# Cardiac Manifestations of Pallister–Killian Syndrome

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Pallister–Killian syndrome (PKS) is a sporadic multisystem genetic diagnosis characterized by facial dysmorphia, variable developmental delay and intellectual impairment, hypotonia, hearing loss, seizures, differences in skin pigmentation, temporal alopecia, diaphragmatic hernia, congenital heart defects, and other systemic abnormalities. Although congenital heart defects have been described in association with PKS, the full spectrum of heart disease is still not entirely known. Here, we describe the pattern of cardiac findings of 81 probands with PKS who have had at least one cardiac evaluation, demonstrating structural heart difference in 37% of our cohort (n = 30). Septal defects such as atrial or ventricular septal defects (n = 12) were the most commonly seen congenital heart differences. Additional findings included the occasional occurrence of bicuspid aortic valve, aortic dilatation, and cardiac hypertrophy/cardiomyopathy. We suggest cardiac evaluation for all individuals with PKS at the time of diagnosis as well as subsequent longitudinal follow-up to monitor for the development of cardiomyopathy and aortic dilatation. © 2014 Wiley Periodicals, Inc.

Key words: bicuspid aortic valve; aortic dilation; 12p; isochromosome

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## INTRODUCTION

Pallister–Killian syndrome (PKS) (OMIM# 601803) is a sporadic multisystem developmental disorder characterized by facial dysmorphia (a prominent forehead with sparse temporal hair, a broad nasal bridge, telecanthus, and a wide mouth), variable developmental delay and intellectual disability, hypotonia, seizures, differences in skin pigmentation, diaphragmatic hernia, congenital heart defects, and other systemic abnormalities [Pallister et al., 1977; Teschler-Nicola and Killian, 1981; Mathieu et al., 1997; Wilkens et al., 2012]. PKS is typically caused by the presence of a supernumerary isochromosome composed of the short arms of chromosome 12 resulting in tetrasomy 12p, which is often present in a tissue-limited mosaic state [Peltomaki et al., 1987].

At the Children's Hospital of Philadelphia (CHOP) and through close collaboration with PKS family support groups, we have collected clinical information to deepen our understanding of the phenotypic spectrum of PKS. We recently published a comprehensive clinical summary of individuals with PKS [Wilkens et al., 2012]; however, the clinical information used in the Wilkens et al. article was mainly based on parental report, allowing for the possibility of recall bias. Additionally, our previous paper did not break down the individual patterns of congenital heart defects (CHD). To obtain more precise information, the parents of PKS probands were asked to submit medical records. Using the newly obtained medical records as well as both of our previously reported clinical data and information from newly enrolled probands, this article reports the phenotypic spectrum of cardiac manifestations seen in PKS.

CHD have been reported in probands with PKS with an estimated prevalence of 7–40% [Doray et al., 2002; Wilkens et al., 2012]. In addition to these structural defects, cardiomyopathy has also been reported, and recently aortic dilatation was added to the list of cardiovascular abnormalities seen in PKS [Ward et al., 1988; Jamuar et al., 2012]. The prevalence and full phenotypic spectrum of these cardiac problems, however, remains unknown. This article

reports another new case of aortic dilatation, provides detailed descriptions of four patients with cardiac defects that required close monitoring, and summarizes the patterns of cardiac abnormalities observed in patients with PKS in order to make recommendations for improving evaluation and management of these patients.

## METHODS
### Subjects

The data represent the findings from children evaluated at the PKS family support group meetings held between 2006 and 2013 and/or the outpatient clinic at CHOP and is an expansion of the cardiac data described by Wilkens et al. [2012]. Since the time of our previous article, 37 new probands have been enrolled into our study. All subjects were enrolled under an institutional review board-approved protocol of informed consent held at CHOP. At each group meeting or clinical encounter a detailed medical interview was performed. Every patient included in this study carries a clinical diagnosis of PKS and has had at least one medical interview and evaluation by a clinical geneticist. Many children attended multiple support group meetings between 2006 and 2013 and were followed longitudinally using research charts created at each patient's first visit. In 2012, a detailed cardiac questionnaire also was given to each attending family in order to supplement the collection of cardiac data, and this optional survey was completed by 23 families (see supplemental document in supporting information online). In addition, we obtained echocardiogram reports and cardiology notes when available.

## RESULTS
### Patients

We collected patient data from 90 probands (40 males, 50 females) with PKS and also obtained detailed cardiac questionnaires filled out by 23 of their families who attended the PKS family conference in 2012 (Fig. 1). The cohort we used in this study was created from 81 of these 90 probands who had at least one formal cardiac evaluation (Fig. 1). Structural heart differences were found in 30 of 81 probands (37%: 11 males and 19 females). Table I summarizes the cardiac findings in our patient cohort compared to the prevalence reported in the general population. The cardiac finding reported with the highest frequency was PFO (n = 13) followed by ASD (n = 9) and PDA (n = 8). Other findings included hypertrophy (n = 5), VSD (n = 3), and aortic dilatation (n = 1), and we also found four patients to have bicuspid aortic valve (BAV).

Table II demonstrates the patterns of cardiac findings found within our cohort. Of the 13 patients with PFO, 8 were isolated findings while 5 also reported having a history of PDA, ASD, VSD or BAV. The most common patterns of cardiac structural difference were isolated PFO (n = 8), isolated ASD (n = 4), and isolated BAV (n = 3). Of the 30 patients with cardiac abnormalities, 30% had two or more defects (n = 9). Cardiology notes and/or echocardiogram reports were available for 12 of these 30 patients with cardiac abnormalities.
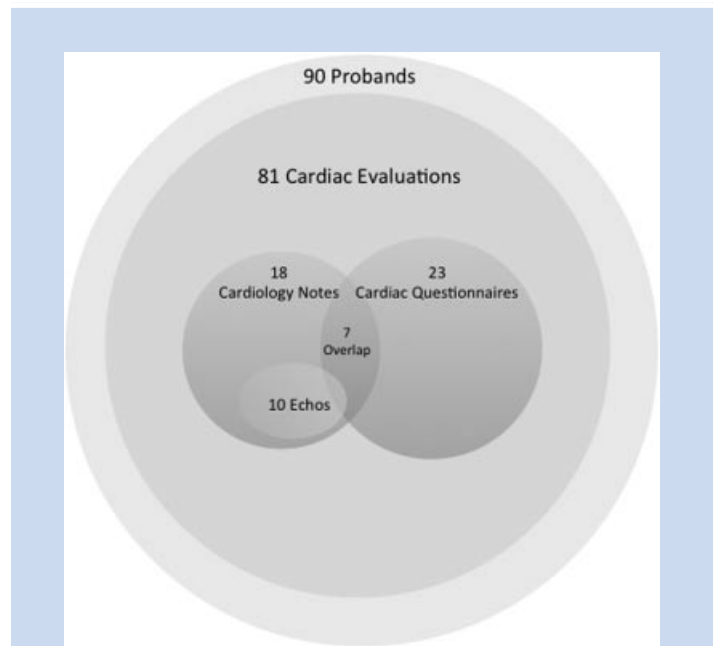


FIG. 1. Venn diagram illustrating the relationship between different subgroups of our cohort. Data were collected on 90 total probands with PKS, and 81 of these patients had at least one echocardiogram and were included in our cohort. In this cohort of 81 probands, 23 filled out a voluntary cardiac questionnaire and 18 submitted cardiology notes. Seven patients both provided a cardiology note and filled out the cardiac questionnaire, and echocardiogram results were available from two of these seven patients.

## Detailed Cardiac Evaluations

A cardiology note was obtained for 18 out of 81 probands (Fig. 1). Of these 18 patients, 10 had also submitted at least 1 echocardiogram result. Table III summarizes our findings from this subgroup

TABLE I. Spectrum of Cardiac Phenotype in PKS Represented by 30 Probands With PKS

| CHD | No. of CHOP cases | Percent of total cohort | Prevalence in general population% |
|---|---|---|---|
| ASD | 9 | 11 | 0.2 |
| VSD | 3 | 4 | 0.3 |
| Hypertrophy | 5 | 6 | |
| Bicuspid Ao. valve | 4 | 5 | 1 |
| SVC syndrome | 1 | 1 | |
| Aortic dilatation | 1 | 1 | |
| PFO | 13 | 16 | 25 |
| PDA | 8 | 10 | 0.1 |

PFO, patent foramen ovale; PDA, patent ductus arteriosus; ASD, atrial septal defect; VSD, ventricular septal defect; BAV, bicuspid aortic valve; SVC, superior vena cava.
Nine of the 30 patients represented by this data had two or more cardiac defects. Prevalence references: Braverman [2011] and van der Linde et al. [2011].

**TABLE II. The Patterns of Cardiac Abnormalities in Our PKS Cohort of 81 Patients**

| CHD | No. of CHOP cases | Percent of cohort |
|---|---|---|
| Isolated PFO | 8 | 10 |
| Isolated ASD | 4 | 5 |
| Isolated BAV | 3 | 4 |
| Isolated PDA | 3 | 4 |
| Isolated hypetrophy[a] | 2 | 2 |
| PDA, ASD | 2 | 2 |
| Isolated VSD | 1 | 1 |
| PFO, BAV | 1 | 1 |
| PFO, PDA, VSD | 1 | 1 |
| PFO, ASD, SVC | 1 | 1 |
| PFO, PDA | 1 | 1 |
| VSD, LVH | 1 | 1 |
| ASD, hypertrophy | 1 | 1 |
| PFO, PDA, ASD, hypertrophy | 1 | 1 |
| Totals | 30 | 37 |

PFO, patent foramen ovale; PDA, patent ductus arteriosus; ASD, atrial septal defect; VSD, ventricular septal defect; BAV, bicuspid aortic valve; LVH, left ventricular hypertrophy; SVC, superior vena cava syndrome.
[a]Hypertrophy: one case of isolated LVH at birth (Patient 32 with later normal echo), one case of isolated right septal hypertrophy with mild hypertrophic cardiomyopathy (Patient 8).

of 18 patients, which includes probands both with and without CHD (12 of these 18 patients overlap with the group of 30 that have cardiac abnormalities). Complex heart malformations or cyanotic heart defects like tetralogy of Fallot were not reported in our cohort of 81; however, based on the detailed cardiology notes and echocardiograms available for these 18 patients, 4 were found to have had cardiac abnormalities that required close medical attention. A brief clinical description of these four cases is provided below.

Patient 8 (Fig. 2A) was diagnosed with mild hypertrophic cardiomyopathy at 15 months of age. She had a history of intestinal malrotation and diaphragmatic eventration and was diagnosed with PKS at 17 months of age when the chromosome analysis of a skin biopsy sample demonstrated mosaic isochromosome 12p. A screening cardiac evaluation demonstrated mild hypertrophic cardiomyopathy, although she did not have any cardiovascular symptoms. At the last evaluation at the age of 27 months, although she remained asymptomatic, an echocardiogram continued to show a mildly hypertrophic heart with no evidence of left ventricular outflow tract obstruction. Her family history was negative for cardiomyopathy or sudden death.

Patient 71 had a moderate-to-large secundum ASD and pulmonary hypertension. A cardiac anomaly was first detected by prenatal ultrasonography and was confirmed postnatally. Pulmonary hypertension was thought to be secondary to the ASD. An echocardiogram at 19 months showed a 1.2-cm secundum ASD with

**TABLE III. Pattern of CHD in PKS Whose Cardiology Notes and/or Echo Results Were Available**

| ID | Sex | Mosaicism (%) | Age at PKS diagnosis | Tissue demonstrated i(12p) | Age at cardiac evaluation | Detected abnormalities | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | PFO | PDA | ASD | VSD | LVH | BAV | DilAo | DilPA | Septal | Others |
| 31 | F | 80 | 8 months | Buccal smear | Neonatal | | | [+] | | | | | | | |
| 29 | M | N/A | Prenatal | Amniocentesis | 4 days | [+] | | | | | [+] | | | | |
| 10 | F | 36 | 6 years | Skin | 1 month | [+] | [+] | | | | | | | | SVC |
| 67 | F | 100 | Prenatal | Amniocentesis | 1 month | [+] | [+] | | | | | | | | |
| 16 | M | 86 | 3 months | Skin | 4.5 months | [+] | | | | | | | | | |
| 81 | F | 1.5 | 6 months | Blood | 10 months | | | | | | | | | | |
| 73 | M | 0.8 | 10 months | Blood | 11 months | | | [+] | | | | | | | |
| 8 | F | 8 | 1 year | Skin | 15 months | | | | | | | | | [+] | |
| 48 | M | N/A | N/A | N/A | 16 months | | | | | | | | | | |
| 49 | M | 71 | 4 years | Skin | 18 months | | | | | | | | | | |
| 85 | F | 5 | 2 days | Blood | 2 days | [+] | [+] | [+] | | [+] | | | | | |
| | | | | | 6.5 months | [+] | [+] | [+]a | | [+] | | | | | |
| | | | | | 18 months | [+] | [+] | [+]a | | [+] | | | | | |
| 71 | F | 1 | 1 day | Blood | 20 months | | | [+] | | | | | [+] | | |
| 61 | F | 41 | 2 years | Skin | 30 months | | | | | | | | | | |
| 19 | M | 85 | 5 months | Skin | 6 years | [+] | | | | | | | | | |
| 74 | F | N/A | Prenatal | Amniocentesis | 6 years, 6 months | | | | [+]a | [+] | | | [+] | | |
| | | | | | 7 years, 4 months | | | | [+]a | [+] | | | [+] | | |
| 76 | F | N/A | N/A | N/A | 13 years | | | | | | | | | | |
| 23 | M | N/A | Prenatal | N/A | 14 years | | | | | | | | | | |
| 80 | F | N/A | N/A | N/A | 20 years | | | | | | [+] | | | | |

Note that 12 of these patients overlap with our subgroup of 30/81 (37%) that had structural heart differences. PFO, patent foramen ovale; PDA, patent ductus arteriosus; ASD, atrial septal defect; VSD, ventricular septal defect; LVH, left ventricular hypertrophy; BAV, bicuspid aortic valve; DilAo, dilated aorta; DilPA, dilated pulmonary artery; Septal, septal hypertrophy; SVC, superior vena cava.
N/A, specific information not available.
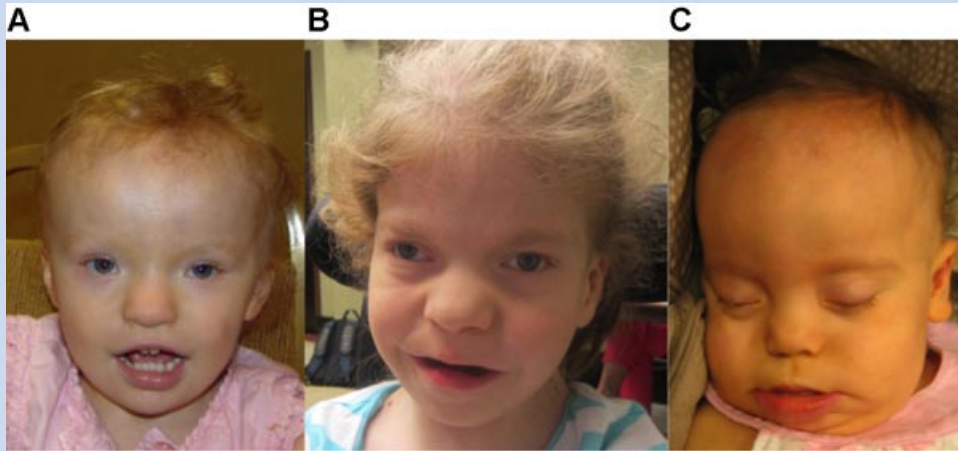[a]Already closed spontaneously at time of echo or cardiology report.

**FIG. 2. Facial characteristics of probands with PKS. (A) Patient 8, (B) Patient 74, and (C) Patient 85. Note prominent forehead, upslanted palpebral fissures, bulbous nasal tip, and thin upper lip in these probands [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com].**

significant left-to-right shunting, moderate right atrium and right ventricle dilatation, and moderate dilatation of the main and branch pulmonary arteries. A main pulmonary artery Z-score was 5.09 (diameter = 2.01 cm). Although she remained asymptomatic at the age of 22 months, this patient was monitored monthly by a cardiologist. The diagnosis of PKS was made when she was 1 day old with peripheral blood chromosome analysis showing 1% of isochromosome 12p cells, which was also confirmed by array-comparative genomic hybridization (CGH).

Patient 74 (Fig. 2B) had aortic dilatation and a history of a spontaneously closed VSD. When she was 5 years old, she developed a cardiac arrhythmia with bigeminy and decreased left ventricular function, which were thought to be a side effect of the ketogenic diet she was being administered for the treatment of intractable myoclonic seizure. She was receiving a ketogenic diet for 3½ years before she developed cardiomyopathy. After discontinuation of the ketogenic diet, her ventricular function normalized. Hence, it was concluded that left ventricular dysfunction was most likely a side effect of the ketogenic diet rather than a primary cardiomyopathy [Best et al., 2000; Bergqvist et al., 2003]. When the patient was 6½ years old, her ascending aorta had a diameter >99.99th centile (Z score = 5.26, diameter = 2.7 cm), requiring close monitoring of the aortic diameter. At age 7 her latest echocardiogram revealed moderate to severe dilatation of the ascending aorta with effacement of the sinotubular junction and mild aortic insufficiency with a mildly dysplastic aortic valve. Her right and non-coronary aortic cusps appeared to be thickened but opened normally. No aortic stenosis was documented. The Z-score of the ascending aorta diameter was 7.1 (diameter = 3.1 cm), suggesting a worsening of the aortic dilatation. The last available echocardiogram showed a normal interventricular septum, left ventricular posterior wall, and left ventricular mass. No other aortic abnormalities were demonstrated. The diagnosis of PKS was made prenatally by the detection of isochromosome 12p on amniocentesis at 18 weeks of gestation,

and she has an unremarkable family history of cardiac disease or sudden death.

Patient 85 (Fig. 2C) had biventricular hypertrophy, a fenestrated ASD that closed spontaneously, and PFO. Biventricular hypertrophy was detected at 2 weeks of age, and at the last clinic visit at the age of 18 months, echocardiography still indicated mild concentric left ventricular hypertrophy with remaining PFO, although the ASD had closed. She remained asymptomatic from a cardiovascular standpoint. It was recommended that the patient visit a cardiologist every 2 years to monitor the ventricular hypertrophy. The diagnosis of PKS was made at the age of 1 week after the demonstration of isochromosome 12p from her peripheral blood sample.

None of the 81 probands had a past medical history of cardiac surgery. However, the cardiology notes of Patient 71 reported that surgical intervention likely would be needed in the future to correct an ASD. This same patient had right heart overload with a dilated pulmonary artery and was scheduled to have cardiac catheterization within 5 months to evaluate pulmonary pressure.

## DISCUSSION

Here, we report on the spectrum of cardiac phenotypes associated with PKS and demonstrate that PFO, ASD, and PDA represent the predominant cardiac findings in PKS, which is consistent with our previous report [Wilkens et al., 2012]. We also demonstrated that VSD, cardiac hypertrophies, and BAV are occasionally noted in the probands with PKS. In addition, we describe a case of aortic dilatation associated with PKS, a defect which has only been previously reported once. Recognizing that it can be difficult to distinguish between PFO and ASD (especially during infancy), we included all PFO findings in this report even though it is a common finding in the general population. Unfortunately, due to the nature of the study, we were unable to distinguish between pathological PFO and isolated PFO that closed spontaneously. Although we did

not have echocardiogram reports or cardiology notes available for the majority of our patients, all probands included in our cohort of 81 had at least one baseline cardiology evaluation in the form of an echocardiogram. Interestingly, we did not notice any correlation between the mosaic ratio and CHD patterns (Table III).

Septal defects continue to be a major form of CHD in PKS with 12 of 81 individuals (14.8%) in our cohort manifesting these abnormalities: 9 ASD and 3 VSD. This frequency is comparable with a previous literature search described by Wilkens et al. (9 of 77 patients had septal defects: 4 ASD and 5 VSD). While 37% of our cohort (n = 30) had cardiac differences, if we exclude the probands with isolated PFO (n = 8), isolated PDA (n = 3), and the PFO + PDA pattern (n = 1) due to their unclear pathogenicity, then we estimate the overall prevalence of CHD in our cohort to be 22% (n = 18) which is higher than the estimated <1% prevalence of CHD in the general population [Reller et al., 2008; Moons et al., 2009; van der Linde et al., 2011]. Such a high prevalence warrants a screening echocardiogram at the time of the initial PKS diagnosis.

Recently, Jamuar et al. [2012] described a patient with PKS who had dilatation of the thoracic aorta and main pulmonary artery, and in our cohort, we also identified one case with aortic dilatation in the same location. The etiology of aortic dilatation in PKS is unknown at this point, and we have not identified an association between aortic dilatation and BAV. We will continue to follow our cohort closely to monitor the development of aortic dilatation.

The other previously reported potentially life-threatening cardiac complication in PKS is cardiomyopathy [Ward et al., 1988]. In our cohort, no patients with severe cardiomyopathy were identified; however, there was one patient with mild hypertrophic cardiomyopathy (Patient 8). This patient was found to have borderline septal thickness, as indicated on an echocardiogram at 15 months of age, and continued to have a mildly hypertrophic heart at the age of 2 years 4 months. Since this patient did not have concurrent structural heart anomalies, the mechanism of cardiac hypertrophy was not due to compensatory changes related to a CHD. There were four other patients with cardiac hypertrophy in our cohort, although the diagnosis of cardiomyopathy has not been made. Patient 85 had septal and posterior wall hypertrophy but also had coexisting structural heart anomalies that may have caused compensatory hypertrophy, although the ASD is unlikely to have caused this hypertrophy. Two of the other patients had left ventricular hypertrophy. We recognize that different cardiologists evaluated each patient, and therefore it is unclear how they differentiated between the diagnoses of cardiac hypertrophy and hypertrophic cardiomyopathy.

In our cohort, no patients have required surgical intervention to date, and this finding may imply that serious CHDs are rare in PKS, at least in those who survive the neonatal period. However, this result should be interpreted with caution because of the bias inherent to the method of patient enrolment in this study. The more severe cardiac phenotype of PKS is probably underrepresented in our cohort as individuals who are affected with severe heart defects may not survive long enough or may not be healthy enough to attend a PKS family meeting where our patients were enrolled. In fact, previously, tetralogy of Fallot, Ebstein anomaly, hypoplastic left heart syndrome, and complex CHD were reported in associa-

tion with PKS, and these severe CHDs are mainly reported in prenatally ascertained PKS cases [Gilgenkrantz et al., 1985; Wilson et al., 1994; Grech et al., 1999; Langford et al., 2000; Li et al., 2000; Doray et al., 2002]. Therefore, the severe end of the cardiac phenotypic PKS spectrum remains to be determined. Our previous literature review found the frequency of complex heart anomalies to be low except for severe heart defects seen prenatally, supporting our conclusion that serious CHDs requiring surgical intervention may be rare in PKS individuals who survive the neonatal period.

Another limitation of our study was recall bias, because the clinical information was mainly collected from forms completed by the families. In addition, not all of the families answered the cardiac questionnaires, and cardiac evaluation documents (echocardiogram results and cardiology notes) were not obtained by all of the families who attended the family meeting. These facts can cause selection bias; however, it is also possible that families with severely affected children are more likely to return responses, causing bias that skews toward the severe phenotype.

The molecular mechanisms of CHD and cardiac abnormalities in PKS remain unknown. Several genes on 12p—including FOXM1, FOXJ2, and KRAS—are known to be involved in heart formation during embryogenesis, and extra copies of these genes may play a role in the development of the cardiac phenotype seen in PKS [Niihori et al., 2006; Schubbert et al., 2006; Martin-de-Lara et al., 2008; Bolte et al., 2011]. Multiple copies of these three genes may play a role in the development of CHD and cardiac hypertrophy seen in PKS. Extra copies of 12p genes could also cause the PKS cardiac phenotype by modulating downstream gene expression on other chromosomes. Previously, we demonstrated that skin fibroblast samples from patients with PKS showed significantly suppressed expression levels of GATA6, a gene located on chromosome 18 that encodes a transcription factor which regulates the expression of multiple myocardial genes during cardiogenesis [Kaur et al., 2010]. Mutations of GATA6 have been found in patients with a wide variety of cardiac anomalies, including ASD as well as BAV [Kodo et al., 2009; Lin et al., 2010; Maitra et al., 2010]. These cardiac defect patterns are occasionally seen in individuals with PKS, which may be mediated by suppression of the gene expression level of GATA6. We acknowledge that suppressed expression may not lead to the same clinical phenotype resulting from the mutation of GATA6; however, further studies are needed.

In summary, we demonstrated that septal defects represent one of the most commonly associated cardiac abnormalities in PKS but also observed the rare occurrence of aortic dilatation and cardiac hypertrophy. Based on these findings, we recommend cardiac evaluation at the time of PKS diagnosis and subsequent longitudinal follow-up to monitor for the development of cardiac hypertrophy and aortic dilatation.

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## SUPPORTING INFORMATION

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