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The combination of left ventricular non-compaction and hypertrophic cardiomyopathy in one family with a pathogenic variant in the *MYBPC3* gene (rs397516037)

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The article presents the results of clinical, instrumental and molecular genetic tests of three generations of a family with inherited cardiomyopathy caused by a new variant in the *MYBPC3* gene. A specific feature of this case is the phenotypic heterogeneity of the mutation — a combination of hypertrophic cardiomyopathy and left ventricular non-compaction in family members. Attention is drawn to the various severity of clinical manifestations in relatives of carriers of mutation: from asymptomatic to severe heart failure and acute cerebrovascular accident.

Key words: left ventricular non-compaction, hypertrophic cardiomyopathy, heart failure, sudden cardiac death, thromboembolism, acute cerebrovascular accident, *MYBPC3*.

Relationships and Activities: none.

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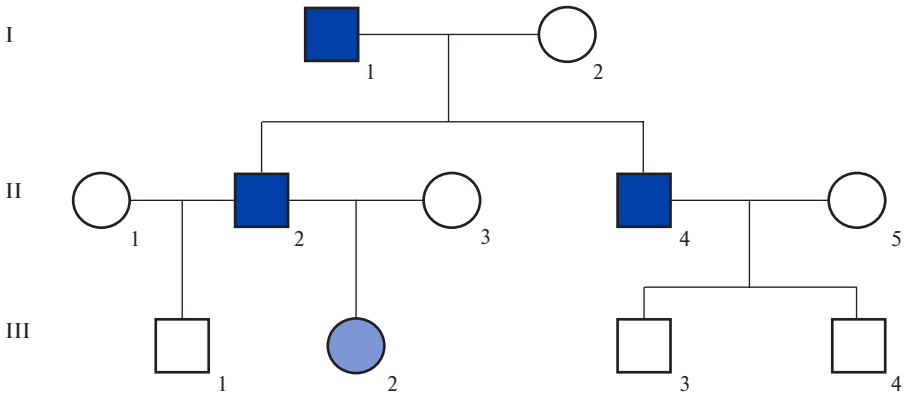
Left ventricle noncompaction (LVNC) is characterized by a two-layered myocardial structure with a thin, compacted outer (epicardial) band and a much thicker, non-compacted inner (endomyocardial) layer and deep myocardial trabeculae, particularly in the apex and free wall of the left ventricle. The clinical performance of the disease is extremely diverse, but the following symptoms usually predominate: heart failure (HF), cardiac arrhythmias and thromboembolic events. These disorders can be either sporadic or familial. Of particular interest is familial LVNC. Currently, genes have been identified that lead to LVNC. The largest number of mutations associated with this disease are localized in sarcomere protein genes. This category also includes the *MYBPC3* gene, a mutation in which is most often associated with hypertrophic cardiomyopathy (HCM) and dilated cardiomyopathy (DCM). In this article, we present a family with *MYBPC3* gene mutation and different types of cardiomyopathy in generations.

The aim of our study was to demonstrate a familial case of cardiomyopathies of different phenotypes.

Material and methods

On the basis of a multicenter registry of LVNC patients, a family (Figure 1) with a familial LVNC in combination with HCM was selected. All participants signed informed consent. The study design was approved by the ethics committee of the National Medical Research Center for Therapy and Preventive Medicine (Moscow, Russia). All participants underwent diagnostic tests according to the protocol described earlier [1]. The LVNC was established on the basis of echocardiography and magnetic resonance imaging (MRI) [2, 3].

DNA isolation was performed using a QIAamp DNA Blood Mini Kit (Qiagen, Germany). The DNA concentration was determined on a Qubit 4.0 fluorometer (Thermo Fisher Scientific, USA). Next-generation sequencing was performed on a Nextseq550 system (Illumina, USA). Whole-



Number	Diagnosis	Mutation in the *MYBPC3* gene
I-1	57 years old. HCM. First-degree AV block. Second-degree AV block. VT. NYHA class II, stage 2A HF. ICD implantation.	+
I-2	57 years old, healthy. Increased LV trabecularity.	-
II-1	30 years old, healthy.	no data
II-2	34 years. Combination of hypertrophic and dilated type of LVNC. NYHA class IIA, stage 2A HF. Pulmonary hypertension. Lysed thrombus in the LV apex. ICD implantation.	+
II-3	35 years old, healthy.	no data
II-4	36 years. Combination of hypertrophic and dilated type of LVNC. NYHA class IIA, stage 2A HF. Stroke.	+
II-5	Not known.	no data
III-1	2 years old, healthy.	-
III-2	11 years. Increased LV trabecularity.	+
III-3	5 years old, not examined.	+
III-4	2 years, not examined.	-

Figure 1. Family lineage.
Abbreviations: AV — atrioventricular, HCM — hypertrophic cardiomyopathy, VT — ventricular tachycardia, ICD — cardioverter defibrillator, LV — left ventricle, LVNC — left ventricular noncompaction, HF — heart failure.

Table 1

Echocardiography parameters

№	LVNC criteria			EDV	IVST	EF
	Stollberger	Jenni	Chin			
I-1	-	-	+	121	2,5	69%
I-2	+	-	-	75	0,8	61%
II-2	-	+	+	150	1,6	41%
II-4	+	+	+	225	2,0	48%
III-2	-	+	-	51	0,5	70%

Abbreviations: EDV — end-diastolic volume, IVST — interventricular septal thickness, EF — ejection fraction.

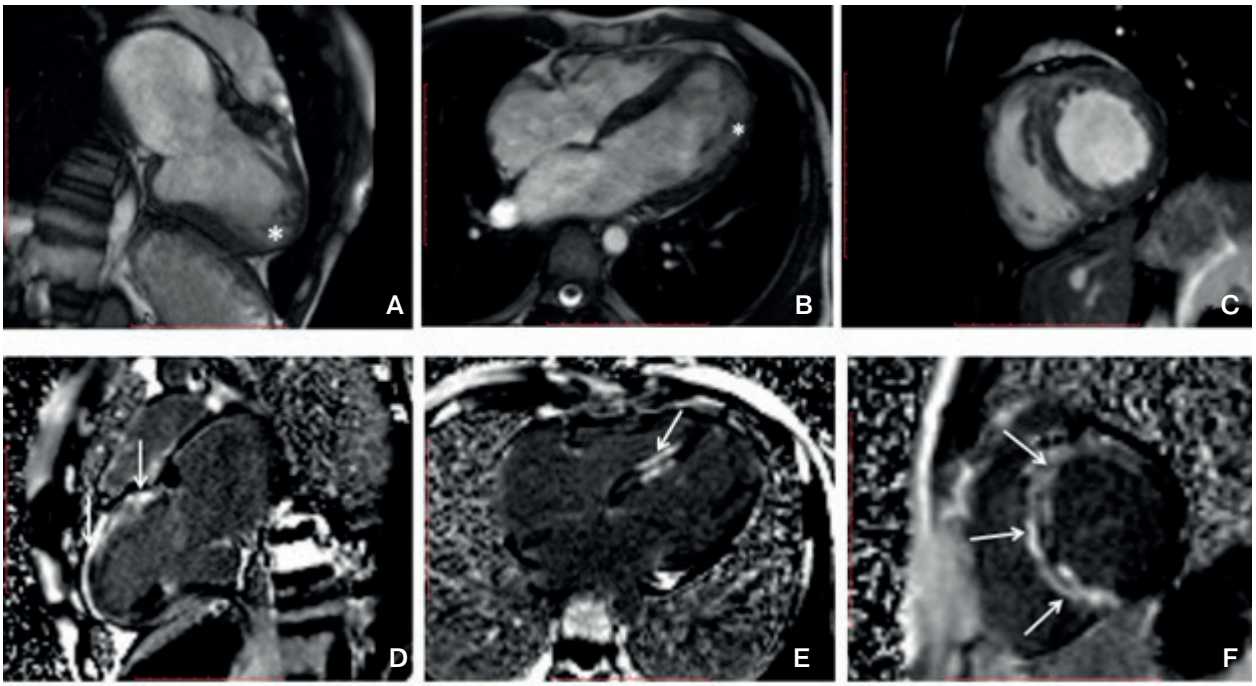


Figure 2. (**A**-**C**) Cardiac MRI of the proband, SSFP sequence: **A** — long axis 2-chamber view, **B** — long axis 4-chamber view, **C** — short axis.
Note: * — NC layer (**D**-**F**) — delayed contrast enhancement, IR sequence with suppression of the myocardial signal. Arrows indicate extended areas of subepicardial and intramyocardial contrast enhancement in the middle septal and anterior segments.

exome sequencing was performed using IDT-Illumina TruSeq DNA Exome (Illumina, USA). As a result of sequencing and bioinformatics analysis, .fastq and .vcf files were obtained. For clinical interpretation, genetic variants with frequencies in the gnomAD database <0,5% were selected. The assessment of the pathogenicity was carried out in accordance with the ACMG/AMP 2015 guidelines. The identified variants were validated by Sanger sequencing. The nucleotide sequence of PCR products was determined using the ABI PRISM® BigDye™ Terminator v.3.1 kit with subsequent analysis of the reaction products on an Applied Biosystem 3500 DNA Analyzer (Thermo Fisher Scientific, USA).

Results

The 34-year-old proband was cared due to HCM from childhood. At the age of 20 years, LV ejection fraction (EF) was 78%, interventricular septum (IVS) thickness — 15 mm. After this, the patient was not observed for a long time and did not take therapy. At 31, he noted an increase in shortness of breath and the development of edema, which required hospital treatment. Echocardiography revealed LVEF of 35-40%, pulmonary artery systolic pressure of 60 mm Hg, hypokinesis of the apex and LV anteroseptal wall, a mobile thrombus in the LV apex. Chest multislice computed tomography revealed a LV thrombus, bilateral hydrothorax. No data for pulmonary embolism were obtained. With HF therapy with anticoagulants,

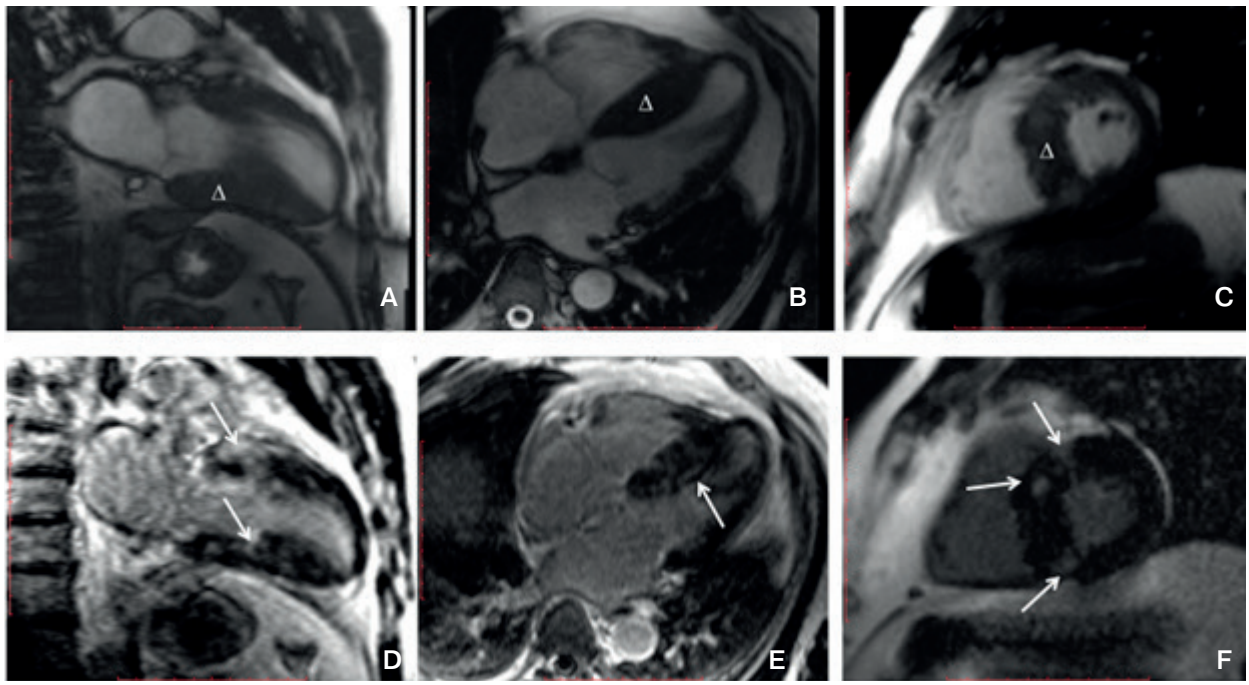


Figure 3. (**A**-**C**) Cardiac MRI of the proband's father, SSFP sequence: **A** — long axis 2-chamber view, **B** — long axis 4-chamber view, **C** — short axis, (**D**-**F**) — delayed contrast enhancement.
Note: Δ — asymmetric hypertrophy of the IVS myocardium and LV inferior wall, IR sequence with suppression of the myocardial signal. Arrows indicate intramyocardial foci of contrasting in hypertrophied segments.

HF symptoms regressed and LV thrombus was lysed. Echocardiography revealed left atrium of 5,4 cm, end diastolic volume of 150 ml, IVS thickness of 1,4-1,9 cm. In the region of the apex, lateral wall, posterior wall of the LV, signs of noncompaction (Jenni, Stollberger criteria) was detected. We also revealed a LV ejection fraction of 41%, hypokinesis of the anteroseptal wall with involvement of the apex, pulmonary artery systolic pressure of 44 mm Hg (Table 1). Contrast-enhanced cardiac MRI identified IVS hypertrophy up to 16 mm, signs of noncompaction of the apex, lateral wall, and posterior wall of the LV (Figure 2). The thickness of compacted layer in these segments was 6 mm, and the non-compacted layer — 18 mm. The noncompaction mass index was 20 g/m^2 (20% of the LV mass). LVEF was 48%. Pronounced LV myocardial fibrosis was noted.

According to 24-hour Holter monitoring, paroxysmal ventricular tachycardia (VT) were recorded (maximum, 7 complexes). Given the high risk of sudden cardiac death (SCD), a dual-chamber cardioverter-defibrillator (ICD) was implanted. Despite the regular use of prescribed therapy of HF with beta-blockers (BB), angiotensin II receptor blockers and neprilysin inhibitors, mineralocorticoid receptor antagonists (MCRA), loop diuretics, the patient has annual hospitalizations due to decompensated HF. Given the pronounced LVM, a history of LV apex thrombosis, the presence of systolic dysfunction, in order to prevent thromboembolism, the patient was prescribed vitamin K antagonists. After this, there were no signs of recurrent intracardiac thrombosis according to echocardiography.

The 57-years-old proband's father. At the age of 35, the HCM was verified during a routine examination. At the same time, he noted rare cardiac interruptions. No drug therapy was prescribed. From the age of 50, he began to notice the shortness of breath with a gradual decrease in exercise tolerance. At the age of 54, due to his son's illness, he was examined at the clinic. Echocardiography revealed normal contractility, asymmetric LV hypertrophy, IVS fibrosis, moderately pronounced LVNC in the apex and lateral wall. LV false chords and LVEF of 69% was established. According to the 24-hour Holter monitoring, first-degree atrioventricular (AV), second-degree transient AV block with 16 pauses up to a maximum of 4 seconds, 1542 ventricular premature beats, 5 episodes of VT was detected. Contrast-enhanced cardiac MRI (Figure 3) revealed an asymmetric non-obstructive biventricular HCM, intramyocardial fibrosis, and LVEF of 74%. The noncompaction mass index was 10 g/m^2. No congestion in the systemic circulation was observed, but the level of pro-brain natriuretic peptide was 833 pg/ml. Given the high risk of SCD, a dual-chamber ICD was implanted for the primary prevention of SCD. After discharge from

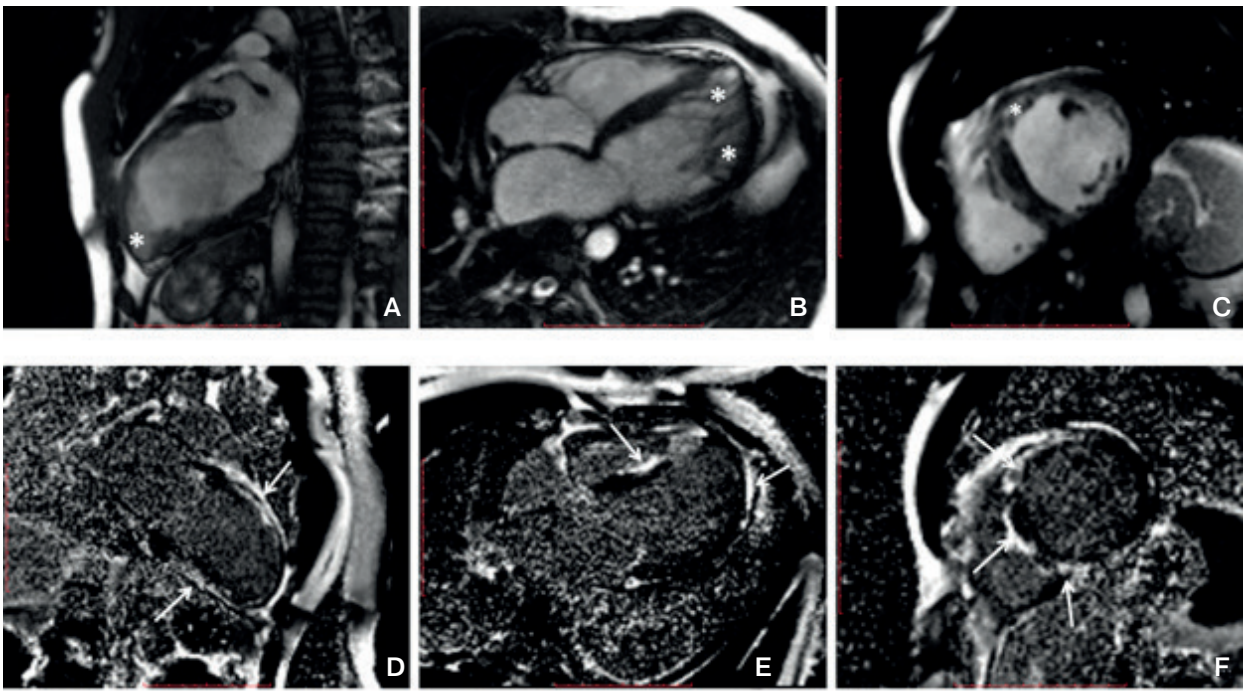


Figure 4. (**A**-**C**) Cardiac MRI of the proband's brother, SSFP sequence: **A** — long axis 2-chamber view, **B** — long axis 4-chamber view, **C** — short axis.
Note: * — NC layer (**D**-**F**) — delayed contrast enhancement, IR sequence with suppression of the myocardial signal. Arrows indicate extended areas of subepicardial and intramyocardial contrast in the middle septal, anterior and lower segments.

the hospital, he regularly takes BB, angiotensin-converting enzyme (ACE) inhibitors, MCRA, loop diuretics, against which the heart failure was compensated and stable episodes of paroxysmal VT were not recorded.

The 36-year-old proband's brother, which in childhood was cared simultaneously with his brother due to HCM. He did not take any medications, and was not further examined. Due to brother's illness, he was examined at the clinic. According to the 24-hour Holter monitoring, there was a rare ventricular premature beats and no VT runs. Echocardiography revealed a LV dilatation. End diastolic dimension was 6,4 cm, EF — 48%, IVS thickness — 20 mm. There were signs of noncompaction of the apex, lateral and posterior walls of the LV. He did not take the recommended therapy with BB, ACE inhibitors, MCRA. Contrast-enhanced cardiac MRI (Figure 4) 18 months after the echocardiography established IVS hypertrophy up to 14 mm, signs of noncompaction of the apex, anterior, lateral and posterior walls of the LV. The noncompaction mass index was 24 g/m^2, which is 22% of the LV mass. LVEF was 35%. Fibrosis of the IVS, the anterior, inferior and apical segments of the LV was revealed. HF therapy with BB, ACE inhibitors, MCRA, and also, taking into account the systolic dysfunction and a pronounced LVNC, vitamin K antagonists was recommended. The patient did not take the recommended therapy. Later, left middle cerebral artery (MCA) stroke developed.

The 57-year-old proband's mother was examined for LVNC with other family members. Echocardiography showed nondilated cardiac chambers, normal LV systolic function, and increased trabecularity of the apex and lateral wall of the LV, corresponding to the noncompaction criteria (Stollberger). Cardiac MRI did not reveal LVNC (Figure 5), while a significant number of additional LV false chords were visualized.

Cardiac screening examination of 11-year-old proband's daughter was performed. Echocardiography showed nondilated cardiac chambers, normal IVS, and increased trabecularity of the LV apex. According to cardiac MRI, increased LV trabecularity did not meet criteria for LVNC (Figure 6).

Genetic analysis. The proband had a heterozygous variant rs397516037 in exon 33 of the *MYBPC3* gene (hg19: chr11: 47353740) NM_000256.3:c.3697C>T, which led to the stop codon NP_000247.2:p.Gln1233Ter. This variant was detected in proband (II-2), in the proband's father (I-1), brother (II-4), daughter (III-2), and nephew (III-3). It was not detected in the proband's mother (I-2), son (III-1) and second nephew (III-4).

Discussion

C-MYBPC3 (cardiac myosin-binding protein-C) is arrayed transversely in sarcomere A-bands and

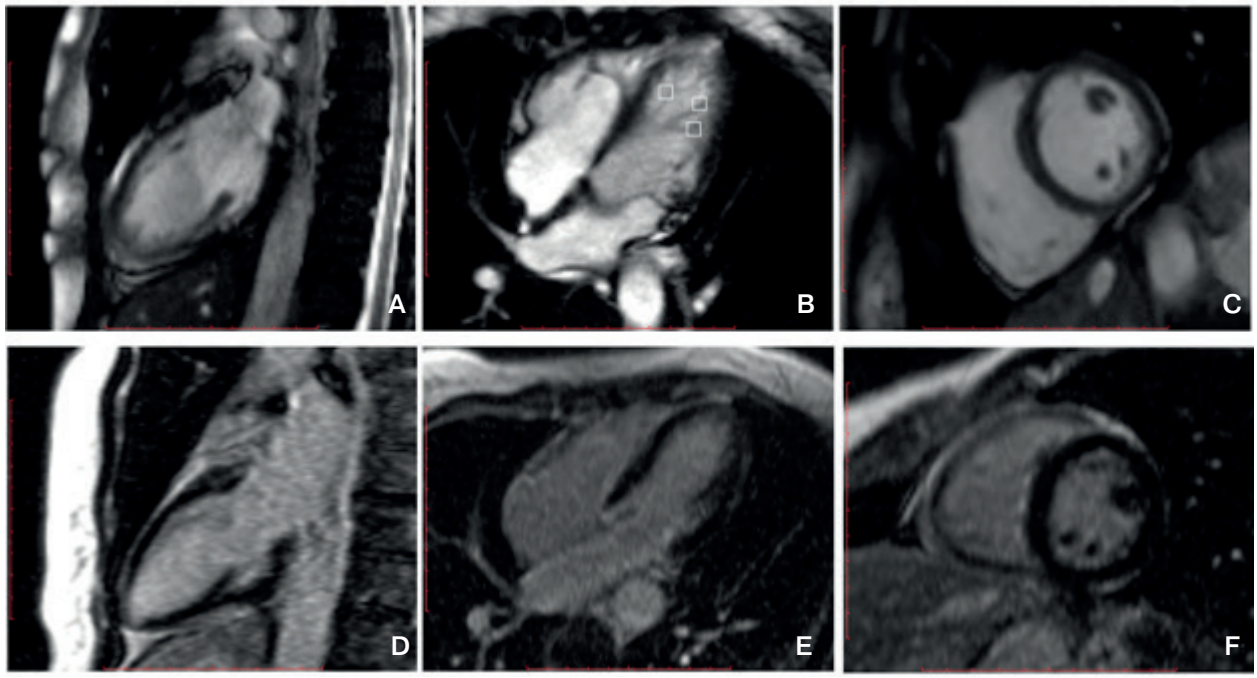


Figure 5. (**A**-**C**) Cardiac MRI of the proband's mother, SSFP sequence: **A** — long axis 2-chamber view, **B** — long axis 4-chamber view, **C** — short axis, (**D**-**F**) — delayed contrast enhancement.
Note: □ — additional LV chords, IR sequence with suppression of the myocardial signal. There were no areas of intramyocardial contrasting.

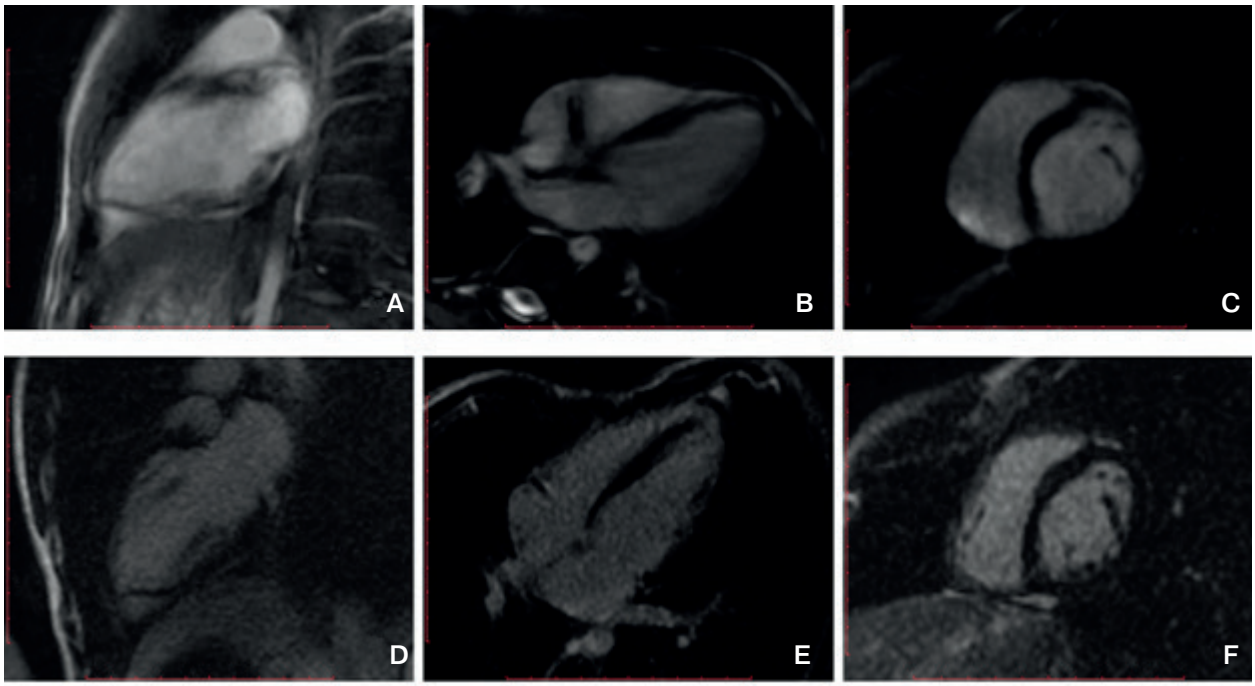


Figure 6. (**A**-**C**) Cardiac MRI of the proband's daughter, SSFP sequence: **A** — long axis 2-chamber view, **B** — long axis 4-chamber view, **C** — short axis, cardiac chambers are not enlarged, not hypertrophied, contractility is not reduced, (**D**-**F**) — delayed contrasting IR sequence with suppression of the myocardial signal. There were no areas of intramyocardial contrasting.

binds myosin heavy chain in thick filaments and titin in elastic filaments [4]. Previs MJ, et al. found that C-MYBPC3 slows actomyosin motion generation in native cardiac thick filaments. This mechanical effect was localized to where cMyBP-C resides within the thick filament (i.e., the C-zones) and was modulated by phosphorylation and site-specific proteolytic degradation. The authors concluded that

Table 2

Cardiac MRI parameters

№	EDV, ml/m^2	LVEF, %	Grothoff				Jacquier, %	Petersen
			NC Mass index, g/m^2	NC mass-to-total mass ratio, %	Noncompacted-to-compacted myocardial mass ratio ⩾3:1 in one segment 1-3, 7-16	Noncompacted-to-compacted myocardial mass ratio ⩾2:1 in 4-6 segments		
I-1	55	74	10	12	-	-	12	-
I-2	61	60	6	12	-	-	12	-
II-2	100	48	20	20	+	-	20	+
II-4	123	35	24	22	+	+	22	+
III-2	73	57	14	20	-	-	20	-

Abbreviations: EDV — end diastolic volume, NC — noncompaction, LVEF — left ventricular ejection fraction.

Table 3

Cardiac MRI data by segments

№	Noncompacted-to-compacted myocardial mass ratio by segments																
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
I-1	0,0	0,0	0,0	0,0	1,1	0,9	0,8	0,0	0,0	0,0	1,9	0,9	0,0	0,0	0,0	1,0	0,0
I-2	1,5	0,0	0,0	0,0	0,6	0,0	2,4	0,0	0,0	2,3	1,7	0,0	0,0	0,0	0,0	3,0	0,0
II-2	1,4	2,3	0,0	1,0	1,0	1,2	2,5	0,7	1,5	2,0	2,2	3,0	1,1	0,0	0,8	1,6	2,8
II-4	2,7	1,0	0,0	2,1	1,3	2,0	3,7	0,0	0,0	1,4	2,9	3,8	3,6	0,0	3,4	1,1	3,3
III-2	0,0	0,0	0,0	0,0	0,0	0,0	1,5	0,0	0,0	0,0	0,0	0,0	1,8	0,0	0,0	0,0	0,0

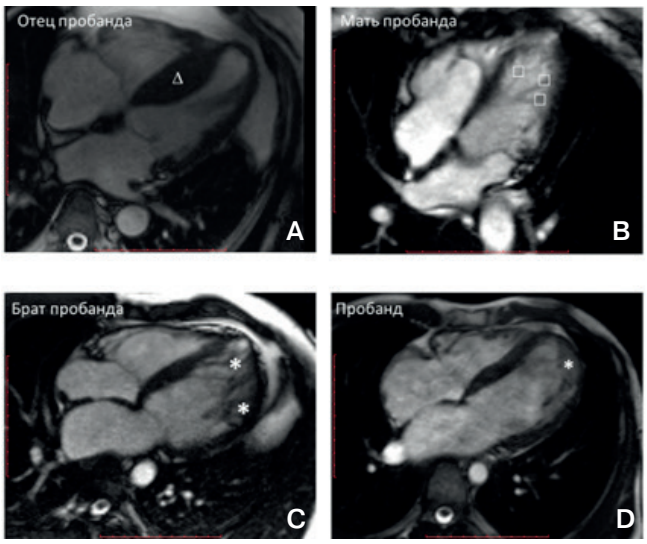


Figure 7. (**A**-**D**) Cardiac MRI, SSFP sequence, long axis 4-chamber view.
Note: Δ — hypertrophied segments of the myocardium, * — noncompact layer of the myocardium, □ — additional LV chords.

cMyBP-C should be considered a member of a tripartite complex with actin and myosin that allows fine tuning of cardiac muscle contraction [5].

A mutation in the *MYBPC3* gene was first described in patients with HCM in 1995 [6]. Subsequently, mutations in this gene have also been described in DCM and LVNC [7, 8].

In 2017, the study by Sedaghat-Hamedani F, et al. was published, which demonstrated the mutation in the *MYBPC3* gene in a large family of several generations with diagnosed LVNC [9]. The authors also asked how different alleles in the same gene can lead to significantly different phenotypes of the disease. Thus, a pathogenic variant in the *MYH7* gene was identified, which was described as HCM, but the proband's phenotype in this study was LVNC. In the study by Richard, et al., 95 patients with LVNC were examined and they underwent exome sequencing, according to the results of which possible genetic causes were found in 50% of cases and a mutation in the *MYBPC3* gene was detected in only 4% of cases [10].

In the study by Waning JI, et al. in 2019, 172 papers were analyzed and the correlation of genotypes and phenotypes of LVNC was carried out [11]. Both variants in the *MYBPC3* and *TTN* genes were associated with cardiac events and had a poorer prognosis. Also in 2019, the same group of authors presented data from work on familial LVNC [12]. All patients were divided into 4 types of LVNC: dilated, hypertrophic, isolated NC, combination of dilated and hypertrophic types. A comparative analysis of

remodeling types in LVNC showed that hypertrophic type had a more favorable prognosis compared to othyrs. It is important to note that the *MYBPC3* gene mutation aggravated the disease course and also led to a poor prognosis.

The presented case of familial LVNC confirms the above facts of the phenotypic heterogeneity of myocardial remodeling in the presence of *MYBPC3* gene mutation, as well as a more unfavorable prognosis in patients with signs of LV dilatation.

In one family, we see that the proband's father has nonobstructive HCM, the proband and his sibling have IVS hypertrophy and signs of LVNC. The proband's daughter has increased trabeculariry without criteria for LVNC, HCM and LV cavity dilatation (Figure 7). The most pronounced degree of LVNC in the proband's brother: 3 Grothoff criteria for LVNC, noncompaction mass of 24 g/m^2; the Grothoff criterion for the relative mass of LVNC in both brothers is slightly below the threshold value (25%) due to the pronounced IVS hypertrophy (Table 2). In addition, the number of segments with LVNC in the proband's brother is significantly greater than in the proband himself (Table 3). Also noteworthy is the presence of massive myocardial fibrosis in the father and brothers as a possible cause of VT, while the proband's brother has fibrosis in almost all LV segments (Figure 4). The disease course in brothers with LVNC is significantly more severe than in the father with HCM. The proband has progressive heart failure with a high risk of SCD, and the proband's brother has severe consequences of stroke as an element of thromboembolic events in LVNC. It should be noted that the proband's brother refused to take HF therapy and anticoagulants.

Despite the absence of clinical manifestations, the 11-year-old proband's daughter needs close attention and dynamic observation, since the presence of morphological changes that are currently slightly manifested, as well as mutations in the *MYBPC3* gene, may lead to the formation of pathological changes in the myocardium (fibrosis, IVS hypertrophy).

Conclusion

Phenotypic heterogeneity of mutations in genes associated with cardiomyopathies both as manifestations of HCM, DCM and LVNC in members of the same family, and as a combination of various types of myocardial remodeling in LVMC, dissolve the boundaries between pathogenetic and etiological aspects of genetically determined cardiomyopathies. At the same time, the presence of LVNC undoubtedly requires additional measures of therapy and prevention.

Relationships and Activities: none.