A large familial pathogenic Plakophilin-2 gene (*PKP2*) deletion manifesting with sudden cardiac death and lone atrial fibrillation: Evidence for alternating atrial and ventricular phenotypes

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Introduction

A single genetic culprit giving rise to varied forms of ventricular cardiomyopathy is a well-documented phenomenon and likely arises, at least in part, secondary to a combination of genetic modifiers and environmental factors.[1,2] Recent work has begun to implicate cardiomyopathy genes in "lone" atrial fibrillation (AF), suggesting that atrial cardiomyopathy may be a subphenotype of the arrhythmia.[3–6] It is conceivable that within certain patients and families, cardiomyopathy gene mutations may preferentially manifest with atrial rather than ventricular phenotypes. In the current report, we describe a family with a large pathogenic *PKP2* deletion, implicated as the probable cause of sudden death in the proband, that appeared to manifest with predominant atrial phenotypes in other family members.

KEY TEACHING POINTS

- Pathogenic mutations associated with arrhythmogenic right ventricular cardiomyopathy may manifest with isolated atrial phenotypes, potentially secondary to differential penetrance in the atria and ventricles.
- Atrial cardiomyopathy is a potential genetic subphenotype of atrial fibrillation (AF), a concept that may provide insight into the natural history of the arrhythmia and its response to treatment.
- The increased prevalence of AF observed in genetic ventricular cardiomyopathies may be secondary to a common underlying genetic culprit.

Case report

A 20-year-old athletic man with no prior cardiac history and no family history of sudden death died during sleep. Three years prior to his death he had undergone a surface electrocardiogram (ECG) (Figure 1A) and echocardiogram following an incidental finding of bradycardia. Aside from sinus bradycardia that was likely secondary to his athletic status, both investigations were within normal limits (Table 1). Cardiac autopsy was suggestive of both chronic and subacute myocarditis. Multiple minute foci of active lymphohistiocytic myocarditis, along with overlapping acute myonecrosis, cardiomyocyte dropout, and interstitial fibrous tissue deposition were observed in a classical subepicardial distribution. Given the nature of the fibrous tissue identified, the inflammatory process was felt to likely have been present for months prior to death. A molecular autopsy was initially deferred owing to a presumptive diagnosis of myocarditis.

Cascade screening of family members was subsequently initiated to evaluate the possibility that the sudden death in the proband may have been secondary to an underlying genetic etiology. Evaluation of the proband's asymptomatic 26-year-old brother (Figure 2; II-3) revealed AF on surface ECG (Figure 1B) that was persistent on Holter monitoring, and echocardiography demonstrated moderate biatrial dilation. Aside from these atrial abnormalities, his surface ECG, signal average ECG, Holter monitor, echocardiogram, and cardiac magnetic resonance imaging (MRI) were otherwise within normal limits (Table 1). Given that persistent AF is a very rare clinical finding at 26 years of age, it was

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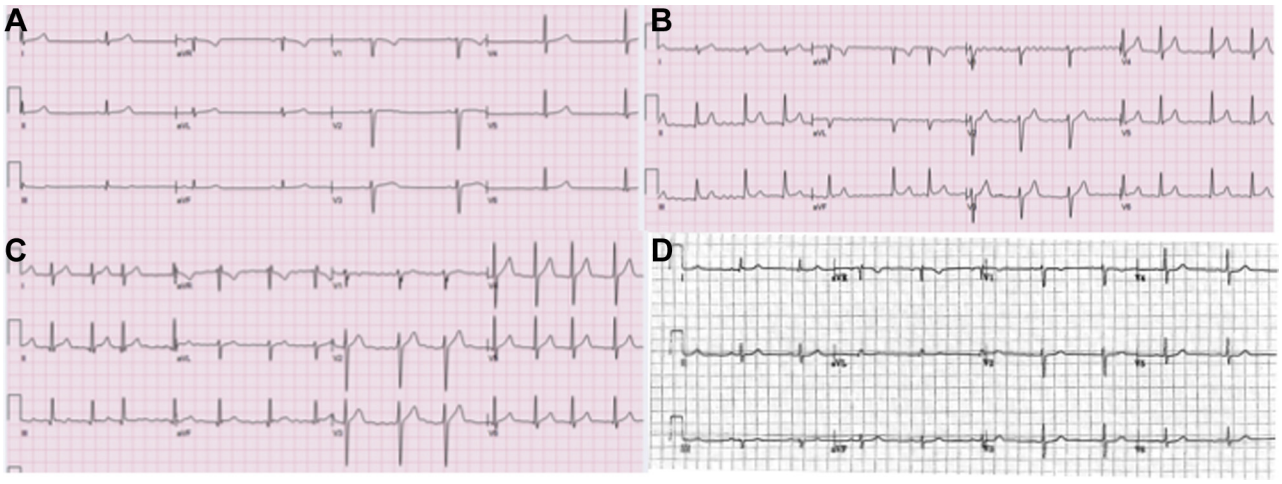

Figure 1 Twelve-lead surface electrocardiograms of family members possessing the large *PKP2* deletion. **A:** Deceased proband. **B, C:** Proband's brothers with atrial fibrillation, aged 26 (**B**) and 24 (**C**). **D:** Proband's mother.

hypothesized that his arrhythmia and the sudden death of his brother may have been secondary to a common underlying genetic culprit.

The patient underwent genetic evaluation with a commercial arrhythmia panel involving 30 genes (GeneDx, Gaithersburg, MD; full list provided in Supplemental Appendix). No pathogenic variants were identified on direct DNA sequencing; however, targeted array analysis revealed a large deletion involving exons 4 to 14 of the *PKP2* gene (GRCh37 genomic coordinates: chromosome 12:32,944,898-33,022,251) (Figure 3). Consistent with prior reports of large *PKP2* deletions being causative for arrhythmogenic right ventricular cardiomyopathy (ARVC),[7–9] the deletion was assumed to be pathogenic and was used for cascade screening to attempt to clarify its role in the sudden death of the proband and its potential impact on other family members.

Subsequent evaluation identified the *PKP2* deletion in the deceased proband, a 24–year-old brother, and the 45-year-old mother (Figure 2 and Table 1). The father is estranged from the family and was not accessible for clinical or genetic screening. Clinical evaluation of the 24-year-old brother (Figure 2; II-2) was initially within normal limits; however, at 27 years of age he was diagnosed with asymptomatic paroxysmal AF. Echocardiography was reported as normal, including normal biatrial size, while cardiac MRI revealed mild biventricular dilation and normal function. The mild biventricular dilation was considered potentially reflective of athlete's heart, given that he was a competitive football player. Results of Holter monitoring are summarized in Table 1, while the remainder of his investigations, including surface ECG (Figure 1C), were within normal limits. Aside from his genetic mutation, he had no features that met Major or Minor ARVC Task Force criteria.[10]

Table 1 Clinical and genetic features of family members possessing the large *PKP2* deletion

Family member*	Age†	Arrhythmia	ECG	Treadmill test	24 Hour Holter monitoring	SAECG LP	Echo	cMR
Proband (II-1)	20	SCD	Sinus bradycardia	NP	NP	NP	Normal	NP
Brother (II-2)	26	Persistent AF	AF	AF	Persistent AF	-ve	Biatrial dilation	Biatrial dilation
Brother (II-3)	27	Paroxysmal AF	Normal	AF developed during recovery	68 PACs, 8 atrial couplets, and 43 PVCs	-ve	Normal	Mild biventricular dilation‡
Mother (I-1)	45	Nil	Normal	PVCs, ventricular couplets, and short runs of AT	58 PACs, 2 atrial couplets, short runs of AT, and 16 PVCs	-ve	Normal	Normal

AF = atrial fibrillation; AT = atrial tachycardia; cMR = cardiac magnetic resonance imaging; ECG = electrocardiogram; Echo = echocardiogram; LP = late potentials; NP = not performed; PAC = premature atrial contraction; PVC = premature ventricular contraction; SAECG = signal average electrocardiogram; SCD = sudden cardiac death.

*Roman and Arabic numerals correspond to generation and pedigree number within a generation, as shown in Figure 2. The father is estranged from the family and was unavailable for evaluation.

†Age in years at onset of arrhythmia, if present, or initial evaluation.

‡Mild biventricular dilation felt to potentially be secondary to athlete's heart.

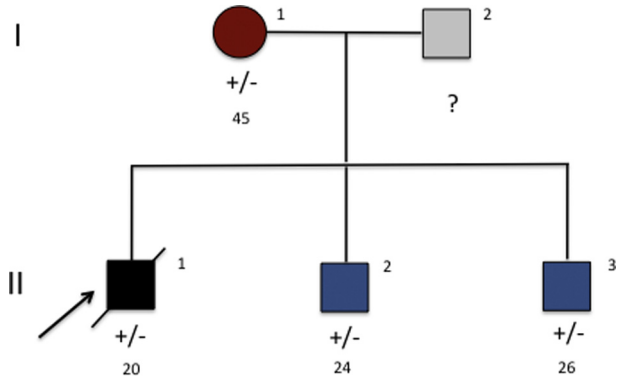

Figure 2 Kindred structure. Black, navy blue, and red fill denote sudden cardiac death, atrial fibrillation, and nonsustained atrial arrhythmias, respectively. The family member inaccessible for evaluation is shaded in gray. Genotype is denoted as +/- and age at evaluation or at time of death is provided below.

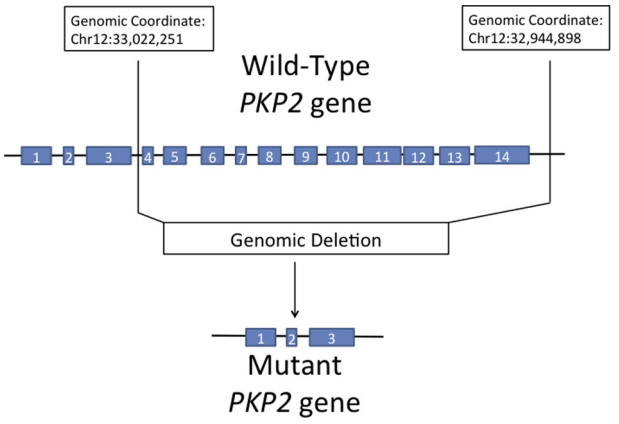

Figure 3 Wild-type *PKP2* gene (14 exons) and the large familial genomic deletion resulting in a truncated gene limited to exons 1–3. GRCh37 genomic coordinates.

Clinical screening of the 45-year-old mother (Figure 2; I-1) possessing the *PKP2* deletion revealed a normal ECG (Figure 1D), signal average ECG, echocardiogram, and cardiac MRI. Treadmill testing demonstrated frequent isolated premature ventricular contractions and ventricular couplets during exertion that possessed a left superior axis and left bundle branch block morphology, suggesting an origin from the inferior right ventricle, that resolved in recovery. Multiple runs of atrial tachycardia lasting up to 12 beats occurred during the recovery period. Twenty-four-hour ambulatory monitoring revealed premature atrial contractions, atrial couplets, and 3 nonsustained runs of atrial tachycardia lasting up to 11 beats, along with very rare isolated premature ventricular contractions (Table 1).

During 4 years of follow-up, none of the living family members possessing the *PKP2* deletion developed clinical features sufficient to meet Major or Minor Task Force Criteria for ARVC.

Discussion

Our report of a family with a large *PKP2* deletion is, to our knowledge, the first to suggest that a gene associated with ARVC may potentially give rise to a phenotype of lone AF. Given that genes causative for ventricular cardiomyopathy may serve similar functions within the atria, alternating atrial and ventricular phenotypes may arise secondary to differential penetrance. In an analogous fashion, penetrance of a mutation in both chambers may account for the increased prevalence of AF observed in ventricular cardiomyopathies.[11,12] Atrial cardiomyopathy being reflective of a genetic subphenotype of AF has been suggested by recent studies implicating the *MYL4*, *MYH6*, and *PLEC* genes in the pathogenesis of the arrhythmia.[3–6]

The relevance of the large *PKP2* deletion to the clinical phenotypes of the family members, although not definite, is supported by a combination of their clinical and genetic features. The sudden death of the proband was initially felt to be secondary to a malignant ventricular arrhythmia arising from a myocarditis; however, recognition that he possessed a pathogenic *PKP2* mutation strongly suggests that the inflammatory and fibrotic changes observed on autopsy may have been secondary to early manifestations of ARVC.[13] The *PKP2* deletion being responsible for the atrial arrhythmias identified in the family members is supported by the absence of another genetic culprit identified in a large arrhythmia panel and the observed genotype-phenotype segregation.

Although the living family members carrying the *PKP2* deletion have yet to manifest definite clinical features associated with ARVC, the ventricular ectopy observed in the mother and younger brother may be reflective of an emerging phenotype. Consistent with clinical guidelines, ongoing surveillance for development of an ARVC phenotype is merited in all carriers of pathogenic mutations.[14]

Conclusion

The present report, to our knowledge, represents the first description of a pathogenic mutation associated with ARVC manifesting as apparent lone AF. The observations from our reported family serve to highlight that mutations associated with ventricular cardiomyopathy may alternately manifest with atrial phenotypes, potentially in isolation. They also serve to reinforce the notion that atrial cardiomyopathy may represent a genetic subphenotype of AF.

Appendix

Supplementary data

Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.hrcr.2018.07.009.

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