


Cardiomyopathy in limb girdle muscular dystrophy R9, *FKRP* related

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Abstract

Introduction: Reported frequencies of cardiomyopathy in limb girdle muscular dystrophy R9 (LGMDR9) vary. We describe the frequency and age at onset of cardiomyopathy in an LGMDR9 cohort.

Methods: Echocardiograms from 56 subjects (157 echocardiograms) with LGMDR9 were retrospectively reviewed. The cumulative probability of having an abnormal echocardiogram as a function of age was assessed by survival analysis for interval-censored data by genotype. Correlations between cardiac and clinical function were evaluated.

Results: Twenty-five (45%) participants had cardiomyopathy. The median age at first abnormal echocardiogram for subjects homozygous for the c.826C>A variant was 54.2 y compared to 18.1 y for all other fukutin-related protein (*FKRP*) genotypes ($P < .0001$). There was a weak correlation between ejection fraction and 10-Meter Walk Test speed ($r = 0.25$), but no correlation with forced vital capacity ($r = 0.08$).

Discussion: Cardiomyopathy is prevalent among those with LGMDR9 and occurs later in subjects homozygous for the c.826C>A mutation. These data will help to guide surveillance and management.

KEYWORDS

All neuromuscular disease, cardiomyopathy, dystroglycanopathy, *FKRP*, limb-girdle muscular dystrophy, muscular dystrophy

Abbreviations: 10MWT, 10-Meter Walk Test; CMR, cardiac magnetic resonance imaging; CI, confidence interval; MDC1C, congenital muscular dystrophy; EF, ejection fraction; FVC, forced vital capacity; *FKRP*, fukutin-related protein; LV, left ventricle; LGMDR9, limb girdle muscular dystrophy type R9; SF, shortening fraction.

1 | INTRODUCTION

Hypoglycosylation of alpha-dystroglycan, a component of the dystrophin-glycoprotein complex, is the hallmark of a subset of muscular dystrophies collectively known as the dystroglycanopathies.¹⁻³ Dystroglycanopathies are caused by mutations in one of >18 known genes. The gene most commonly associated with disease is fukutin-

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related protein (*FKRP*). *FKRP* mutations rarely cause congenital muscular dystrophy (MDC1C), and more typically cause limb girdle muscular dystrophy type R9 (LGMDR9), which is one of the more common types of LGMD.⁴⁻¹⁰ There is a common founder *FKRP* mutation, c.826C>A (p. L276I), which is present in at least one copy in most patients with LGMDR9.^{8,11}

Glycosylated α -dystroglycan is present in cardiac as well as skeletal muscle.² In mice, glycosylated α -dystroglycan protects against cardiomyopathy and prevents the spread of myocardial damage to adjacent cardiac myocytes after exercise-induced stress.¹² Cardiomyopathy has been variably reported in patients with mutations in *FKRP*.^{11,13-19} Among published cohorts, reported frequencies of cardiac abnormalities have ranged from 10% to 83%.^{11,14,17-23} Furthermore, published information is inconsistent regarding the relationship between development of cardiomyopathy and genotype. One study suggested that individuals homozygous for the common c.826C>A *FKRP* mutation are at greater risk of developing cardiomyopathy than those with compound heterozygous mutations, while another study proposed the reverse relationship.^{14,22} Additionally, little is known about the relationship of cardiomyopathy with age, sex, and muscle disease severity.¹⁴

We reviewed echocardiogram data from a cohort of children and adults with mutations in *FKRP* to determine frequency of cardiomyopathy and association between cardiomyopathy and genotype, sex, motor function, and respiratory function.

2 | METHODS

2.1 | Participants

Inclusion criteria for this analysis are participation in the University of Iowa Wellstone Center dystroglycanopathy natural history study, which included functional motor evaluation (clinicaltrials.gov NCT00313677), *FKRP* mutations and clinical phenotype consistent with LGMDR9, and echocardiogram images or reports available for review (see Figure 1). The natural history study began in 2006 and continues to enroll. Data collection for this study ended November 2019. Potential participants were excluded if they were taking cardio-protective medications prior to their first abnormal echocardiogram. Participants were not excluded if they were taking medications specifically for documented hypertension. If the indication for cardiac medications was unclear, they were excluded from the study. Participants in this analysis are from across the United States and Canada.

2.2 | Approval and patient consent

Institutional Review Board approval was obtained for all recruitment and data collection methods. Written informed consent was obtained from all participants or their legal guardians. Additional consent was obtained for review of medical records.

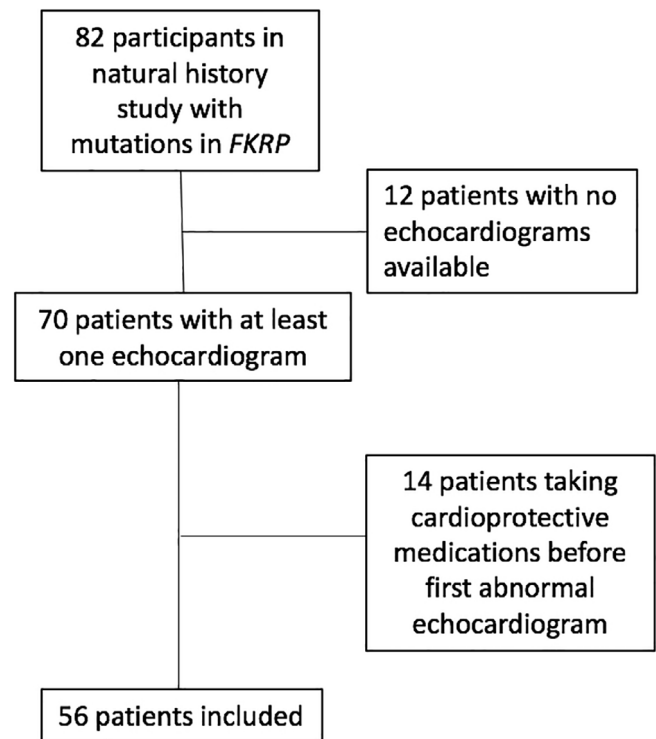


FIGURE 1 Flowsheet diagram of subject inclusion

2.3 | Echocardiogram review

Echocardiogram reports and images were requested from participants' medical centers. From 2006-2010, echocardiograms were completed as part of the natural history study. After 2010, echocardiograms were obtained only when indicated as part of clinical care. To determine reliability of echocardiogram reports, two cardiologists (B.N. and B.R.) independently reviewed the 58 echocardiogram films that were available to us from participants with any dystroglycanopathy. They evaluated ejection fraction (EF), shortening fraction (SF), left ventricle (LV) size, and characteristics of wall motion for each echocardiogram. Each echocardiogram was assessed as normal or abnormal. The reviewers were blinded to genetic diagnosis and original interpretation of the study. If disagreement on EF or SF values affected the classification of an echocardiogram as normal or abnormal, a third cardiologist (E.E.) reviewed the film. The kappa statistic was used to measure inter-rater agreement between the reviews of cardiologists at the University of Iowa and the original reports. A kappa statistic of 0.83 validated the agreement. Based on the kappa statistic, we determined that review of external reports was an acceptable surrogate for independently reviewing all images.

When the echocardiogram image was unavailable, we extracted the data from the report. When both image and report were available, interpretation of a locally obtained film took precedence over the report. An echocardiogram was classified as normal if wall motion, subjective ventricular contractility EF, and SF were normal. Normal was defined as: EF \geq 55% and SF \geq 28% for patients aged 15 y and older, 31%-41% for patients aged 4-14 y, 33%-43% for patients aged

TABLE 1 Participant demographics

Genotype	Study population (%)	Male (%)	Length of follow-up, y								
			All subjects			With abnormal echo			No abnormal echo		
			Median (IQR)	n	Median (IQR)	Range	n	Median (IQR)	Range		
c.826C>A, c.826C>A	29 (52)	12 (41)	33.3 (27.0-41.4)	9	33.3 (31.1-39.7)	18.0-54.2	20	33.1 (17.6-43.8)	10.6-62.3		
Other <i>FKRP</i> genotypes	27 (48)	15 (56)	15.4 (9.2-19.8)	16	17.2 (12.1-21.5)	3.6-44.5	11	10.3 (7.1-17.2)	7.0-48.7		
Total	56	27 (48)	20.6 (12.2-36.2)	25	21.3 (15.9-33.3)	3.6-54.2	31	19.8 (11.6-41.4)	7.0-62.3		

TABLE 2 Echocardiogram results

Genotype	Number of participants	Number of echocardiograms reviewed	With abnormal echocardiogram count (%)	Age at first abnormal echocardiogram, y Median (95% CI)
c.826C>A, c.826C>A	29	86	9 (31)	54.2 (39.7-54.2)*
Other <i>FKRP</i> genotypes	27	71	16 (59)	18.1 (14.3-18.1)*
Total	56	157	25 (45)	33.3 (18.0-54.2)

Abbreviation: CI, confidence interval.

*Significantly different between genotypes.

2-3 y, and 35%-45% for infants. Echocardiograms that did not meet these criteria were denoted as abnormal. We identified participants as having cardiomyopathy if they had at least one abnormal echocardiogram. When a report had discrepant information (eg, normal EF but comment of low LV contractility) that made classification unclear, all available information was reviewed by a cardiologist (B.R.) for categorization.

2.4 | Clinical information

Demographics and genetic diagnosis were collected from the natural history study. Participants completed seated forced vital capacity (FVC) percent predicted and 10-Meter Walk Test (10MWT) at each annual research visit. FVC percent predicted was measured by either a physical therapist or nurse trained in spirometry. The best of three tests was recorded. The 10MWT measured the time taken for ambulatory participants to walk or run 10 m at their fastest self-identified speed without the use of an assistive device. 10MWT times were converted to speeds, meters/second.

For correlation with cardiac function, we recorded seated FVC percent predicted and 10MWT speed from the visit that coincided most closely with the date of the first abnormal echocardiogram (for those with cardiomyopathy), or from the visit that coincided most closely with the last normal echocardiogram (for those without cardiomyopathy). For individuals with multiple echocardiograms, we recorded seated FVC percent predicted and 10MWT speed within 6 mo of each available echocardiogram. FVC was measured in liters using a Renaissance II or MicroLoop spirometer and resulting percent predicted was based on age, gender, weight, and height.

2.5 | Statistical analysis

We used non-parametric survival analysis for interval-censored data to estimate the cumulative probability of developing cardiomyopathy, followed by the generalized log rank test to compare cardiomyopathy "survival" distributions between genotype groups, and between male and female participants. Median (95% confidence interval [CI]) age to first abnormal echocardiogram was derived from the estimate of the cumulative probability distribution of developing cardiomyopathy. For individuals whose only echocardiogram was abnormal, the interval-censored data used in the analysis was the interval between age 1 and the age at the abnormal echocardiogram. Length of follow-up was computed using years to last echocardiogram for those with no abnormal echocardiogram, and years to first abnormal echocardiogram for those with abnormal findings, as no further studies were included in the analysis for these patients. Relationships between cardiac function and motor and respiratory function were evaluated using linear mixed models for assessing correlation in the presence of repeated measures with cardiac EF as the measure of cardiac function, and 10MWT speed and FVC percent predicted, as the measures of motor and respiratory function, respectively.²⁴

3 | RESULTS

We collected 269 echocardiogram reports or images from 56 patients. One hundred twelve echocardiograms were not included in this analysis as they occurred after a patient's first abnormal echocardiogram, resulting in a total of 157 echocardiograms analyzed (Figure 1). The number of echocardiograms analyzed ranged from one to eight per subject. Demographics and

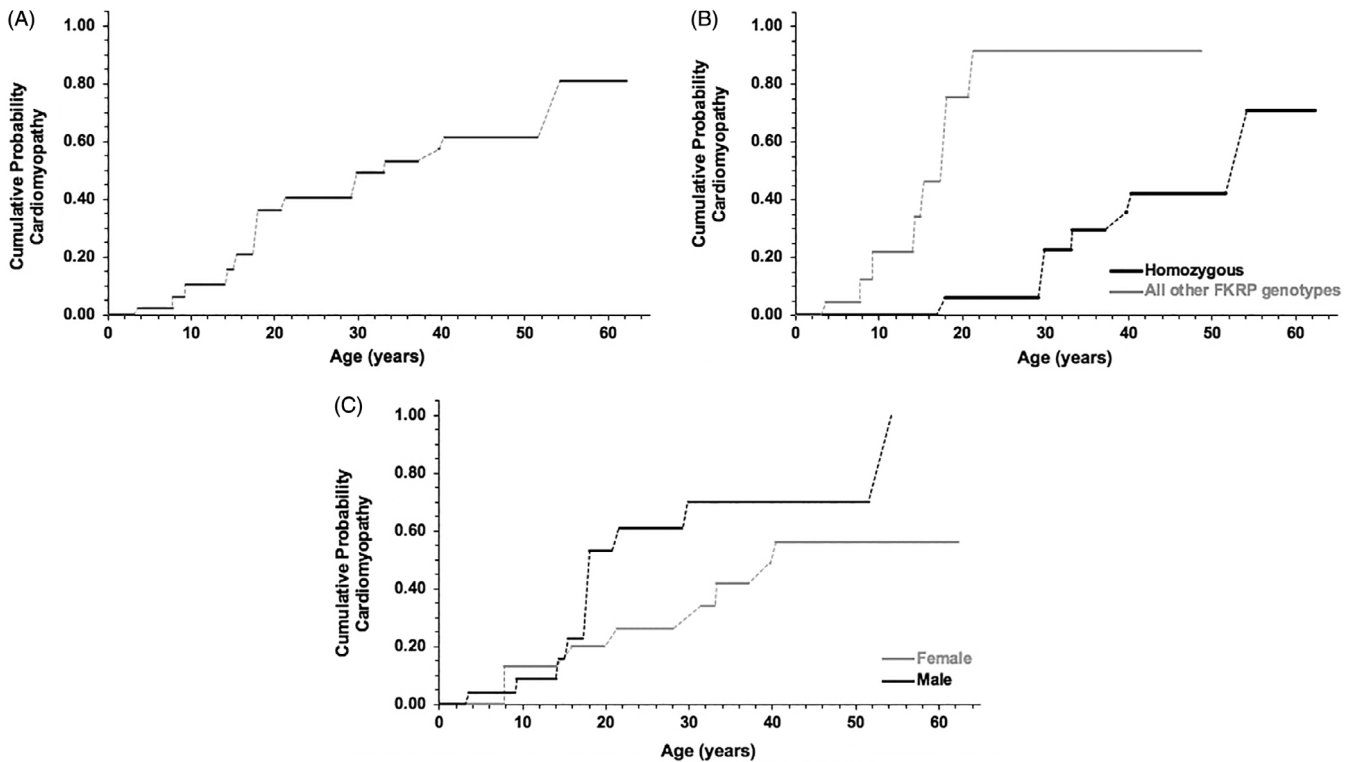


FIGURE 2 Cumulative probability of developing cardiomyopathy over time (age, years). (A) All subjects. (B) *FKRP* homozygotes (c.826C>A, c.826C>A) vs. other *FKRP* genotypes. (C) *FKRP* subjects: male vs female

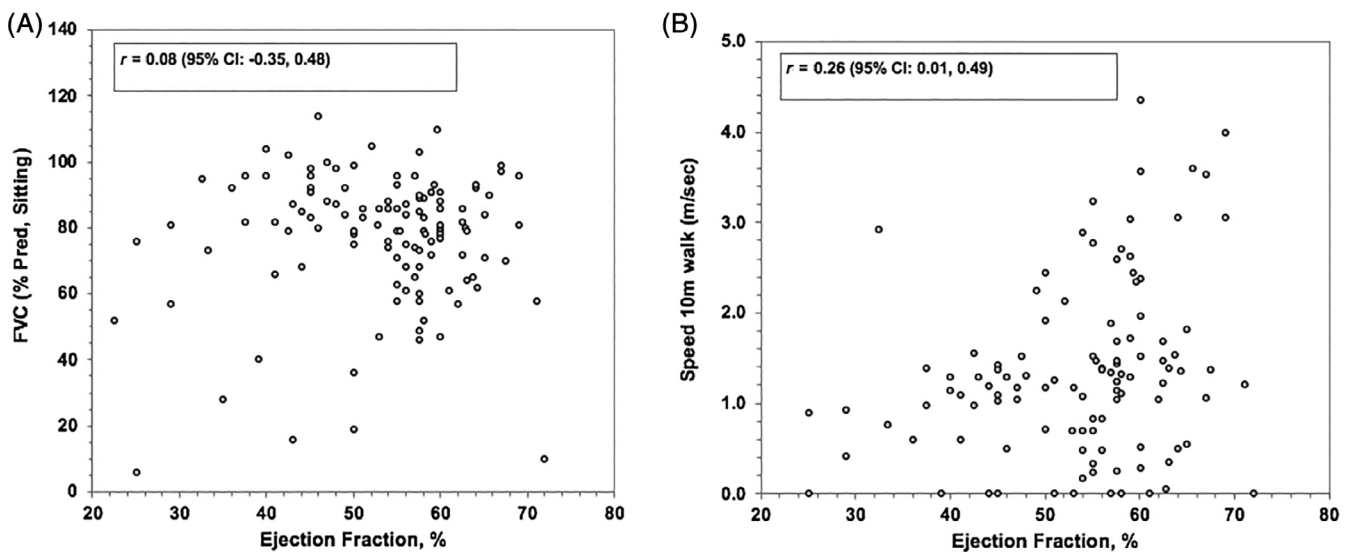


FIGURE 3 Correlation of ejection fraction with (A) FVC (% predicted) and (B) 10MWT (m/s) in patients with *FKRP* mutations

years of follow up are summarized in Table 1. All patients were Caucasian non-Hispanic. The age range for the participants was 3.6 to 62.3 y old. The cohort included 27 males and 29 females. Twenty-nine (52%) participants were homozygous for the common c.826C>A mutation. Twenty-five individuals (45%) had at least one abnormal echocardiogram. These results are provided for each subject in Supporting Information Table S1, which is available online,

and are summarized in Table 2. Figure 2A shows the cumulative probability of first abnormal echocardiogram by age.

We examined the effect of *FKRP* genotype on the age at onset of cardiomyopathy. Figure 2B shows the cumulative probability of having an abnormal echocardiogram, as a function of age, for those who are homozygous for the c.826C>A *FKRP* mutation compared to other *FKRP* genotypes. The cohort homozygous for the c.826C>A mutation

had a significantly slower rate of developing an abnormal echocardiogram, with greater median age at onset of cardiomyopathy compared to those with other *FKRP* genotypes (log rank test $P < .0001$; hazard ratio of 7.48 [95% CI: 3.01, 18.60]) as shown in Table 2. There was a similar percentage of each genotype group for whom the first echocardiogram was abnormal: 2/9 (22%) for the homozygous c.826C>A group and 4/16 (25%) for the group with other genotypes.

There was no significant difference in the age at onset of cardiomyopathy between males and females ($P = .115$), as shown in Figure 2C. The median age at onset of cardiomyopathy was 17.98 (95% CI: 17.98, 29.87) y for males and 40.33 (95% CI: 31.46, NA, cannot be computed from the observed data) y for females.

Finally, there was no correlation between EF and FVC percent predicted, and there was a weak correlation between EF and 10MWT speed, as shown in Figure 3. Only one patient with a 10MWT speed of ≥ 2.5 m/s (10MWT time of 4 s or less) had an EF $< 50\%$. This patient had an EF $> 50\%$ 6 mo prior and again 6 mo later after starting a beta blocker.

4 | DISCUSSION

Previous reports have focused largely on the percentage of patients with mutations in *FKRP* who have cardiomyopathy, and the frequencies have varied. These studies had fewer patients than reported here (< 38 patients) and cardiomyopathy frequency ranged from 10% to 83%, despite similar subject ages.^{11,14,17-23} In this cohort, the first abnormal echocardiogram occurred in children as young as 3 y, supporting previous reports of cardiomyopathy in early childhood or even infancy.^{25,26} Case reports have also illustrated the variability of cardiomyopathy associated with *FKRP* mutations.²⁷⁻²⁹

FKRP genotype is known to impact skeletal muscle phenotype, with c.826C>A homozygotes having a milder phenotype than those with most other genotypes.³⁰ We found a similar genotype effect related to cardiomyopathy, when looking at either prevalence or age at onset. Some previous reports have suggested that *FKRP* genotype does not significantly affect prevalence of cardiomyopathy.^{11,22} Wahbi et al. described a cohort of 23 patients (mean age, 32 y), 10 (43%) of whom were homozygous for the c.826C>A mutation, and found no significant difference between genotype groups in the percent with cardiomyopathy.¹¹ Sveen et al. described a cohort of 38 patients (mean age, early 30s), 27 (71%) of whom were homozygous for the common c.826C>A mutation.²² They reported a higher percentage of those homozygous for the common c.826C>A mutation had an EF $< 50\%$ or dilated cardiomyopathy compared to compound heterozygotes, but the difference was not statistically significant.²² In contrast with our series, these cohorts were smaller and were almost exclusively adults. These studies also simply reported prevalence. However, using methods similar to ours, Poppe et al. found a strong effect of genotype on the age at onset of cardiomyopathy in a cohort of 38 subjects (aged 10-61 y, 61% c.826C>A homozygous genotype).¹⁴ Median ages at onset of cardiomyopathy by genotype were

similar in the Poppe et al. cohort and the cohort reported here. Among those homozygous for the c.826C>A mutation, median age at first abnormal echocardiogram was 54 y (current cohort), compared to 51 y in the Poppe et al. cohort. Similarly, for subjects with all other *FKRP* genotypes, we found median age at first abnormal echocardiogram to be 18 y, compared to 20 y in the Poppe et al. cohort. The difference between genotype groups' rates of cardiomyopathy was significant in both studies. The reason for the milder cardiac phenotype in those homozygous for the c.826C>A mutation remains unclear, as it does in skeletal muscle.^{30,31}

There was no significant difference between males and females in the age at onset of cardiomyopathy in our cohort. Poppe et al. found that males had a higher frequency of cardiomyopathy compared to females (83% vs 42.3%), but this might reflect the fact that males were more likely to be compound heterozygous than females in that cohort (58% vs 31%).¹⁴ Males and females were similarly represented in the genotype groups in our cohort.

Given the genotype-phenotype effect seen in both skeletal and cardiac muscle, it is of interest that we found no correlation between EF and measures of respiratory muscle weakness. However, the majority of our subjects had normal respiratory function.

We found a weak correlation between motor function, as measured by 10MWT, and cardiac function, as measured by EF. We note that, while difficulty walking did not necessarily predict cardiomyopathy, all but one patient who completed the 10MWT in 4 s or less (ie, speed ≥ 2.5 m/s) had an EF $> 50\%$. While this is reassuring when managing a patient who is able to walk well, it has not been universally observed. Margeta et al. reported two patients homozygous for the common c.826C>A mutation who developed cardiomyopathy, requiring cardiac transplant, despite maintaining good motor function.²⁶ Others have also reported a lack of correlation between severity of cardiac and skeletal muscle dysfunction.^{11,22,32} Different measures of motor function have been used in different series. More information will be needed to clarify the relationship between motor function and cardiomyopathy.

There are several limitations to this study. The study required collection of images and reports from other medical centers; thus, the data may be incomplete. In addition, most of the echocardiograms were done based on local clinical style, so the interval between normal and first abnormal echocardiogram was variable. We exclusively collected echocardiograms and echocardiogram reports. The use of cardiac magnetic resonance imaging (CMR) is becoming increasingly commonplace in the clinical care and detects cardiac abnormalities in patients with LGMDR9 earlier than conventional diagnostic methods.¹⁶ However, echocardiography remains the first-line imaging test when cardiomyopathy is suspected clinically, and remains a commonly used monitoring test due to lower cost and convenience, so our results have clinical utility.³³ Information obtained through echocardiography is diagnostic and can be used to stratify risk and guide treatment.³⁴ In our cohort, three patients had had clinical CMR. For those patients, EF values were very similar by those obtained by echocardiogram, and CMR values would not have changed their cardiomyopathy classification. Our findings likely underestimate the age

at onset of cardiomyopathy, by assuming, for those whose first echocardiogram was abnormal, that the left-side bound of the interval censor data (ie, last normal) was at age 1. This is a conservative assumption that was used for a similar percentage of the two genotype groups.

Based on this study and previously reported cohorts, it is clear that patients with mutations in *FKRP* are at risk for cardiomyopathy, and this risk starts in childhood. There is a relationship between genotype and age at onset of cardiomyopathy that can be used by clinicians to guide cardiac monitoring frequency. Patients who are homozygous for the c.826C>A mutation should have baseline cardiac imaging at diagnosis, but imaging can be repeated every 2-3 y in childhood and young adulthood for asymptomatic patients with normal cardiac function. In contrast, cardiac monitoring should be performed at least annually in patients with other *FKRP* genotypes. Early use of cardioprotective medications may be considered, particularly in those with higher risk genotypes or with trends toward declining function.

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ETHICAL PUBLICATION STATEMENT

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

CONFLICTS OF INTEREST

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