Myocardial strain measured via two-dimensional speckle-tracking echocardiography in a family diagnosed with arrhythmogenic left ventricular cardiomyopathy

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Research Article

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Abstract

Background: Arrhythmogenic cardiomyopathy is a myocardial disorder characterized by ventricular arrhythmias, right and/or left ventricular involvement, and fibro-fatty infiltrations in the myocardium. We report a family diagnosed with arrhythmogenic left ventricular cardiomyopathy (ALVC) and depict their echocardiographic characteristics.

Methods and results: Fifteen family members were divided into three groups based on whether they carried the TMEM43 mutation and had been diagnosed with ALVC, were evaluated. Eight of them had TMEM43 mutations, and four were diagnosed with ALVC according to the Padua criteria. Only the proband experienced sudden cardiac death and had a dilated left ventricle. Left ventricular ejection fraction was reduced in two patients, however left ventricular global longitudinal strain was depressed in three patients. Low QRS voltages in limb leads were evident in three patients, and five patients had frequent ventricular extrasystoles. Late gadolinium enhancement was evident in three patients. Left ventricular layer-specific strain showed that the transmural strain gradient ratio was increased in patients diagnosed with ALVC, and it was elevated in the genotype-positive and phenotype-negative group than in healthy individuals.

Conclusion: Global left ventricular longitudinal strain evaluated left ventricular function better than left ventricular ejection fraction. The transmural strain gradient ratio was elevated in patients diagnosed with ALVC, suggesting that it was valuable for the diagnosis and evaluation of ALVC.

Introduction

Arrhythmogenic cardiomyopathy (ACM) was defined by an expert panel of the Heart Rhythm Society (HRS) as an arrhythmogenic disorder of the myocardium that is not explained by ischemic, hypertensive, or valvular disease(1). Arrhythmogenic right ventricular cardiomyopathy (ARVC) is a classic phenotype characterized by fibro-fatty myocardial replacement in right ventricle. Recent studies have shown that myocardial scarring is also evident in left ventricle or biventricle (2, 3). Arrhythmogenic left ventricular cardiomyopathy (ALVC) is characterized by left ventricular involvement predominantly with no or minor RV abnormalities(4). Several studies have provided significant insights into the diagnosis of ALVC based on contrast-enhanced cardiac magnetic resonance (CE-CMR) tissue characterization findings, depolarization/repolarization ECG abnormalities, and ventricular arrhythmia features for the diagnosis of the LV phenotype (4, 5); however, echocardiographic characteristics of ALVC were not well described. We report a family with a TMEM43 mutation diagnosed with ALVC and emphasize on the characterization of the left ventricular longitudinal strain in this family, with the aim to provide an advanced understanding on ALVC.

Methods

1. Population and data collection

The study was approved by the local research ethics committee, and all individuals provided their written informed consent. Fifteen pedigree members were included in this study, and four of them were diagnosed with ALVC at the First Affiliated Hospital of Soochow University. Clinical evaluation included 12-lead ECG, 24-hour Holter, echocardiography and contrast-enhanced cardiac magnetic resonance (CE-CMR). Clinical manifestations, disease history, and family history of the pedigree members were also collected.

Diagnosis was based on the padua criteria for ALVC, developed by multidisciplinary team of basic researchers and clinical cardiologists at the Medical School of the University of Padua, taking into account the tissue characterization findings by contrast-enhanced cardiac magnetic resonance, depolarization/repolarization ECG abnormalities, and ventricular arrhythmia features for the diagnosis of the left ventricular phenotype, which are grouped into six categories (4). LV late gadolinium enhancement (LGE) of ≥ 1 bull's eye segment (s) of CE-CMR and family history/genetics were included as the major criteria, and the minor criteria were considered as follows: 1. Global LV systolic dysfunction with or without LV dilatation; 2. Regional LV hypokinesia or akinesia of the LV free wall, septum, or both; 3. Inverted T waves in the left precordial leads (V4-V6); 4.Low QRS voltages in limb leads; 5. Frequent ventricular extrasystoles (> 500 per 24 h), non-sustained or sustained ventricular tachycardia with an RBBB morphology; 6. Family history and(or) genetics.

2. Echocardiography

Echocardiographic measurements were performed by a board-certified echocardiographer. Two-dimensional biographic imaging of all subjects was performed using the GE Vivid E95 equipment (Norway) with a 2.5 MHz transducer. All images were stored in a digital format for offline analysis (EchoPAC version 113; GE Healthcare). Dynamic 2D images of the apical four- and two-chamber views were used to analyze the auto-EF, three anchor points were set within the LV cavity, including two at the level of the mitral valve annulus and one at the LV apex. Endocardial borders were then detected and traced automatically by the software during the whole heart cycle to calculate left ventricular end-diastolic volume, left ventricular end-systolic volume, and left ventricular ejection fraction (LVEF). When needed, corrections were performed manually.

Left ventricular longitudinal strain was assessed using two-dimensional speckle tracking echocardiography in three standard apical views. The region of interest was adjusted to ensure optimal analysis of most of the LV walls based on the American Society of Echocardiography /European Association of Echocardiography consensus statement (6). Each apical view assessment produced six segmental values of the peak systolic longitudinal strain. For each segment, the software automatically separated the myocardium into subendocardial and subepicardial layers. The peak systolic longitudinal strain of the subendocardial myocardium and subepicardial myocardium were derived. The "transmural strain gradient" was defined as absolute difference between subendocardial and subepicardial myocardium in longitudinal vectors, and "strain ratio" as stransmural strain gradient divided by subepicardial myocardial strain.

3. CMR

All participants underwent CMR at 1.5 T or 3 T (Aera and Avanto 1.5 T; Prisma 3 T scanner; Siemens Healthcare, Erlangen, Germany). All images were analyzed using the CVI42 software (Circle Cardiovascular Imaging Inc., Calgary, Canada). Measurements were performed by two experienced cardiologists blinded to both clinical and genetic data (E.N. and S.M.F.). LV late gadolinium enhancement (scar) quantification was performed in the short-axis slices using manually drawn endocardial and epicardial borders and a semi-automated 5 SD approach with minimal manual adjustment and expressed in grams and as a percentage of the total LV mass.

4. Gene studies

The chip capture sequencing technique was used to capture all exons and shear sites related to ACM, and high-throughput sequencing was used to test the genetic mutations. Sanger sequencing was performed to verify suspected mutation sites responsible for the disease which were detected by high-throughput sequencing. All gene assay were perfomed using Mygenostics.

5. Statistics

Statistical analysis was performed using SPSS 25.0 and GraphPad Prism 8.0.1. The family members were divided into three groups based on whether they carried the TMEM43 mutation and had been diagnosed with ALVC. Differences in continuous variables between the two groups were analyzed using Student's t-test.

Results

1. Clinical information

Figure 1 shows the pedigree of the ALVC family. In July 2018, the proband (patient IV:6) was admitted to the intensive care unit because of sudden cardiac arrest. After 12 days, he regained consciousness and was transferred to the cardiovascular department and implanted with an implantable cardioverter defibrillator. Fifteen family members were also evaluated.

TMEM43 mutations were detected in eight family members, in which 4 family members were diagnosed with ALVC according to the Padua criteria (Table 1), which were included in the group with genotype-positive and phenotype-pisitive (patient IV:5, IV:6, V:1 and V:2). The 4 patients who brought TMEM43 mutation and wasn't diagnosed with ALVC were divided into the group with genotype-positive and phenotype-negative (patient IV:7, V:10, V:12 and VI:1). One patient experienced sudden cardiac death, and three experienced dyspnea. Regional left ventricular hypokinesia or akinesia of the left ventricular free wall were evident in four patients, and five had a reduced segmental left ventricular longitudinal strain value in the bull's eye map. One have a dilated left ventricle. Left ventricular ejection fraction was depressed in 2 family members, and three had a reduced global longitudinal strain. Three patients had low QRS voltage in limb leads. 24-hour Holter monitoring indicated that five patients had frequent ventricular extrasystoles (> 500 per 24 h) and three had non-sustained ventricular tachycardia. Coronary artery disease was excluded by coronary angiography or coronary computed tomographic angiography in all eight patients with TMEM43 mutation. Two-dimensional echocardiography revealed normal right ventricular function and strain. Late gadolinium enhancement was detected in three patients. Male patients showed more severe clinical features and were diagnosed with ALVC at an earlier age than women.

Table 1
Clinical diagnostic features in genetically affected individuals.

ID	IV:5	IV:6	V:1	V:2	IV:7	V:10	V:12	VI:1
Age	53	51	48	43	48	29	18	24
Sex	F	M	M	M	F	F	M	M
LVEDVI(ml/m^2)	55.9	78.5	61.5	44.1	43.4	29.2	42.3	45.2
LVEF (%)	60	40	48	59	62	62	62	62
LV regional wall motion abnormality	posterior and lateral wall	posterior and lateral wall	posterior and lateral wall	Posterior wall	(-)	(-)	(-)	(-)
Reduction in segmental longitudinal strain	posterior and lateral segments	Posterior, lateral and anterior segments	Posterior and lateral segments	Posterior and lateral segments	Lateral and septal segments	(-)	(-)	(-)
GLS	-20.1%	-13.75%	-14.1%	-17.9%	-23%	-23%	-22.7%	-18.5%
TMEM43	(+)	(+)	(+)	(+)	(+)	(+)	(+)	(+)
ECG	Low QRS voltages in limb leads	Low QRS voltages in limb leads	Low QRS voltages in limb leads, V4-V6 inverted/ flattened T waves	(-)	(-)	(-)	(-)	(-)
Holter	Ventricular extrasystoles: 1075 /24 h	Ventricular extrasystoles: 15367 /24 h, VT (+)	Ventricular extrasystoles:1075 /24 h, VT (+)	Ventricular extrasystoles: 1516 /24 h, VT (+)	Ventricular extrasystoles: 824 /24h	Ventricular extrasystoles: 3 /24 h	Ventricular extrasystoles: 4 /24 h	Ventricular extrasystole 4 /24 h
LGE	(-)	(+)	(+)	(+)	(-)	(-)	(-)	(-)
Diagnostic Criteria	1 M + 3m	2M + 3m	2 M + 4 m	2 M + 2m	1 M + 1 m	1M	1 M	1 M

ID, individual number on pedigree (Fig. 1); M, male; F, female; LVEDVI, left ventricular end-diastolic volume index; LVEF, left ventricular ejection fraction; LV, left ventricle; GLS, global longitudinal strain; ECG, electrocardiogram; CMR, cardiovascular magnetic resonance; LGE, late gadolinium enhancement; M, major criteria; m, minor criteria.

Padua criteria: Major criteria include left ventricular late gadolinium enhancement (LGE) of ≥ 1 bull's eye segment (s) of CE-CMR and family history/genetics. Minor criteria include global LV systolic dysfunction with or without LV dilatation, regional LV hypokinesia or akinesia of the LV free wall, septum, or both, inverted T waves in the left precordial leads (V4-V6), low QRS voltages in limb leads, frequent ventricular extrasystoles (> 500 per 24 h), non-sustained or sustained ventricular tachycardia with an RBBB morphology and family history and(or) genetics. Diagnosis is fulfilled by 2 major or 1 major and 2 minor criteria from different categories.

2. Echocardiographic parameters and 24-Holter monitoring in different groups

Global longitudinal strain and left ventricular ejection fraction were reduced, while the number of ventricular extrasystoles in 24 hours and LVEDVI were increased in patients diagnosed with ALVC. Global longitudinal strain and LVEF in genotype-positive and phenotype-negative patients were not significantly reduced compared to those in healthy individuals (Fig. 2, Fig. 3).

3. Left ventricular layer-specific strain

The left ventricular layer-specific strain showed that the transmural strain gradient ratio was increased in patients diagnosed with ALVC, and it was elevated in the genotype-positive and phenotype-negative group compared with that in healthy individuals (Fig.5, Fig.6).

Discussion

Arrhythmogenic cardiomyopathy is an inherited cardiac disease characterized by fibro-fatty replacement of the myocardium, not only in the right ventricle but also in the left ventricle(1). We report a family with arrhythmogenic left ventricular cardiomyopathy which included 15 family members. TMEM43 mutations were evident in eight patients, and according to the Padua criteria, four of them were diagnosed with ALVC (4).

Mutant TMEM43 was first described in families from Newfoundland (Canada) in 2008, as the cause of a fully penetrant aggressive disease with a high incidence of malignant ventricular arrhythmias, and was defined as ACM/ARVC type 5 (2). Previous studies reported that one of the clinical characteristic of the mutation is dilated left ventricle (7). However, in our report, the left ventricular volume index increased mildly only in the proband. Male patients showed more severe clinical features and were diagnosed with ALVC at an earlier age than women, which is consistent with prior studies (4, 7).

Inverted T waves in left precordial leads, low QRS voltages in limb leads, frequent ventricular extrasystoles, and non-sustained or sustained ventricular tachycardia were ECG depolarization, repolarization abnormalities, and ventricular arrhythmias in Padua criteria (4). In the current report, three patients had low QRS voltages in limb leads, frequent ventricular extrasystoles were detected in 5 patients, and the number of ventricular extrasystoles was higher in the genotype-positive group diagnosed with ALVC than in the other groups. Three patients had non-sustained ventricular tachycardia in the current report.

Five family members underwent CMR, and LGE was evident in three patients, suggesting cardiac scarring. Fibro-fatty myocardial replacement was confirmed by endomyocardial biopsy in prior studies (8). Previous studies indicated that half of the ALVCs with LV LGE had no wall abnormalities, and LV fibrosis may deteriorate left ventricular systolic function and lead to a higher prevalence of subepicardial fibrosis (8).

Left ventricular ejection fraction was reduced in two patients, while GLS was decreased in all 4 patients who were diagnosed with ALVC according to the Padua criteria, suggesting that left ventricular strain evaluate left ventricular function better than left ventricular ejection fraction. Region left ventricular akinesia or dyskinesia was evident in five patients, and it was more apparent in the posterior and lateral LV walls. The reduction of the segmental left ventricular longitudinal strain in bull's eye map was similar to that of two-dimensional echocardiography, which showed that left ventricular strain values were reduced in the posterior and lateral left ventricular walls more frequently. Regional left ventricular hypokinesia or akinesia was one of diagnostic criteria for ALVC, however, the reduction of left ventricular strain value in the bull's eye segments was more sensitive and accurate than two-dimensional echocardiography, which should be considered in the future diagnostic criteria for ALVC.

Left ventricular layer-specific strain showed that the transmural strain gradient ratio was increased in patients diagnosed with ALVC, and it was elevated in the group with genotype-positive and phenotype-negative patients compared with that in the normal group. A previous study showed that fibro-fatty myocardial replacement affects the subepicardial left ventricle more than other layers (8), which may explain the layer-specific strain results. It has also been confirmed by CMR that cardiac scar was more apparent in subepicardium of left ventricle(8). Left ventricular layer-specific strain may play an important role in the diagnosis of ALVC.

Conclusion

In this family diagnosed with ALVC, global left ventricular longitudinal stain evaluated left ventricular function better than left ventricular ejection fraction, and the segmental left ventricular strain was more accurate and consistent with 2D echocardiography well. The transmural strain gradient ratio was elevated in patients diagnosed with ALVC, suggesting that it was valuable for the diagnosis and evaluation of ALVC.

Declarations

Acknowledgements

None.

Authors' contributions

Draft the work,CSM & JLF; Conception, BYZ & FJL; Design of the work, JLF & CMZ; Interpretation of data, CMZ & JLF & BYZ; Analysis, XZ & BYZ; Data acquisition, CMZ & LW & BS & YZM & YPL; Supervision, JLF & BYZ & XZ &YZM & YPL. The author(s) read and approved the final manuscript.

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Availability of data and materials

The datasets during and/or analysed during the current study available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

The study was approved by the institutional enrolling board of the First Affiliated Hospital of Soochow University.

Consent for publication

Informed consent was confirmed by the IRB.

Competing interests

The authors declare that they have no confict of interests.

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Figures

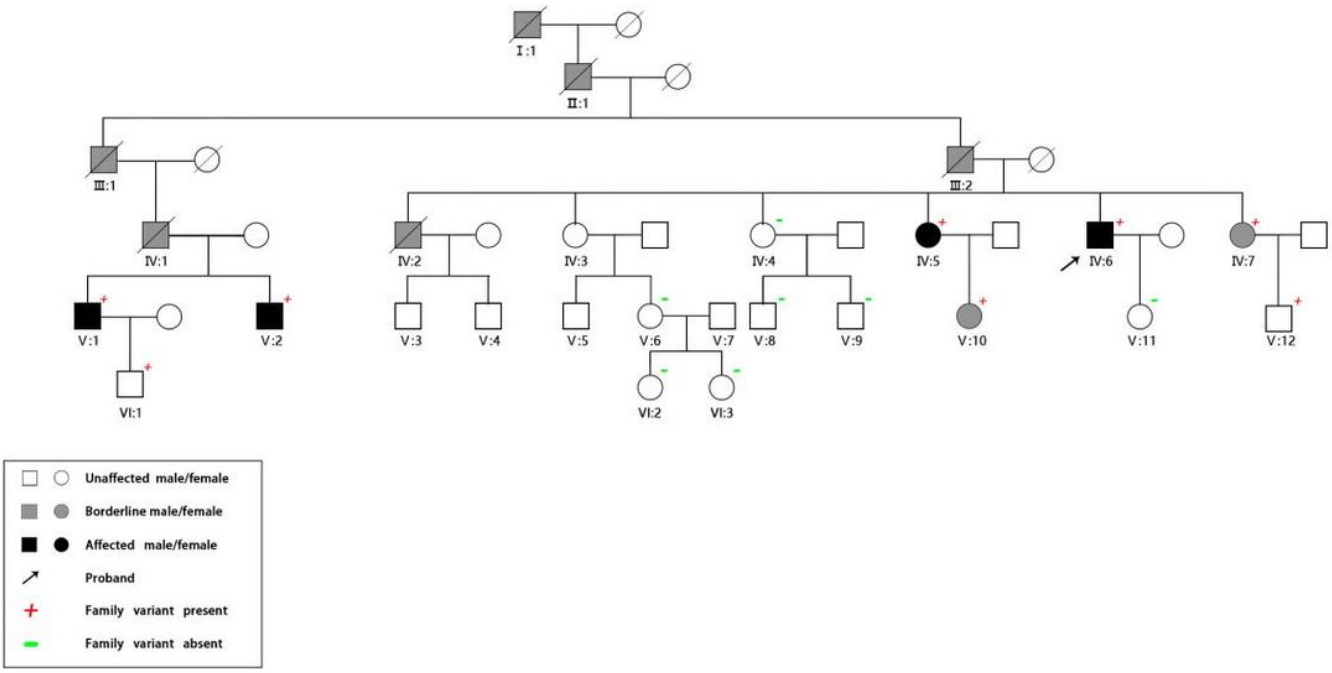

Figure 1

Pedigree of the studied family, males (squares) and females (circles) diagnosed with ALVC are shown in black. Patients marked in gray refer to suspected ALVC or borderline males/females.

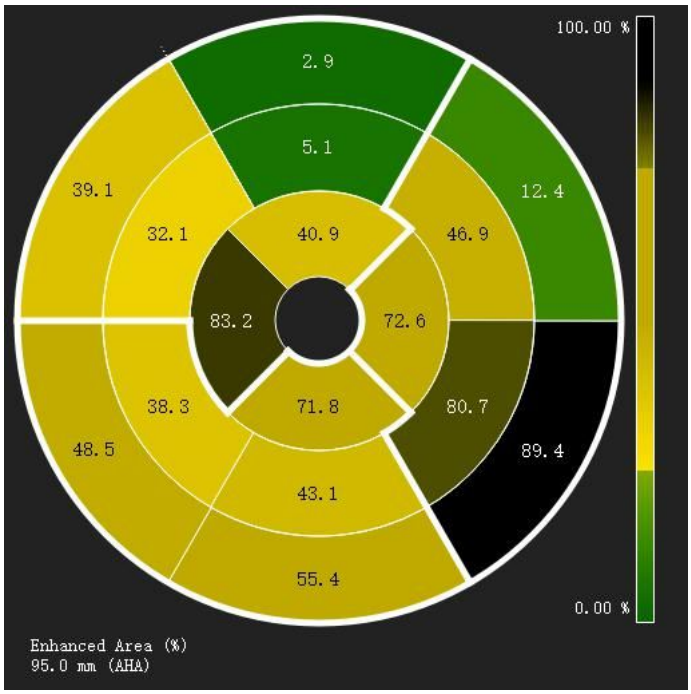

Figure 2

Distribution of left ventricular LGE of the proband in bull's eye view of the 17-segment American Heart Association.

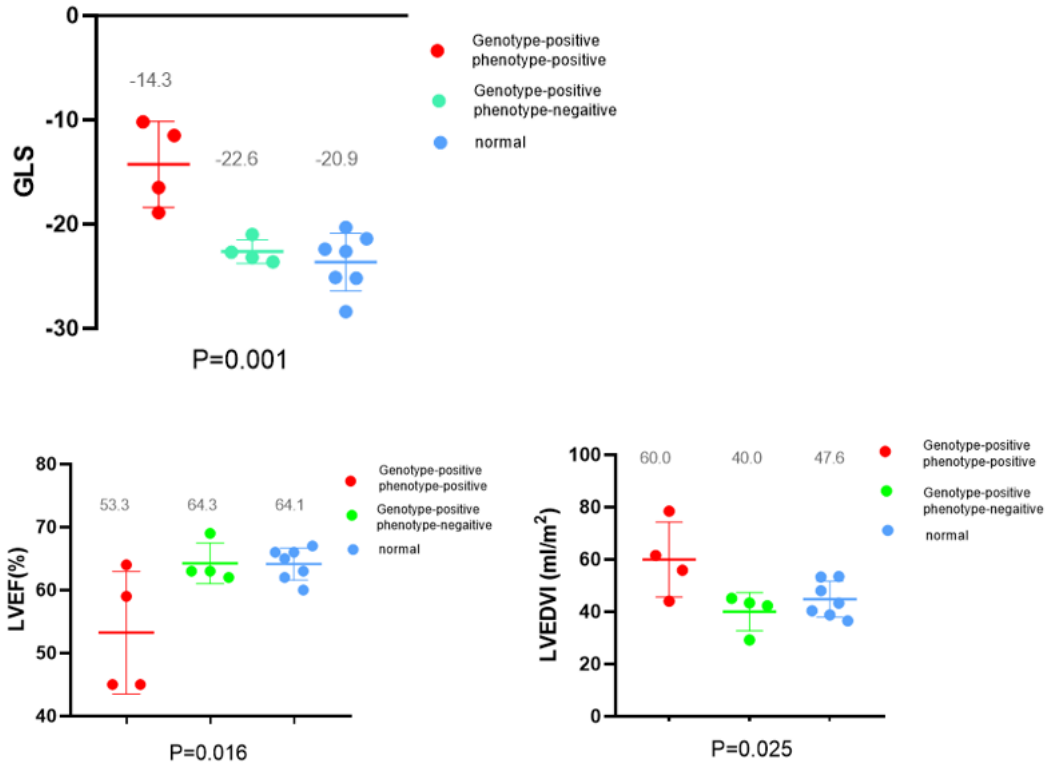

Figure 3

Echocardiographic parameters in different groups. (A) Global longitudinal strain; (B) Left ventricular ejection fraction; (C) Left ventricular end-diastolic volume index.

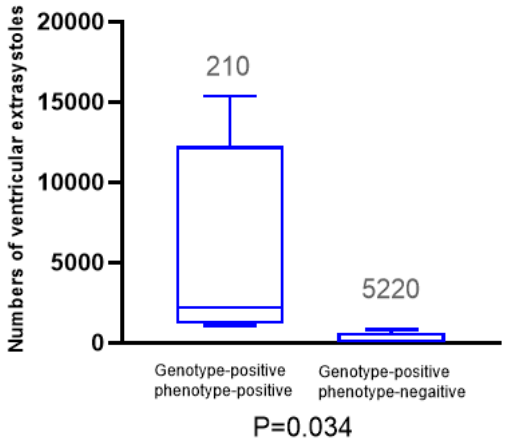

Figure 4

Numbers of ventricular extrasystoles in24-Holter monitoring in different group.

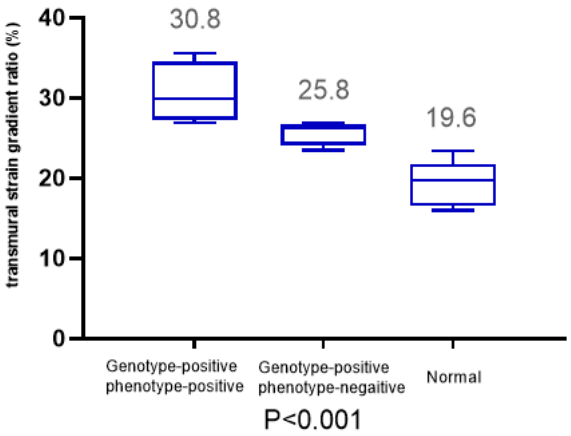

Figure 5

Transmural strain gradient ratio in genotype-positive and phenotype-positive patients, genotype-positive and phenotype-negative patients, and normal members in this family.

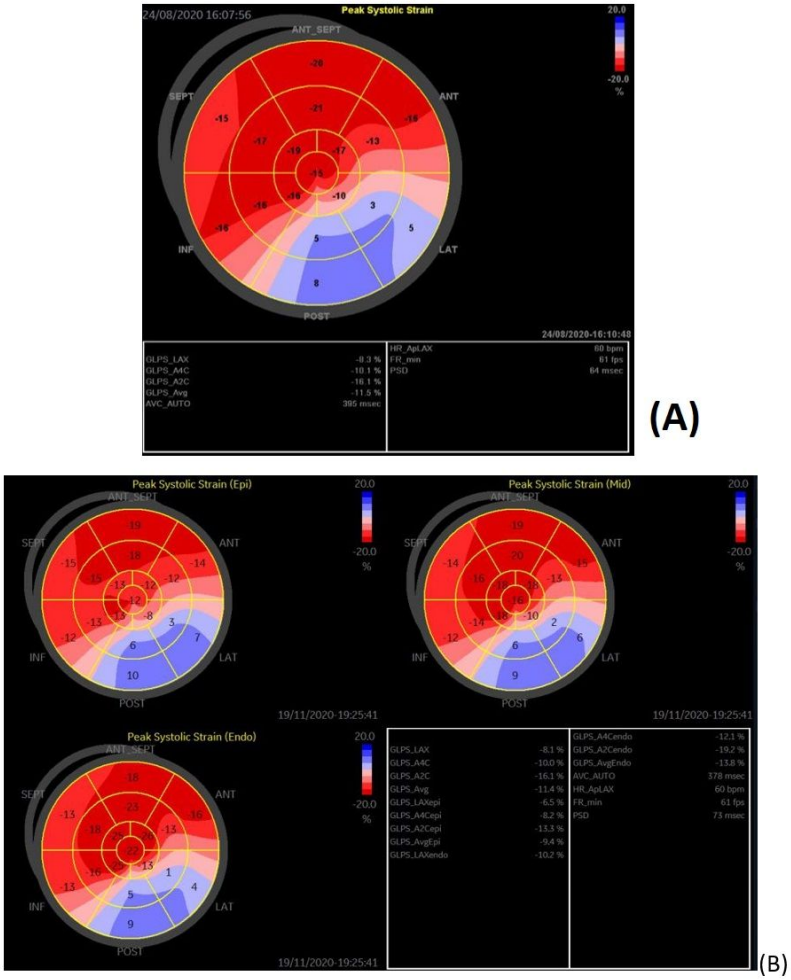

Figure 6

(A) Left ventricular longitudinal strain of the proband. (B) Left ventricular layer-specific strain of the proband.