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Variant of the *FLNC* gene nucleotide sequence in a family with different phenotypic manifestations of left ventricular non-compaction

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Left ventricular non-compaction is a heterogeneous heart disease with various phenotypic and clinical manifestations. The article presents the results of clinical, instrumental and molecular genetic investigations of a family with diagnosed left ventricular non-compaction (LVNC) with different clinical and phenotypic manifestations. As a result of a molecular genetic testing, all family members with the LVNC phenotype were found to have a likely pathogenic variant in the *FLNC* gene. Variants in this gene are associated with a number of cardiomyopathies: dilated, hypertrophic, and restrictive. In the international scientific literature, isolated clinical cases of LVNC development with variants of the *FLNC* gene nucleotide sequence are presented. In our work, we present a case report of LVNC with a variety of clinical manifestations within the same family.

Keywords: left ventricular non-compaction, atherosclerosis, heart failure, sudden cardiac death, familial forms, thromboembolism, stroke, filamin C, *FLNC*.

Relationships and Activities: none.

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Non-compact left ventricular myocardium (NLVM) — a heterogeneous heart disease characterized by the presence of bilayered myocardial structure and increased trabecularity [1]. Despite the relatively short history of study of this disease, it is obvious that its phenotypic manifestations are extremely diverse. Thus, the study by Towbin JA, et al. identified 8 NLVM phenotypes [1]. The study by Waning JI, et al. identified only 3 phenotypes of the disease and showed genetic diversity of NLVM [2]. Given the pronounced heterogeneity of NLVM, as well as the clinical course variability — the presence of both asymptomatic forms and forms with progressive heart failure (HF), life-threatening arrhythmias and thromboembolic complications, more and more studies are aimed to assess the genotype-phenotype correlation and to assess the disease prognosis [3]. A number of studies have shown a link between NLVM development and variants of nucleotide sequence in the gene *FLNC* [4]. Filamin C (FLNC) is a structural protein that has an actin binding domain and a C-terminal dimerization domain. Expression of filamin C is restricted to the transverse striated muscles and is localized around the Z-disk, sarcolemma, myotendinous junction, and intercalated discs. Its main role is to maintain the sarcomere structural integrity by cross-linking actin filaments and attaching sarcolemmal proteins to cytoskeleton. The main FLNC interacting elements are either part of the Z-disk (myotilin, myosenin, myopodin, and calcarcin) or sarcolemma-associated proteins (integrin β1, sarcoglycan delta). Proteases, such as calpain, can regulate the interaction between FLNC and sarcoglycans by cleaving the corresponding FLNC binding domains [5].

The gene *FLNC* corresponds to chromosome 7q32-35 and has two major transcripts, NM_001127487.2 and NM_001458.4. It consists of 49 coding exons [6]. The difference between two transcripts is the presence or absence of exon 31, which encodes the hinge region between Ig-like domains 15 and 16 [7]. Variants in the gene *FLNC* were initially described in patients with myofibrillar myopathy [8, 9], later, when analyzing a large cohort of patients with cardiomyopathies, the important role of *FLNC* in development of hypertrophic (HCMP) [10] and dilated (DCMP) cardiomyopathies was determined; a few cases of restrictive cardiomyopathy (RCMP) have also been described [11]. In this paper, we want to present a family with NLVM resulting from mutation in the gene *FLNC*, with different phenotypes of the disease and a rather late onset.

Material and methods

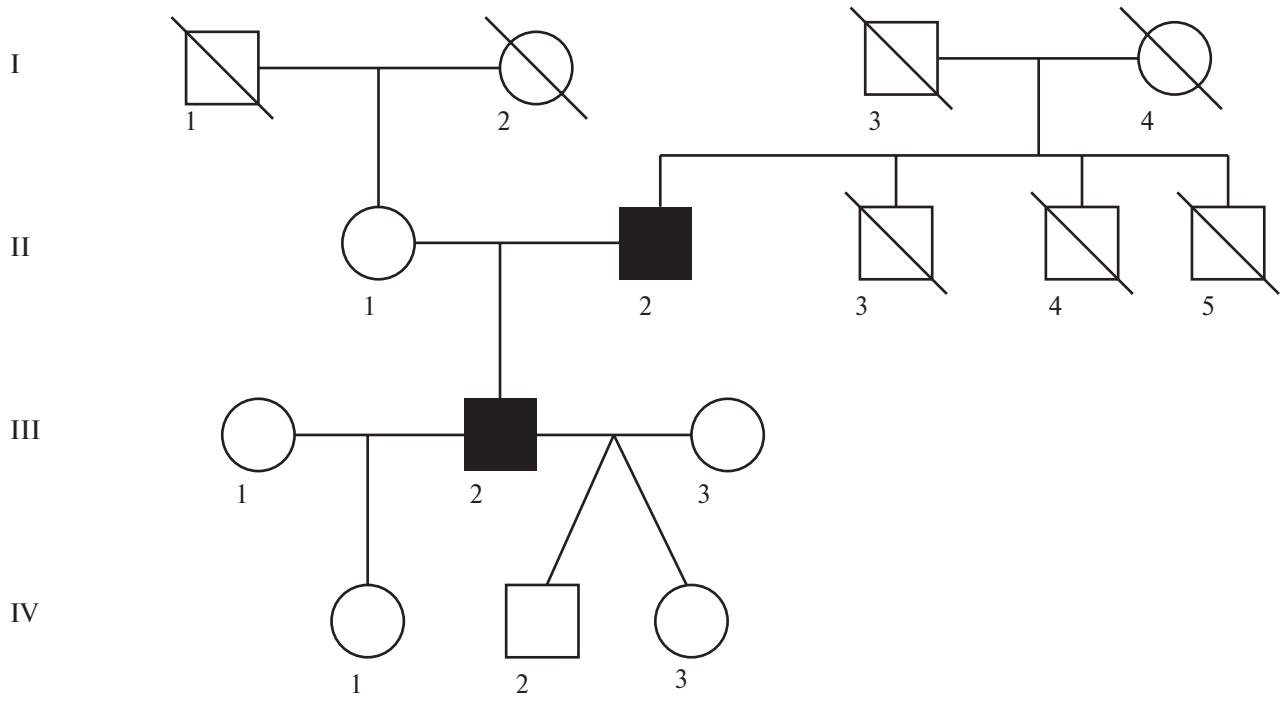
Based on the multicenter register "Non-compact myocardium", a family with a familial form of NLVM was selected (Figure 1). All participants signed an informed consent to participate in the study and to process personal data. The study design was approved by the Ethics Committee of the FSBI "National Medical Research Center for Therapy and Preventive Medicine" of the Ministry of Health of Russia. All participants underwent a clinical and instrumental examination according to the protocol described earlier [12]. The NLVM diagnosis was established based on the criteria of noncompact myocardium by echocardiography (EchoCG) [13] and magnetic resonance imaging (MRI) [14].

Deoxyribonucleic acid (DNA) was isolated using the QIAamp DNA Blood Mini Kit (Qiagen, Germany). DNA concentration was determined on Qubit 4.0 fluorimeter (Thermo Fisher Scientific, USA). The next generation sequencing was performed on Ion S5 device (Thermo Fisher Scientific, USA). Ampliseq libraries were prepared using Ion Chef (Thermo Fisher Scientific, USA) using a custom panel developed by Ion AmpliSeq Designer (Thermo Fisher Scientific, USA). The panel included the sequences of exons of 137 genes associated with NLVM and other types of cardiomyopathies [15]. As a result of sequencing and bioinformatic analysis, files in FASTQ and VCF formats were obtained. Genetic variants with frequencies in the gnomAD database of <1% were selected for clinical interpretation (https://gnomad.broadinstitute.org/) [16]. The variant pathogenicity was assessed in accordance with the ACMG/AMP 2015 recommendations [17]. Validation of the identified variant was performed by Sanger sequencing. The nucleotide sequence of polymerase chain reaction products was determined using an ABI PRISM BigDye Terminator v.3.1 reagent kit followed by analysis of reaction products on an Applied Biosystem 3500 DNA Analyzer (Thermo Fisher Scientific, USA). All sequencing steps were performed according to the manufacturers' protocols.

Results

Proband — a 47-year-old patient with normosthenic physique. Height: 187 cm. Weight: 90 kg. Body mass index: 35,7 kg/m^2.

At the age of 39, in 2013, he first noticed dyspnea on light exercise, general weakness, swollen legs. In January 2014, he had a short-term episode of loss of consciousness, for which he was hospitalized, where EchoCG revealed mitral regurgitation of the 4th degree, dilatation of the left heart, decreased left ventricular ejection fraction (LV EF) to 40%. In this connection, in July 2014, mitral valve prosthetics with a mechanical prosthesis and tricuspid valve plastic surgery according to De Vega were performed. In the early postoperative period, he suffered an ischemic stroke in the basin



I-1	Died at the age of 68, the cause is unknown
I-2	Died at the age of 72, the cause is unknown
I-3	Died at 56, cardiomyopathy, heart failure
I-4	Died at the age of 70, the cause is unknown
II-1	65 years old, disease none
II-2	69 years old, cardiomyopathy, heart failure, cardiac arrhythmias
II-3	Died at 64, cardiomyopathy, heart failure
II-4	Died at 65, myocardial infarction
II-5	Drowned at 2 years old
III-1	40 years old, not examined
III-2	Proband, 42 years old, cardiomyopathy, heart failure, cardiac arrhythmias
III-3	38 years old, not examined
IV-1	12 years old, not examined
IV-2	1 year old, disease none
IV-3	1 year old, disease none

Figure 1. Pedigree.

of the right middle cerebral artery. After surgical treatment, no significant improvement was noted, the phenomena of chronic HF (CHF) persisted against the background of multicomponent CHF therapy. Consulted by a cardiologist at the FSBI "National Medical Research Center for Therapy and Preventive Medicine" of the Ministry of Health of Russia, it is recommended to conduct an MRI of the heart. According to MRI (Figure 2): end-diastolic dimension (EDD) 8,1 cm, in the apex of the left ventricle thickness of compact layer is 5 mm, noncompact layer — 33 mm, in the area of apex and middle segments of anterior, lateral and lower walls the thickness of noncompact layer was 17 mm, compact 8 mm, DCM, noncompact myocardium, EF — 23%, akinesis myocardium of apex location and diffuse hypokinesis. A transmural area of contrast is detected in the medial anterolateral segment. In 2015, he was on inpatient treatment at the FSBI "National Medical Research Center for Therapy and Preventive Medicine": taking into account the presence of CHF, systolic dysfunction, signs of left leg complete bundle branch block (LLBBB) with a QRS complex width of 160 ms, a resynchronizing device with cardioverter defibrillator (CRT-d) function was implanted and HF therapy was adjusted. However, 6 months later, against the background of atrial flutter, his condition worsened in the

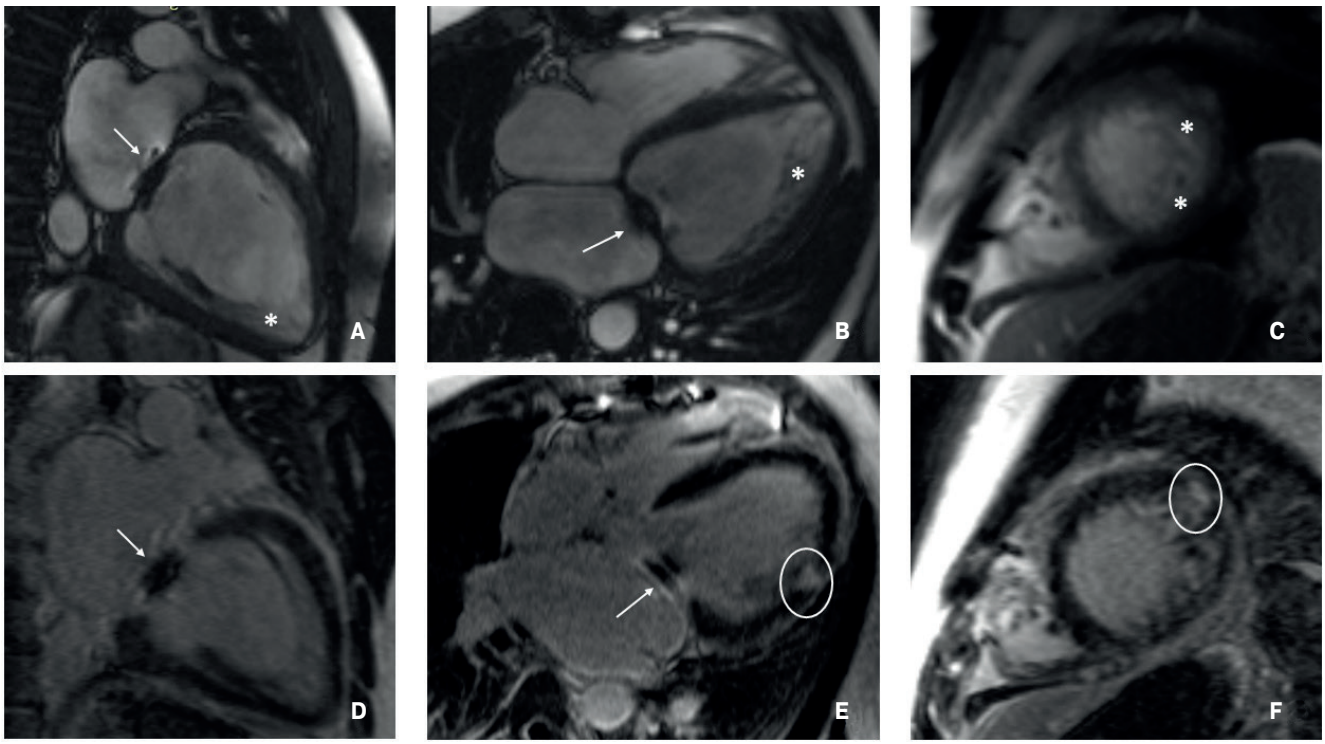


Figure 2. Cardiac MRI, **proband** in cine mode, SSFP-sequencing:
A — long axis, 2-chamber projection, **B** — long axis, 4-chamber projection, **C** — short axis at the level of apical segments.
Notes: the left chamber of the heart significantly expanded (indexed LV EDV — 167 ml/m^2 at the rate of up to 92 ml/m^2), LV EF — 23%; * — noncompact myocardial layer; an arrow indicates the artifact from prosthetic mitral valve; (**D**-**F**) — delayed contrast enhancement, IR sequence with the suppression of signal from myocardium.
A transmural area of contrast (circled) is detected in the medial anterolateral segment.
Abbreviations: EDV — end-diastolic volume, LV — the left ventricle, EF — ejection fraction.

form of decreased tolerance to physical exertion, edema appeared; therefore, the patient underwent radiofrequency ablation of the arrhythmogenic focus in October 2016. After the intervention, the condition is with positive dynamics. According to EchoCG data in 2016: left atrium (LA) — 7,3 cm, EDD — 7,7 cm, interventricular septum thickness (IVST) — 1,2 cm, EF — 42%. He felt satisfactory for a long time. In March 2020, deterioration of the condition due to decompensation of CHF, underwent inpatient treatment at the FSBI "National Medical Research Center for Therapy and Preventive Medicine". EchoCG data showed negative dynamics in the form of sharp increase of heart chambers and decrease of LV systolic function (LV EF — 25%). Holter electrocardiogram monitoring (daily monitoring of ECG) recorded 22 unstable paroxysms of ventricular tachycardia. Drug therapy was adjusted, including the addition of sacubitril/valsartan at a dose of 400 mg/day. At the dynamic examination in 2021, CHF phenomena were relatively compensated, however, according to EchoCG data, the tendency to myocardial remodeling persisted: LV EDD — 9,1 cm, LV EF — 22%, systolic pressure in the pulmonary artery — 58 mm Hg. Taking into account the worsening course, dapagliflozin at a dose of 10 mg was added to the therapy and a waiting list for heart transplantation was recommended.

Proband's father is 75 years old, of normosthenic build, height 178 cm, weight 74 kg.

From the age of 40, he noted an increase in blood pressure to 200/120 mm Hg, from the age of 52, had a constant form of atrial fibrillation (AF), CHF phenomena in the form of shortness of breath during exercise, edema of the lower extremities. Signs of focal changes were recorded on the electrocardiogram (ECG). In 2006, at the age of 60, an acute visual impairment occurred against the background of increased blood pressure up to 200/110 mm Hg, an acute violation of cerebral circulation was diagnosed. In August 2015, as part of a family screening, he underwent a follow-up examination at the FSBI "National Medical Research Center for Therapy and Preventive Medicine". In the tests: N-terminal brain natriuretic peptide 345 (0-125) pg/ml, hemoglobin 105 g/l, D-dimer 847 ng/ml (0-255), creatinine 153 mmol/l. On ECG: AF with a heart rate of 47-100, signs of LV

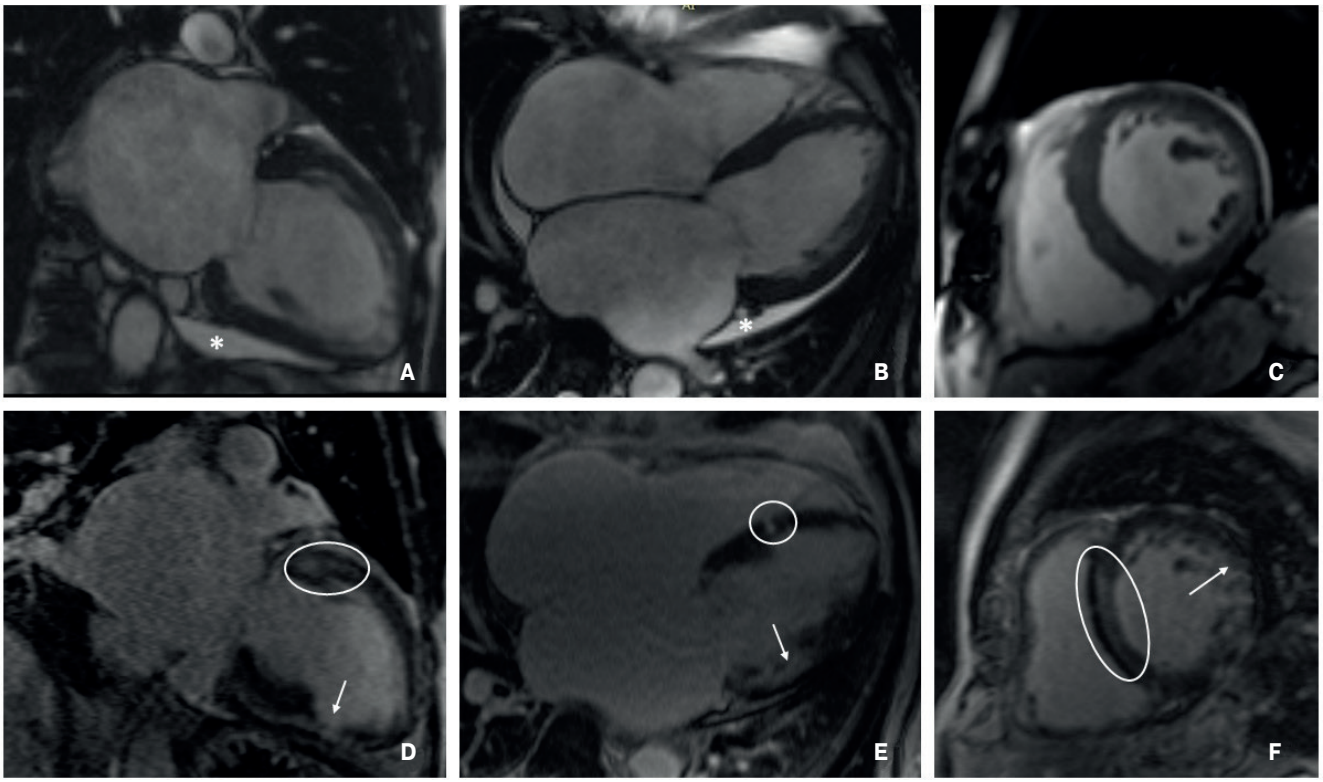


Figure 3. MRI of the **father**'s heart, **proband** in cine mode, SSFP sequence:
A — long axis, 2-chamber projection, **B** — long axis, 4-chamber projection, **C** — short axis at the level of apical segments.
Notes: significant atrial dilation (LA 7,7×7,2 cm, RA — 11,5×8,0 cm), moderate dilation of LV cavity (LV EDD — 6,3 cm, LV EDV — 263 ml), LV EF — <20%; * — moderate hydropericardium; (**D**-**F**) — delayed contrast, IR sequencing with myocardial signal suppression.
The basal and middle septal segments show areas of intramyocardial contrast of non-coronary nature (circled); the basal anterolateral and middle inferior segments show scar changes (indicated by arrows).
Abbreviations: EDV — end-diastolic volume, EDD — end-diastolic dimension, LV — left ventricle, LA — left atrium, RA — right atrium, EF — ejection fraction.

hypertrophy, LLBBB. According to XM-ECG data: AF of 45-144 per minute, transient LLBBB, 215 runs of ventricular tachycardia from 3-4-5-6 complexes. According to EchoCG data: LA — 6,2 cm, EDD — 6,2 cm, IVST — 1,1 cm, LV EF — 42%, zones of non-compact myocardium in the apex, anterior and lateral walls, Stolberger criterion. According to MRI of the heart (Figure 3): EF — 12%, IVST — 1,4 cm, EDV 263 ml; in the area of the apex, apical segments of the anterior and lateral walls, increased trabecularity with a ratio of compact and non-compact layer >2. After contrast agent injection, the basal and middle septal segments show areas of intramyocardial contrast of non-coronogenic nature; basal anterolateral and middle inferior segments show cicatricial changes; marked mitral regurgitation, tricuspid regurgitation, significant dilation of both atria (restrictive cardiomyopathy pattern, NLVM syndrome). According to multispiral computed tomography of coronary arteries: stenosing atherosclerosis with a three-vessel disease. Blood clot in the LA atrial appendage. During coronary angiography: stenosis of the proximal segment of anterior interventricular artery — 80%, stenosis of the middle segment of right coronary artery — 80%, angioplasty with stenting of the anterior interventricular artery and the right coronary artery was performed. After discharge, he felt satisfactory and regularly took the recommended therapy. In the period from 2016 to 2020, he was repeatedly hospitalized for HF decompensation. According to EchoCG data dated March 2021: LA — 7,5 cm, EDD — 6,5 cm, IVST — 1,4 cm, EF — 37%, systolic pulmonary artery pressure — 55 mm Hg, hypokinesis of apical, middle, basal, anterior septal, anterior segments. Currently on therapy: sacubitril/valsartan, dapagliflozin, rosuvastatin, bisoprolol, spironolactone, furosemide, apixaban.

The proband's mother is 65 years old, underwent a comprehensive cardiological and neurological examination. According to the results of EchoCG, there were no signs of non-compact myocardium. IVST — 1,0 cm, EDD — 5,2 cm. No data were obtained for the presence of myopathy.

Son proband 3 years was performed echocardiography, the results of which revealed signs of noncompact myocardium in the area of the apex of the LV.

Proband's 3-year-old daughter also underwent an echocardiogram, according to the results of which no pathology was detected.

Genetic analysis. Genetic analysis by next-generation sequencing in three family members (II-2, III-2, IV-2) revealed an rs1554398369 variant in the gene *FLNC* (hg19:chr7:128481344, NM_001458.5:c.1934A>C, NP_001449.3:p.Asp645Ala). Based on the ACMG/AMP pathogenicity criteria 2015 (Richards et al., 2015), this nucleotide sequence variant was classified as a probable-pathogenic variant (class IV of pathogenicity). In Sanger sequencing, the nucleotide sequence variant rs1554398369 in the gene *FLNC* was confirmed in all three family members (II-2, III-2, IV-2).

Discussion

In the last few years, due to the progressive development of genetic research and the accumulation of knowledge in the field of cardiomyopathy research, more and more attention has been paid to various phenotypic manifestations of cardiomyopathies with variants in the same gene. Within 5 years, a number of papers have been published describing variants in the gene *FLNC* in various cardiopathies. In 2017, Gomez et at. published a paper showing the importance of the gene *FLNS* in HCMP development [10]. 448 patients with HCMP who underwent NGS for the genes *MYH7*, *MYBPC3*, *TNNT2*, *TNNI3*, *ACTC1*, *TNNC1*, *MYL2*, *MYL3*, *TPM1* and *FLNC* were examined. After that, 20 variants of *FLNC* candidates were identified in 22 patients. Based on familial segregation and performed functional studies, 6 of the possible variants (in 7 patients) were definitively classified as probable pathogenic, 10 as variants of uncertain significance, and 4 as probable benign. This was the basis for assuming the influence of *FLNC* as a cause of HCMP development. Later, in the study by Cirino AI, et al., 41 patients with HCMP underwent genetic testing, and a variant in the gene *FLNC* was identified in 1 patient [18].

In addition to HCMP development, a number of studies have demonstrated the relationship between variants in the gene *FLNC* with DCM development, for example, in the study by Ader F, et al. 2019 surveyed 1150 patients with various cardiomyopathy (700 HCMP, 300 DCM, 50 RCMP and 100 NLVM), and 28 patients were identified pathogenic variants in the gene *FLNC* (13 patients with HCMP, 10 with DCM, 4 with RCMP and 1 with NLVM). At the same time, missense variants in the gene *FLNC* led to HCMP development, and nonsense variants led to DCM development [5]. There are significantly fewer studies devoted to the combination of NLVM with variants of the gene *FLNC* [4]: in a 2018 study, a likely pathogenic variant in the gene *FLNC* was identified in one patient with NLVM.

Our work presents a family with proven NLVM in the absence of neurological manifestations and myopathy clinic. Attention is drawn to the burdened inheritance on the paternal side for cardiovascular diseases, with a sufficiently favorable course of the disease in the proband's father. The proband's father did not exhibit clinical symptoms of the disease until he was over the age of 60, and there was no regular medication therapy. It is also worth noting the presence of pronounced restriction and marked fibrosis in the proband's father, which is characteristic of pathogenic variants in the gene *FLNC* [19]. On the contrary, no data for restriction were obtained in the proband, i.e., one can speak about the presence of different NLVM phenotypes within one family, which was demonstrated in our previously published work [12]. The disease in the proband debuted with clinics of CH and progressed after surgical intervention on the mitral valve, which is probably caused by altered myocardial structure, which, in turn, could be the cause of poor response to resynchronization therapy.

The presence of thromboembolic complications (acute cerebrovascular accident, LV cavity thrombosis) in both patients is noteworthy, which may be due to several reasons: the presence of direct noncompaction layer, decreased PV, as well as FP. In this case, there is a set of reasons that led to development of thromboembolic complications.

Given that *FLNC* variants lead to such a variety of clinical manifestations, it is worth mentioning that it is poorly studied, so a more detailed study of mutations in the gene, as well as the identification of links between the genotype and phenotype, will help to identify the connection and predict the development of the disease and its consequences, as well as to develop targeted therapies.

Conclusion

This paper presents a case of familial form of cardiomyopathy in patients with a nucleotide sequence variant in the gene *FLNC*. Proband and his relatives had various phenotypic manifestations of NLVM. The obtained clinical and molecular genetic data confirm the genetic and phenotypic heterogeneity of NLVM, with features characteristic of pathogenic variants in the gene *FLNC*. The study of familial forms of cardiomyopathies expands the information on the disease genesis and confirms the necessity of family screening in order to carry out timely measures aimed at the prevention of cardiovascular complications.

Relationships and Activities: none.

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