sup>23</sup> and cardiomyocytes<sup>24</sup> and may be at least in part responsible for the cardiovascular manifestations of the disease.

Studies in experimental animal models strongly suggest that the polycystins play a role in cardiac development and myocardial function. We have previously suggested an association between ADPKD and IDCM.<sup>25</sup> A few cases of hypertrophic obstructive cardiomyopathy (HOCM) and ADPKD have also been reported.<sup>26,27</sup> Left ventricular noncompaction (LVNC) is being reported with increasing frequency in patients with ADPKD. Patients with ADPKD may also have an increased risk for the development of atrial fibrillation, a common manifestation of cardiomyopathy, after adjusting for other risk factors including hypertension, hyperlipidemia, and chronic kidney disease.<sup>28</sup> Therefore we reviewed our ADPKD database to comprehensively identify the cases of a diagnosis of IDCM, HOCM, or LVNC coexisting with ADPKD. We found that these diagnoses coexisted in this database with a frequency that appears to be higher than expected by chance association alone. However, they did not segregate together in some members of 3 IDMC families and 1 HOCM family. This suggests a possible genetic interaction between these diseases rather than the *PKD* mutations being a direct cause of the cardiomyopathies. The purpose of this report is to raise awareness of this possible association and genetic interaction.

## SUBJECTS AND METHODS

### Study Population

All adult patients with ADPKD who were evaluated at the Mayo Clinic in Rochester, Minnesota, from January 1984 to December 2015 were identified ( $n = 3885$ ). The diagnosis of ADPKD was based on Ravine's criteria in the presence of a positive family history. In the absence of family history, the criteria for a diagnosis of ADPKD were the presence of at least 20 bilateral renal cysts and the absence of clinical findings suggesting the presence of a different cystic disease.

Patients with cardiomyopathies were identified by International Classification of Diseases, 9th Revision (ICD-9) codes and a keyword search of clinical notes through the Mayo Clinic database. The keywords included heart failure, idiopathic dilated cardiomyopathy, left ventricular noncompaction, and hypertrophic obstructive cardiomyopathy. Medical records of all patients with potential cardiomyopathies were reviewed

thoroughly. A diagnosis of IDCM was made for patients with a left ventricular ejection fraction (LVEF)  $\leq 40\%$  with exclusion of coronary artery disease ( $>50\%$  obstruction of 1 or more coronary arteries or positive ischemia on stress test), exclusion of other secondary causes such as active myocarditis or primary or secondary form of heart muscle disease, and exclusion of advanced renal failure (estimated glomerular filtration rate  $\leq 15$  ml/min or the need for renal replacement therapy at time of the cardiomyopathy diagnosis). A diagnosis of HOCM was made for patients with increased left ventricular wall thickness ( $\geq 15$  mm) as determined by any imaging modality (transthoracic echocardiography, magnetic resonance imaging, or computerized tomography). LVNC was diagnosed by transthoracic echocardiography Jenni criteria (thickened left ventricular wall consisting of 2 layers, evidence of flow within the deep intertrabecular recesses on color Doppler echocardiography, prominent trabecular meshwork in the left ventricular apex or midventricular segments of the inferior and lateral wall).

Demographics and clinical data were retrieved from the patients' electronic records. Estimated glomerular filtration rate was calculated by using the Chronic Kidney Disease Epidemiology Collaboration formula.<sup>29</sup> The Mayo Clinic Institutional Review Board approved the study, and all patients provided research authorization.

### Genetic Analysis

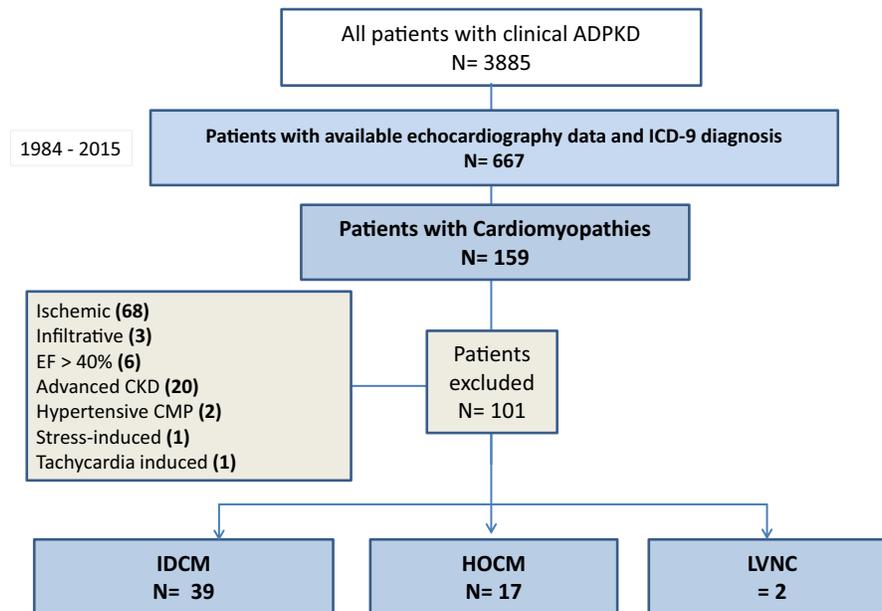
The entire coding and flanking intronic regions of *PKD1* and *PKD2* were screened for mutations by direct sequencing as previously described.<sup>30,31</sup> Pedigrees were completed for all families, and whenever possible, the family members with known ADPKD and/or cardiomyopathy were contacted.

### Statistical Analysis

Data were reported as means  $\pm$  SD for normally distributed data or median and interquartile range (IQR) for skewed data. Survival status was obtained for all patients using a vital records website ([www.archives.com](http://www.archives.com)).<sup>32</sup> Patient survival was analyzed using the Kaplan-Meier method.

## RESULTS

Among the 3885 patients with ADPKD, 159 were identified with a potential diagnosis of cardiomyopathy, but 101 of these were excluded because of evidence of cardiac ischemia, advanced renal failure, or other secondary causes leading to cardiomyopathy (Figure 1). Among the 58 patients included in this case series, 39 had IDCM, 17 had HOCM, and 2 had LVNC.



**Figure 1.** Study flow chart. ADPKD, autosomal polycystic kidney disease; CKD, chronic kidney disease; CMP, cardiomyopathy; EF, ejection fraction; HOCM, hypertrophic obstructive cardiomyopathy; ICD-9, International Classification of Diseases, Revision 9; IDCM, idiopathic dilated cardiomyopathy; LVNC, left ventricular noncompaction.

### Idiopathic Dilated Cardiomyopathy

Thirty-nine of 667 patients with ADPKD (5.8%) for whom echocardiograms were available had a diagnosis of IDCM. Among the 39 patients from 34 families with ADPKD and IDCM, 23 (57%) were male and 100% were Caucasian. Of the 39 patients, 11 were residents of Olmsted County or the 7 neighboring counties, and 14 were residents of other counties in Minnesota, Wisconsin, Iowa, South Dakota, or North Dakota. The remaining patients were from other states ( $n = 13$ ) or countries ( $n = 1$ ). Main indications for the initial evaluation at the Mayo Clinic included nephrology and polycystic kidney disease care ( $n = 16$ ), general medical care ( $n = 12$ ), and cardiology care ( $n = 11$ ).

The mean age at ADPKD diagnosis was 41.1 ( $\pm 13.9$ ) years. The mean age at IDCM diagnosis was 53.3 ( $\pm 12.1$ ) years. The diagnosis of ADPKD preceded, coincided with, or followed the diagnosis of IDCM in 79.5%, 15.5%, and 5% of the patients, respectively. Mean estimated glomerular filtration rate at the time of IDCM diagnosis was 52.3 ( $\pm 21.1$ ) ml/min per 1.73 m<sup>2</sup>. At the time of IDCM diagnosis, 5.1% of patients were in chronic kidney disease stage I, 25.7% in stage II, 48.7% in stage III, and 20.5% in stage IV. About two-thirds of the patients (69.2%) had hypertension at the time of IDCM diagnosis for an average of 9.1 ( $\pm 8.3$ ) years. The majority of these patients (80%) had good blood pressure control while taking, on average, 2.4 ( $\pm 1.1$ ) antihypertensive medications (Appendix Table 1). Of 37 patients with available abdominal imaging results or reports, 15 had measurable total kidney volume with

median total kidney volume of 2031 ml (IQR 1080–3776) (Table 1, Figure 1). Two patients had no available imaging results, but the diagnosis was solid based on clinical records and family history. The patients were followed up, on average, for 10.7 ( $\pm 6.9$ ) years after being diagnosed with IDCM. Thirteen patients reached end-stage renal disease at a mean age of 55.9 ( $\pm 10.1$ ) years.

The median LVEF at initial diagnosis was 25% (IQR 20–30), and average left ventricular end-diastolic diameter was 67.2 ( $\pm 10.2$ ) mm (Table 2). Follow-up transthoracic echocardiography was available for 23 patients with a median LVEF of 39% (IQR 18–48). Overall survival of patients with ADPKD and concomitant IDCM was 85.3%, 70%, and 36.3% at ages 55, 65, and 75 years, respectively. Survival at 5, 10, and 15 years after diagnosis was 81.2%, 64.7%, and 35%, respectively.

Treatment of these patients consisted mostly of medical management including angiotensin-converting enzyme inhibitors,  $\beta$ -blockers, diuretics, and digoxin. Among these patients, 17 had improvement in LVEF with an average  $\Delta$ LVEF of 21.5% ( $\pm 12.3$ ), and 2 had improvement after biventricular pacing. Another 13 patients had progressive worsening of cardiac function with a  $\Delta$ LVEF of -7.2% ( $\pm 5.2$ ); 2 of these patients received heart transplants, 1 was denied heart transplantation because of newly diagnosed malignancy, and 2 received biventricular pacing. Nine patients had unknown outcomes because of lack of long-term follow-up.

**Table 1.** Baseline characteristics

Variable	IDCM (n = 39)	HOCM (n = 17)	ADPKD with echocardiogram without IDCM/HOCM (n = 611)
Male, %	56	58.5	48
Caucasian, %	100	100	91
Age at cardiomyopathy, yr	53.3 ± 12.1	59.9 ± 11.8	—
Age at diagnosis of ADPKD, yr	41.1 ± 13.9	40.2 (± 17.4)	38.4 + 16.1
eGFR, ml/min per 1.73 m <sup>2</sup>	52.3 ± 21.1	55.1 ± 29	—
TKV, ml	2031 (IQR 1080–3776) n = 15	1646 (992–2941) n = 10	1954 (1008–3374) n = 317
Age at ESRD, yr	55.9 ± 10.1 (n = 13)	50.1 ± 6.8 (n = 10)	54.1 ± 11.2 (n = 301)
Mean follow-up, yr	10.4 ± 6.9	6.2 ± 4.7	—
With PKD genetic testing (n)	19	8	166
<i>PKD1</i> truncating mutations (n, %)	6, 31.6	2, 25	83, 50.0
<i>PKD1</i> nontruncating mutations (n, %)	3, 15.8	3, 37.5	52, 31.3
<i>PKD2</i> mutations (n, %)	7, 36.8	0	16, 9.7
No mutation detected (n, %)	3, 15.8	3, 37.5	15, 9.0

ADPKD, autosomal dominant polycystic kidney disease; eGFR, estimated glomerular filtration rate; HOCM, hypertrophic obstructive cardiomyopathy; IDCM, idiopathic dilated cardiomyopathy; IQR, interquartile range; TKV, total kidney volume.

Among the patients who underwent right endomyocardial biopsy, the pathology showed features consistent with IDCM, including moderate myocyte hypertrophy with focal interstitial fibrosis. Cardiac imaging of a representative patient with ADPKD and IDCM is shown in [Figure 2](#).

Nineteen patients from 14 families were genetically screened for the ADPKD genes. Among those with an available DNA sample, 9 patients (9 families) had *PKD1* mutations, 7 (4 families) had *PKD2* mutations, and 3 (1 family) had no mutation detected. Among the *PKD1* mutations, 6 had a truncating effect (nonsense, splice, frameshift) and 3 had a nontruncating functional effect (missense and in-frame). Among the *PKD2* mutations, 4 had truncating and 3 had nontruncating effects. Diagnoses of ADPKD and IDCM segregated together in most families. Three families, however, had at least 1 family member with IDCM without ADPKD. In 1 of these families with a *PKD2* mutation, the diagnosis of ADPKD in a member with IDCM was ruled out by genetic testing. No mutation was detected or no genetic testing had been performed in the other 2 families ([Appendix Table 2](#)).

**Table 2.** Echocardiographic specifications

Echocardiographic specifications	IDCM	HOCM
LVEF, %	25 (20–35)	70 (66.5–74)
Basal septal thickness, mm	10.6 ± 2.6	19.9 ± 2.3
LV diastolic diameter, mm	66.7 ± 10	48.5 ± 7
LV systolic diameter, mm	58.1 ± 11.6	27.4 ± 4.6
LVMI, g/m <sup>2</sup>	161.7 ± 72.3	145.6 ± 36.4

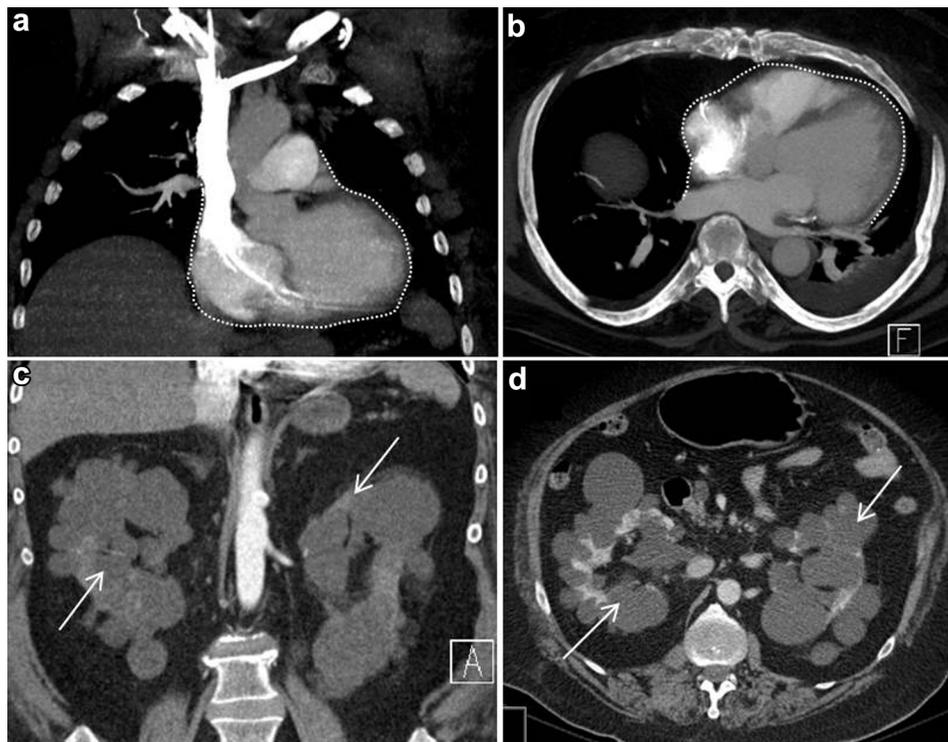
HOCM, hypertrophic obstructive cardiomyopathy; IDCM, idiopathic dilated cardiomyopathy; LV, left ventricular; LVEF, left ventricular ejection fraction; LVMI, left ventricular mass index.

### Hypertrophic Obstructive Cardiomyopathy

Seventeen of 667 (2.5%) patients with ADPKD for whom echocardiograms were available had a diagnosis of HOCM. Among the 17 patients from 15 families with ADPKD and coexistent HOCM, 10 (58.8%) were male and all were Caucasian. Of the 17 patients, 5 were residents of Olmsted County or surrounding counties, and 5 were residents of other counties in Minnesota, Wisconsin, Iowa, South Dakota, or North Dakota. The remaining patients were from other states ( $n = 7$ ). Main indications for the initial evaluation at the Mayo Clinic included nephrology care ( $n = 8$ ), medical care ( $n = 5$ ), and cardiology care ( $n = 4$ ).

Eight patients from 7 families had genetic screening available. Among those with available DNA samples, 5 patients (4 families) had *PKD1* mutations, and 3 patients (3 families) had no mutation detected. None of these patients had a *PKD2* mutation. Among the families with *PKD1* mutations, a nontruncating effect was found in 3 families, and a truncating functional effect was found in 1 family.

The mean age at ADPKD diagnosis was 40.2 (± 17.4) years. The mean age at HOCM diagnosis was 59.9 (± 11.8) years. The diagnosis of ADPKD preceded the diagnosis of HOCM in 94% of the patients. Mean estimated glomerular filtration rate at the time of HOCM diagnosis was 55.1 (± 28.7) ml/min per 1.73 m<sup>2</sup>. At the time of HOCM diagnosis, 17.7% of patients were in chronic kidney disease stage I, 17.7% in stage II, 47% in stage III, 5.9% in stage IV, and 11.7% in stage V. The majority of patients (82.4%) had hypertension at the time of HOCM diagnosis for an average of 17.3 (+ 13.4) years. The majority of these patients (93%) had good blood pressure control while



**Figure 2.** Chest and abdominal computed tomography (CT) scan in a patient with autosomal dominant polycystic kidney disease (ADPKD) and idiopathic dilated cardiomyopathy (IDCM). The patient is a 72-year-old man with ADPKD who was diagnosed with IDCM at age 58. His left ventricular ejection fraction (LVEF) was estimated at 21% at the time of this imaging. He previously underwent biventricular implantable cardiac device placement. His chest CT scan showed cardiomegaly with left ventricular enlargement (dashed lines, panels a and b). His total kidney volume was 2031 ml as measured on the CT scan of the abdomen (arrows, panels c and d).

taking, on average, 2.6 (+ 1.3) antihypertensive medications. Of the 12 patients who had abdominal imaging results or reports available, 10 had measurable total kidney volume with median total kidney volume of 1646 ml (IQR 991–2940) (Table 1). Five patients had no available imaging at our institution but had solid ADPKD diagnoses as determined by clinical records and family history. Mean follow-up after HOCM diagnosis was 6.2 ( $\pm$  4.7) years. Ten patients reached end-stage renal disease at a mean age of 50.1 (+ 6.8) years.

Median LVEF at diagnosis was 70% (IQR 66.5–74), and average basal septum thickness was 19.9 ( $\pm$  2.3) mm (Table 2). Cardiac magnetic resonance images from representative patients are shown in Figure 3. Among the 17 patients with ADPKD and HOCM, 3 patients underwent left ventricular septal myectomy at ages of 54, 63, and 76 years, respectively. Another 2 patients underwent percutaneous septal alcohol ablation (both at age 63 years). Patients who underwent these procedures did well overall and had no postoperative complications. The remaining 12 patients received medical treatment including  $\beta$ -blockers. One of these patients was offered septal reduction therapy but declined. Overall survival of patients with ADPKD and concomitant HOCM was 100% and 75% at the ages of 55 and 75 years,

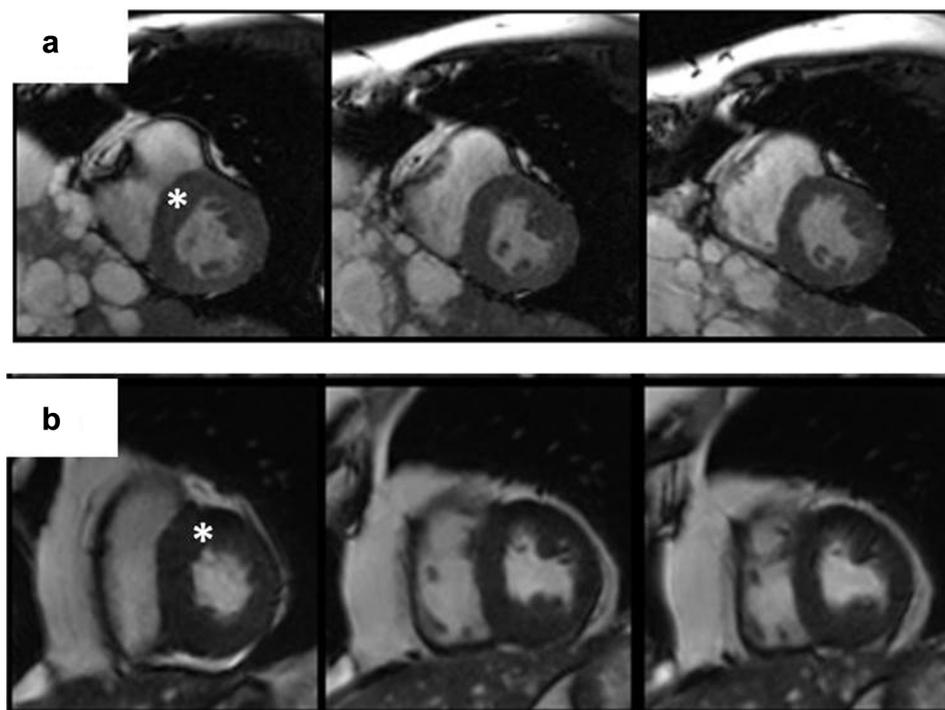
respectively. Survival at 5 and 15 years after diagnosis was 77.8% and 38.9%, respectively.

Among the patients who underwent septal myectomy, pathologic examination revealed features consistent with HOCM including marked myocyte hypertrophy, moderate interstitial fibrosis, mild myocyte disarray, and moderate endocardial fibrosis.

Genetic testing for ADPKD was performed in 7 families, 4 with *PKD1* mutations and 3 with no mutation detected. ADPKD and HOCM segregated together in most patients. One family with no genetic testing available had a member with HOCM and no evidence of ADPKD (Appendix Table 3).

### Left Ventricular Noncompaction Cardiomyopathy

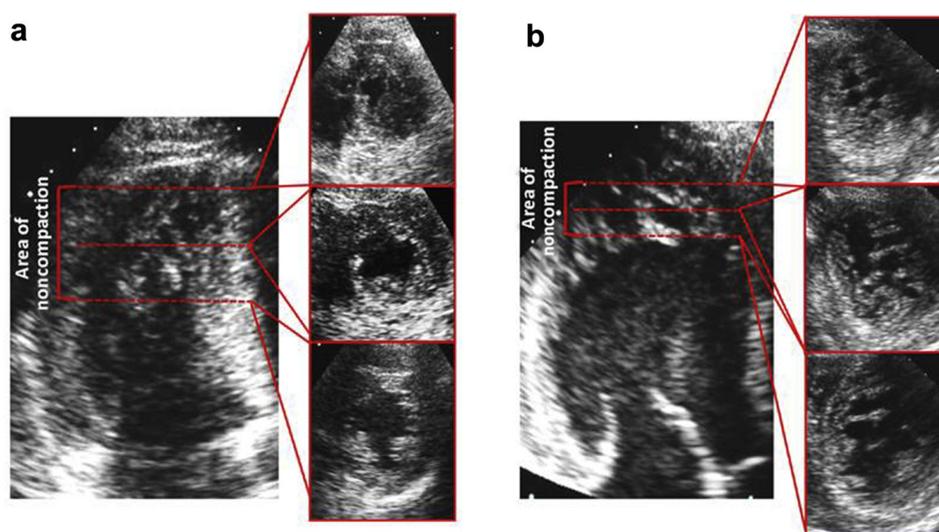
Two of 667 patients with ADPKD (0.3%) for whom echocardiograms were available had a diagnosis of LVNC. One patient is male, diagnosed at age 53 years with an estimated glomerular filtration rate of 43 ml/min and an LVEF of 63% at the time of diagnosis. The second patient is a female, diagnosed at age 54 years, 1 year after reaching end-stage renal disease and LVEF of 53%. Both patients were residents of states other than Minnesota. The main indication for their initial visit was nephrology care. They were diagnosed with



**Figure 3.** Cardiac magnetic resonance imaging (MRI) in patients with autosomal dominant polycystic kidney disease (ADPKD) and hypertrophic obstructive cardiomyopathy (HOCM). (a) A 63-year-old female patient with ADPKD had cardiac MRI findings consistent with asymmetric left ventricular hypertrophy, measuring 21 mm in the basal anterior septum (marked with an asterisk). (b) A 58-year-old male patient with ADPKD had cardiac MRI, which revealed the sigmoid morphologic subtype of hypertrophic cardiomyopathy and maximal end-diastolic myocardial thickness of 19 mm at the basal anterior septum (marked with an asterisk).

ADPKD before they received the diagnosis of LVNC at 49 and 28 years, respectively. Both patients had *PKD1* mutations (1 truncating and the other nontruncating) (Appendix Table 4). One patient had a total kidney volume of 3643 ml. Kidney volume was not available for the other patient. Patients were followed up for

12 and 6 years, respectively. Both patients were treated medically. One patient had worsening trabeculations on echocardiogram 2 years after the initial diagnosis (Figure 4). The other patient underwent right ventricular endomyocardial biopsy, which showed moderate myocyte hypertrophy, and later underwent kidney



**Figure 4.** Echocardiogram of patient with autosomal dominant polycystic kidney disease (ADPKD) and left ventricular noncompaction (LVNC). (a) A 54-year-old male patient with ADPKD who had findings consistent with noncompaction cardiomyopathy on echocardiographic evaluation. Noncompaction is noted at the apex and extends past the mid portion of the myocardium without significant impact on ejection fraction. (b) A 58-year-old female patient with ADPKD who was found to have noncompaction on echocardiographic evaluation. Noncompaction is limited to the apical myocardium only but with impact on left ventricular diastolic function.

transplantation without any cardiovascular complications.

## DISCUSSION

IDCM and HOCM are the 2 main primary cardiomyopathies associated with ADPKD.<sup>33</sup> IDCM is characterized by left ventricular dilatation and systolic dysfunction.<sup>34</sup> Nearly 60% of the cases are inherited predominantly with an autosomal dominant pattern of transmission, and more than 60 genes identified encode mainly cytoskeletal and sarcomeric proteins.<sup>35,36</sup> Hypertrophic cardiomyopathy is characterized by left ventricular hypertrophy, often asymmetric, accompanied by myofibrillar disarrays and diastolic dysfunction. It is inherited with an autosomal dominant pattern, and mutations in more than 20 genes encoding mainly sarcomeric proteins but also components of the Z-disk and intracellular calcium modulators have been identified.<sup>37,38</sup> LVNC is a rare form of cardiomyopathy characterized by prominent left ventricular trabeculae, deep intertrabecular recesses that are continuous with the left ventricular cavity, and a thin compacted layer, as well as left ventricular hypertrophy or dilatation and occasionally associated congenital heart malformations. LVNC most commonly has X-linked recessive or autosomal dominant inheritance, but autosomal recessive and mitochondrial inheritance also occur.<sup>39</sup>

The prevalence of the primary cardiomyopathies is not well established. In Olmsted County, prevalences of IDCM and HOCM were estimated to be 1:2500 or 0.04% and 1:5000 or 0.02%, respectively,<sup>40</sup> but recent estimates by cardiology experts suggest higher prevalences. The prevalence of LVNC in the general population is unknown but is estimated to be detected in 0.014% of echocardiograms performed and found in 3% to 4% of patients with heart failure.<sup>41,42</sup> In our study, IDCM, HOCM, and LVNC were diagnosed in 5.8%, 2.5%, and 0.3% of 667 patients with ADPKD who underwent echocardiograms. These frequencies, however, are subject to several biases and should not be viewed as valid prevalences of these cardiomyopathies in ADPKD. In these patients, the diagnosis of cardiomyopathy was made in middle age, usually after or at the time of the diagnosis of ADPKD. More than half of the patients with IDCM responded well to either medical therapy or cardiac resynchronization therapy. Those who did not respond to either therapy had worse clinical outcomes. Most patients with HOCM experienced improvement with medical treatment, and few required surgical or ethanol septal reduction. These patients had favorable clinical outcomes.

The relatively frequent coexistence of ADPKD and inherited cardiomyopathies in our study raises the possibility of an association between these diseases. However, ADPKD and cardiomyopathy did not segregate together in at least 1 member of 3 IDCM families and 1 member of a HOCM family, suggesting that the *PKD* mutations may be predisposing factors rather than solely responsible for the development of cardiomyopathy. The apparent association of these diseases could be due to genetic interaction.

The likelihood of a genetic interaction between the *PKD* genes and the genes mutated in inherited cardiomyopathies is consistent with a large body of research supporting a role of the polycystins in cardiac development and myocardial function, in addition to known physical interactions between the polycystins and proteins encoded by some inherited cardiomyopathies. *Pkd1* null embryos die on embryonic days 13.5–14.5 from cardiovascular defects that include disorganized myocardial trabeculation, thinning of the myocardial wall, and other abnormalities such as atrial and ventricular septal defects.<sup>19</sup> Reduction of either polycystin has been shown to impair myocardial function, even in the absence of renal cysts.<sup>24,43</sup> Increased cardiomyocyte apoptosis and reduced LVEF have also been observed in a *Pkd1*-haploinsufficient mouse model.<sup>44</sup> Polycystin-1 promotes stabilization of L-type calcium channels, and myocardial function is impaired in *Pkd1*-deficient mice.<sup>43,44</sup> Overexpression of the ≈200-aa, cytoplasmic C-terminal tail of polycystin-1 is sufficient to promote cardiomyocyte hypertrophy.<sup>43</sup> In addition to renal and hepatic cystic disease, mice overexpressing a *Pkd1* transgene develop an eccentric dilated cardiac hypertrophy.<sup>45</sup> PC2 interacts and functionally inhibits cardiac ryanodine receptor (RyR2) channel activity in the presence of calcium, and as a result, PC2-deficient mouse cardiomyocytes have a higher frequency of spontaneous calcium oscillations and reduced sarcoplasmic reticulum calcium stores and release.<sup>15</sup> Hearts from *Pkd2*-mutant zebrafish display impaired intracellular calcium cycling and heart failure with reduced cardiac output.<sup>25</sup> The hearts from -9-month-old, *Pkd2*<sup>+/-</sup> mice display thin left ventricular walls, overall reduction in myofilament proteins, and decreased LVEFs consistent with dilated cardiomyopathy.<sup>46</sup> *Pkd2* haploinsufficiency shortens long-term survival of mutant mice by an undetermined mechanism.<sup>47</sup> The polycystins have been shown to physically interact with proteins<sup>48</sup> encoded by genes mutated in IDCM and/or HOCM, such as troponin I, tropomyosin-1,  $\alpha$ -actinin, desmin, and vinculin.<sup>49–53</sup>

Left ventricular hypertrophy and diastolic dysfunction can develop early in childhood or in

young adults with ADPKD before a diagnosis of hypertension is made but nevertheless correlate with the levels of blood pressure.<sup>54–57</sup> Although patients with ADPKD may have an increased susceptibility to left ventricular hypertrophy and diastolic dysfunction, these seem to be mainly hypertensive complications as shown by their response to antihypertensive therapy<sup>58–60</sup> and by the Halt Progression of Polycystic Kidney Disease (HALT-PKD) clinical trial in which the baseline prevalence of left ventricular hypertrophy in a cohort of 18- to 45-year-old patients with normal renal function and well-controlled hypertension who had cardiac magnetic resonance images available was very low.<sup>60</sup> The magnetic resonance images in a small subset of these patients ( $n = 36$ ) were specifically examined for evidence of LVNC and none was found.<sup>61</sup> However, patients with cardiac disease requiring  $\beta$ -blockers or calcium channel blockers for indications other than hypertension were excluded from participation in the Halt Progression of Polycystic Kidney Disease (HALT-PKD) trial and probably from other studies. This may, in part, account for the nonappearance of cardiomyopathy in this and most previous echocardiographic studies. Nevertheless, in a study of 83 children with ADPKD evaluated by echocardiography, 1 was found to have congenital endocardial fibroelastosis, which would currently be called LVNC. Twelve additional cases of LVNC in patients with ADPKD, not including our 2 cases, have been reported in the literature.<sup>27,55,62–71</sup> (Table 3). Cardiac enlargement was reported in 9.5% of 426 patients with ADPKD in a survey study at the University of Colorado.<sup>72</sup> To our knowledge, an association with ADPKD has not been

reported in epidemiologic studies of primary cardiomyopathies.

The genetic analysis of our cohort is intriguing. We noted that *PKD2* mutations are overrepresented ( $\sim 37\%$ ) in patients with IDMC as compared with the expected distribution of these mutations in the general population with ADPKD ( $\sim 15\%$ ), which is consistent with our previous report.<sup>25</sup> Conversely, patients with HOCM and ADPKD who had DNA available for analysis and identifiable mutations had mostly *PKD1* missense mutations. Given the low number of patients with ADPKD and cardiomyopathy who had genetic testing performed, it is not possible to draw any conclusions, but these findings might correlate with the evidence from the animal studies and the current understanding of polycystins' role in the heart.

The main weakness of our report is that it is based on observations made at a tertiary care center, which can result in a substantial referral bias. On the other hand, the actual prevalence of cardiomyopathy in our cohort of patients with ADPKD could have been underestimated because echocardiography was performed for clinical indications in only 17% of the patients. Because most patients in this study are residents of Olmsted County or surrounding counties or states and were attending our center for general medical or nephrology care when the diagnoses of cardiomyopathy were made, we believe that the association of ADPKD and cardiomyopathies found in our study is not likely to be entirely accounted by referral bias. We were also vigilant to exclude secondary factors such as coronary artery disease, hypertension, and decline in renal function as causes of the cardiomyopathy. The majority of our patients had normal blood pressure or well-controlled hypertension at the time of diagnosis of the cardiomyopathy and by design had neither coronary artery disease nor advanced kidney failure.

In summary, the association between ADPKD and cardiomyopathies found in our study, together with the independent segregation of these diseases in some families, raises the possibility of a genetic interaction between these conditions rather than *PKD* mutations being the direct cause of the cardiomyopathies. A large body of experimental evidence for the importance of polycystins in cardiac development and myocardial function, as well as the known physical interactions between the polycystins and proteins encoded by inherited cardiomyopathy genes, provides credence to this hypothesis. The main purpose of this report is to increase awareness of a possible association and genetic interaction between ADPKD and various cardiomyopathies. Future studies in which the

**Table 3.** Literature review of all published LVNC cases in patients with ADPKD

Reference	Gender, age	Signs	Renal function
Mehrizi et al. 1964 <sup>a62</sup>	Male, 2 mo	HF	BUN 12 mg/dl
Ivy et al. 1995 <sup>a55,63</sup>	Child	NR	NR
Lau et al. 2002 <sup>63</sup>	Male, 44 yr	NR	2 yr HD
Moon et al. 2006 <sup>64</sup>	Female, 45 yr	HF	Cre 1.1 mg/dl
Komeyama et al. 2007 <sup>73</sup>	Female, 59 yr	CVA	Cre 1.2 mg/dl
Lubrano et al. 2009 <sup>66</sup>	Newborn	HF	Stable
Villacorta et al. 2010 <sup>b67</sup>	Female, 65 yr	HF	HD
Villacorta et al. 2010 <sup>b67</sup>	Male, 63 yr	NR	13 yr TX
Pastore et al. 2010 <sup>68</sup>	Male, 40 yr	HF, VT	Cre. 6.5 mg/dl
Ramineni et al. 2010 <sup>27</sup>	Male, 37 yr	PAT, HM	NR
Kim et al. 2013 <sup>69</sup>	Female, 51 yr	Chest discomfort	Normal
Katukuri et al. 2014 <sup>70</sup>	Male, 37 yr	HF	NR
Fukino et al. 2016 <sup>71</sup>	Female, 74 yr	HF	GFR 45 ml/min
Chebib, this report	Male, 53 yr	Ventricular ectopy	GFR 43 ml/min
Chebib, this report	Female, 54 yr	HF	ESRD

BUN, blood urea nitrogen; Cre, creatinine; CVA, cerebrovascular accident; ESRD, end-stage renal disease; GFR, glomerular filtration rate; HD, hemodialysis; HF, heart failure; HM, heart murmur; NR, not reported; PAT, paroxysmal atrial fibrillation; TX, transplant; VT, ventricular tachycardia.

<sup>a</sup>Endocardial fibroelastosis.

<sup>b</sup>Separately reported by Briongos-Figuero et al.<sup>74</sup>

coexistence of ADPKD and cardiomyopathies is examined in multiple large tertiary care centers, longitudinal studies in which echocardiograms are performed in large cohorts, and whole-exome sequencing in these families would be helpful in confirming this genetic interaction.

## DISCLOSURE

All the authors declared no competing interests.

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## SUPPLEMENTARY MATERIAL

**Table S1.** Detailed clinical data of all patients with autosomal dominant polycystic kidney disease and cardiomyopathies.

**Table S2.** Summary of families and mutations in patients with autosomal dominant polycystic kidney disease and idiopathic dilated cardiomyopathy.

**Table S3.** Summary of families and mutations in patients with autosomal dominant polycystic kidney disease and hypertrophic obstructive cardiomyopathy.

**Table S4.** Summary of families and mutations in patients with autosomal dominant polycystic kidney disease and left ventricular noncompaction.

Supplementary material is linked to the online version of the paper at [www.kireports.org](http://www.kireports.org).

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