New Variant of *MYH7* Gene Nucleotide Sequence in Familial Non-Compaction Cardiomyopathy with Benign Course

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Left ventricular non-compaction (LVNC) is a genetically determined cardiomyopathy characterized by different variants of the clinical course. LVNC family cases allow to study in more details the role of genetic factors in cardiomyopathy pathogenesis and prognosis, as well as to determine clinical course features.

Aim. To demonstrate a case of LVNC familial form with a stable benign course and to assess the possible relationship of the detected mutation with the disease prognosis.

Material and methods. A family with LVNC was included in the study. The patient with LVNC and his 1st and 2nd degree of kinship relatives underwent clinical and instrumental examination and exome sequencing. LVNC was diagnosed in proband and proband's father. LVNC diagnosis was established basing on echo and magnetic resonance imaging (MRI) criteria.

Results. This article presents the results of a comprehensive clinical and instrumental examination of a family with LVNC with a new variant in the *MYH7* gene, the absence of intramyocardial fibrosis according to MRI of the heart and a favorable disease course, both in proband's father and proband himself. A comparative analysis of the data obtained with the results of recent large-scale studies and meta-analyses devoted to the study of prognostic factors in patients with LVNC, with identified variants in the *MYH7* gene.

Conclusions. The variant of *p.His1338Pro* identified in the *MYH7* gene may be associated with the development of LVNC with a benign course.

Keywords: *MYH7*, exomic sequencing, left ventricular non-compaction.

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Introduction

Left ventricular non-compaction (LVNC) is a heterogeneous disease characterized by the presence of a two-layer myocardial structure. The endocardium is a spongy structure with multiple outgrowths and intertrabecular spaces communicating with the left ventricle (LV) cavity, without coronary vascular supply. This disease is associated with malignant arrhythmias, thromboembolic events, and LV dysfunction. Considering the hereditary nature of the disease, the identification of family forms of myocardial non-compaction represents a great theoretic and practical interest. The familial form of LVNC is described in approximately 26-64% of all cases of non-compact cardiomyopathy [1,2]. But at that time, the phenotypic manifestation of cardiomyopathy and the clinical picture in family members can be completely different. In this regard, it is of great interest to study the clinical course of LVNC familial forms, as well as to identify genetically determined forms in order to estimate the prognosis in asymptomatic patients.

The aim of the study was to evaluate the possible association of the determined mutation with the prognosis and course of the disease in the familial form of non-compact cardiomyopathy.

Material and methods

The study included a family with diagnosed LVNC. All participants signed an informed consent to participate in the study and provided personal data for the processing. The study design was approved by the Local Ethics Committee of the National Medical Research Center for Therapy and Preventive Medicine. All participants underwent clinical and instrumental examination according to the protocol described in our earlier publications [3]. The diagnosis of LVNC was made according to echocardiographic (ECHO) criteria for a non-compact myocardium [4] and was confirmed with reference to the magnetic resonance imaging (MRI) criteria [5,6]. Criterion A. Jacquier et al. [5]: the ratio of the mass of the non-compact layer to the total mass of the myocardium of 20% or more indicates the presence of LVNC. Criterion S. Petersen et al. [6]: the ratio of the thickness of the non-compact and compact layers of the myocardium more than 2.3 suggests a LVNC diagnosis.

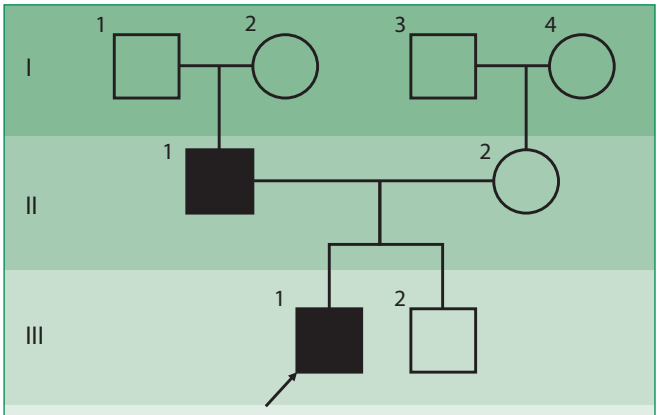
DNA was isolated using the QIAamp DNA Blood Mini Kit (Qiagen, Germany). DNA concentration was determined on a Qubit 4.0 fluorimeter (Thermo Fisher Scientific, USA). The next generation sequencing was carried out using Ion S5 System (Thermo Fisher Scientific, USA). Amplicon libraries were prepared with an Ion Chef System (Thermo Fisher Scientific, USA) using a custom panel developed in the Ion AmpliSeq Designer (Thermo Fisher Scientific, USA). The panel included 137 genes for which, according to recent publications, an association with non-compact and other types of cardiomyopathies was demonstrated *(ABCC9, ACADVL, ACTA1, ACTC1, ACTN2, AGK, AGL, AGPAT2, ALMS1, AMPD1, ANK2, ANKRD1, BAG3, CACNA1C, CALR3, CASQ2, CAV3, COQ2, COX15, COX6B1, CRYAB, CSRP3, CTF1, CTNNA3, DES, DMD, DMPK, DNAJC19, DNM1L, DOLK, DSC2, DSG2, DSP, DTNA, EMD, EYA4, FBN2, FHL1, FHL2, FHOD3, FKTN, FLNC, FOXD4, GATA4, GATA6, GATAD1, GJA5, GLA, GLB1, HADHB, HCCS, HCN4, HFE, HRAS, ILK, JPH2, JUP, KCNE1, KCNE2, KCNH2, KCNJ2, KCNJ8, KCNQ1, LAMA4, LAMP2, LDB3, LMNA, MEF2A, MIB1, MRPL3, MRPS22, MTO1, MURC, MYBPC3, MYH6, MYH7, MYH7B, MYL2, MYL3, MYLK2, MYOM1, MYOT, MYOZ2, MYPN, NEBL, NEXN, NKX2-5, NNT, NOTCH1, PDLIM3, PHKA1, PKP2, PLEC, PLEKHM2, PLN, PMP22, PRDM16, PRKAG2, PSEN1, PSEN2, PTPN11, RAF1, RBM20, RYR2, SCN1B, SCN5A, SCO2, SDHA, SDHD, SGCD, SHOC2, SIX1, SLC25A3, SLC25A4, SURF1, SYNE1, SYNE2, TAZ, TBX1, TBX20, TBX5, TCAP, TGFB3, TMEM43, TMEM70, TMPO, TNNC1, TNNI3, TNNT2, TNNT3, TPM1, TRIM63, TSFM, TTN, TTR, TXNRD2, VCL)*. All stages of sequencing were performed according to the original manufacturers protocols. Data from sequencing and bioinformatic analysis were represented as .fastq and .vcf files. Genetic variants with frequencies <0.5% in the gnomAD database were selected for clinical interpretation. Evaluation of the pathogenic power of the variants was carried out in accordance with the Guidelines ACMG/AMP (2015) [7]. Con-

firmation of the variants was made by Sanger sequencing.

Primers flanking the region with the polymorphisms found in the nucleotide sequences were selected: F_CTGAATGGCGTCCGTCTCAT and R_AGGCCAAGGGATGATGTTGA (polymerase chain reaction [PCR] product size 273 bp). PCR was performed in 20 mcL of a mixture containing 0.2 mM of each nucleotide, 1×PCR buffer, 20 ng of DNA template, 10 ng of each primer, 2.5 U DNA polymerase. Amplification was performed on a GeneAmp PCR System 9700 thermocycler (Thermo Fisher Scientific, USA) with the following parameters: 95°C – 300 s; 30 cycles: 95°C – 30 s, 62°C – 30 s, 72°C – 30 s; 72°C – 600 s. Before the Sanger reaction, the obtained amplicons were purified using a commercial ExoSAP-IT reagent (Affymetrix, USA) according to the protocol of the manufacturer. The nucleotide sequence of PCR products was determined using the ABI PRISM® BigDye™ Terminator reagent kit v.3.1 followed by analysis of the reaction products on an automated DNA sequencer Applied Biosystem 3500 DNA Analyzer (Thermo Fisher Scientific, USA).

Results

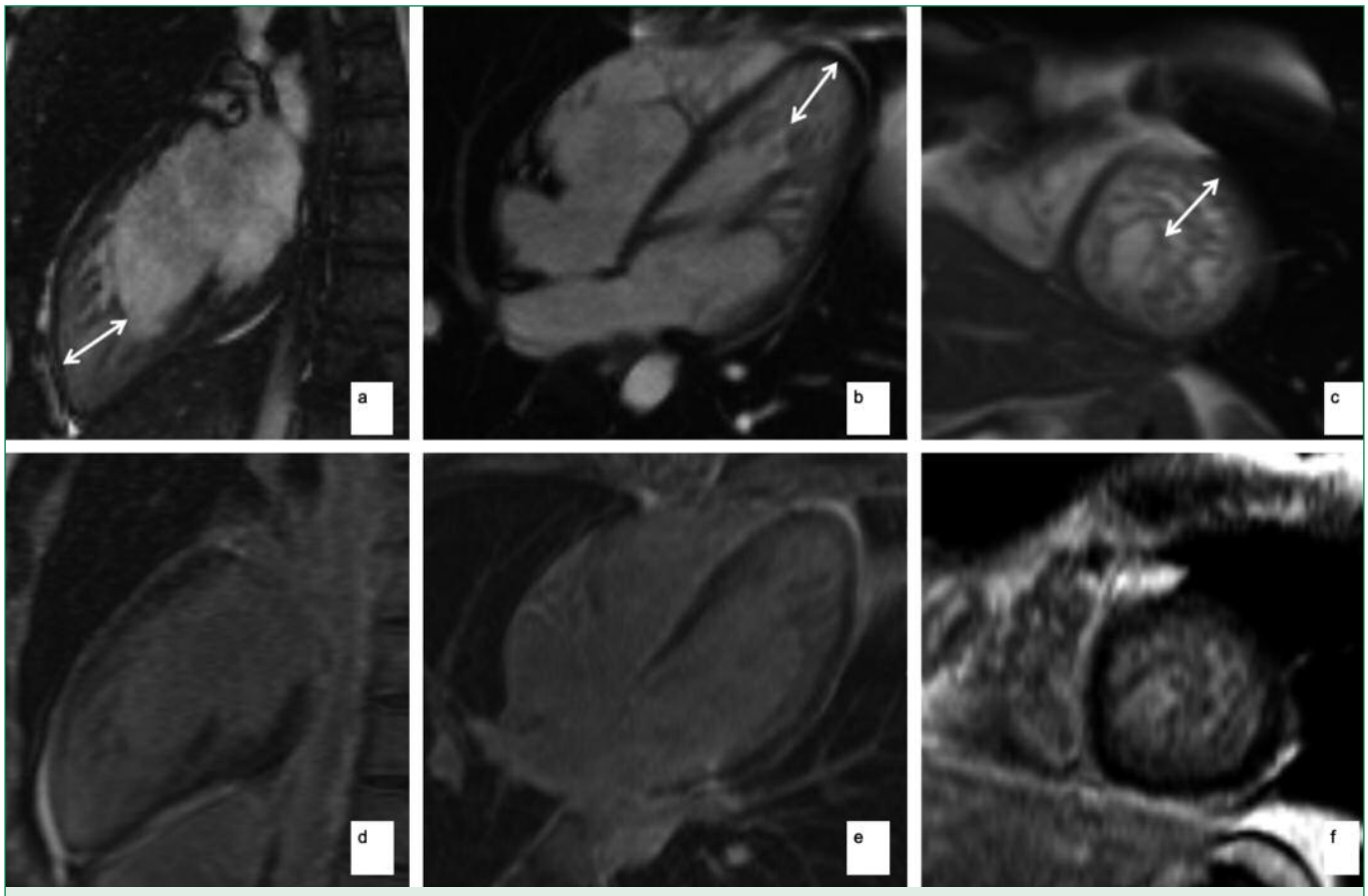
We present clinical demonstration of family with LVNC including the instrumental and laboratory findings and results of the molecular genetic examination (Fig. 1).



I-1 Died at 62, unknown cause
I-2 Died at 75, stroke
I-3 Died at 69, unknown cause
I-4 Died at 75, diabetes
II-1 56 years old, LVNC, cardiac arrhythmias, heart failure
II-2 59 years old, healthy
III-1 Proband 32 years, LVNC, cardiac arrhythmias
III-2 28 years old, healthy
LVNC – left ventricular non-compaction

Figure 1. Genealogy of proband

Proband – a 32-year-old male with asthenic constitution (height 186 cm, weight 65 kg) was under medical supervision at a cardiologist since the 8 months of age due to ventricular extrasystoles (VES) after acute purulent otitis. Considering ventricular ectopy, he was administered potassium, magnesium and amiodarone that contributed to some improvement. In 1999, he was hospitalized at the I.M. Sechenov Pediatric Clinic due to deterioration resulting from acute respiratory infection. ECHO showed mitral valve (MV) prolapse of 6 mm with moderate decrease in the systolic function of the heart and LV volume overload. The patient also presented sinus tachycardia with supraventricular bigeminy on the electrocardiogram (ECG). Based on the medical examination data, the patient was diagnosed with infectious-allergic myocarditis and started therapy with atenolol 25 mg/day and plaquenil 200 mg/day for 2 months. Later the patient remained stable and did not take medications. Since 2009, there has been a deterioration with acceleration of supraventricular and ventricular ectopy. Holter ECG monitoring demonstrated sinus rhythm with an average heart rate of 62 per minute, maximum heart rate of 131 per minute, supraventricular extrasystoles (SVE) of 25000/day, runs of supraventricular tachycardia – 240/day (the longest run of 42 complexes at night). Bisoprolol has been prescribed with a positive effect. The patient remained under medical observation at the local clinic. In 2013, ECHO revealed increased LV trabecularity with signs of non-compact myocardium: mild MV prolapse, lowering of LV ejection fraction (EF) – 46% with LV end-diastolic diameter (EDD) – 4.5 cm. Since 2013 the patient constantly took losartan 25 mg/day and bisoprolol 2.5 mg/day. In April 2016 he was referred to the State Research Center for Preventive Medicine. In blood tests, all indicators were within normal values. Holter ECG monitoring (while taking bisoprolol 2.5 mg/day) showed sinus rhythm with a heart rate of 47-76-125 per minute, VES – 17/day, SVE – 129/day, while pauses were not registered. ECHO revealed EDD – 5.1 cm, the

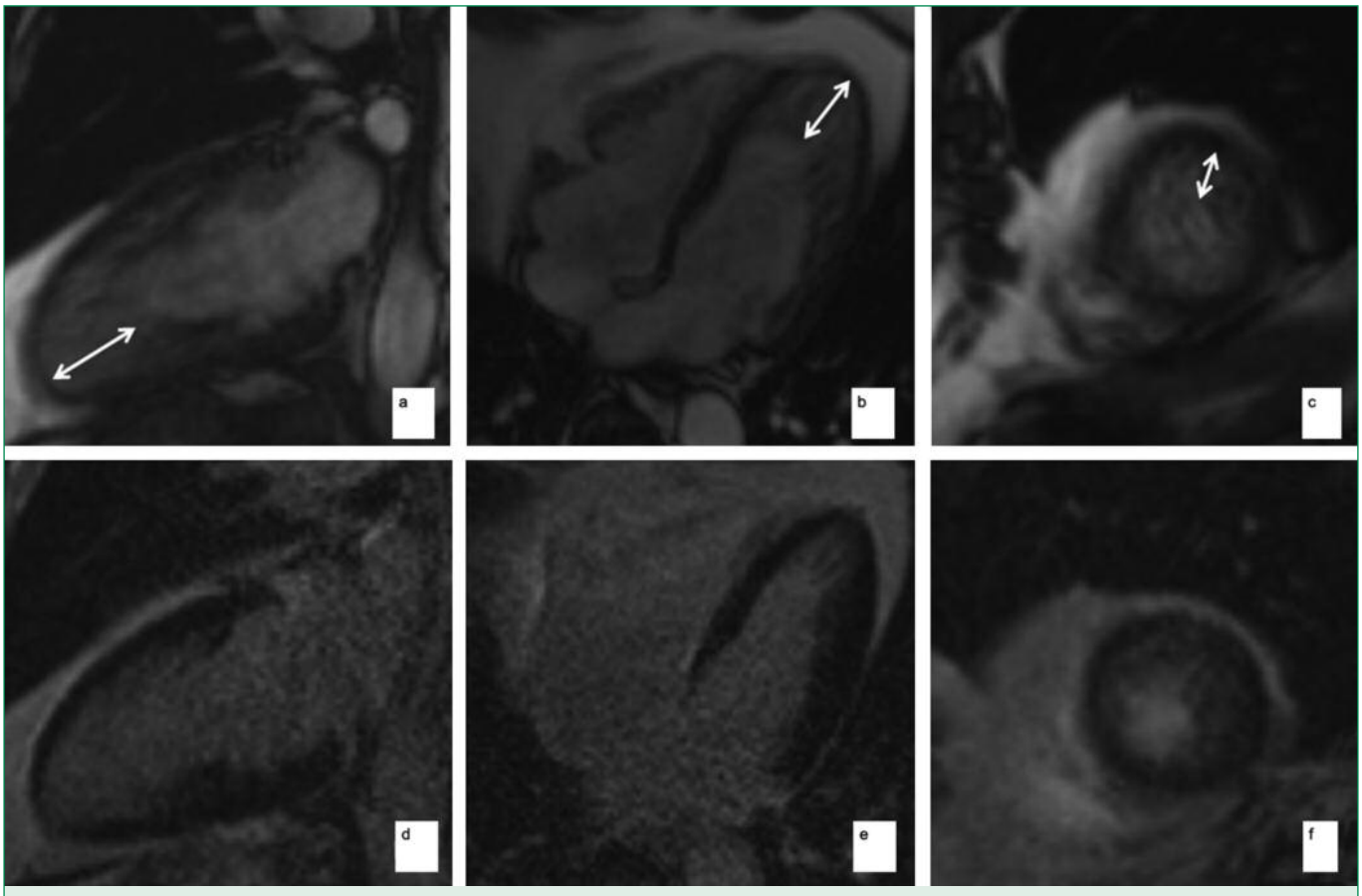


a,b,c – images of cine MRI, arrows indicate the thickness of the non-compact layer; d,e,f – phase of delayed contrast.
There are no areas of myocardial contrast, which indicates the absence of intramyocardial fibrosis
MRI – magnetic resonance imaging

Figure 2. Cardiac MRI of proband

thickness of the interventricular septum (IVS) – 0.8 cm, EF — 43%, and aneurysm of the interatrial septum. It also demonstrated signs of non-compact myocardium of LV and right ventricle (RV) with the myocardium thickness in the apex and lateral wall up to 2.1 cm (1.4 cm as a result of non-compact part). Contrast-enhanced cardiac MRI (at the Radiology Department of Moscow State University named after M.V. Lomonosov) showed non-compact RV and LV cardiopathy, the ratio of the thickness of the non-compact and compact layers of the myocardium was 4:1-8:1; while the mass of a non-compact part comprised 36.8% of the mass of a compact myocardium; LV EDD – 6 cm, EF - 49% (Fig. 2):

Father of proband – a 57-year-old male with normosthenic constitution (height 182, weight 98 kg), was under the cardiologist's consideration in childhood due to rheumatic disease. After tonsillectomy in 1970 he stopped this medical monitoring. Since 2012, he began to experience some arrhythmias. He was referred to Bakulev Center for Cardiovascular Surgery, where coronary angiography (CAG) was performed, showing intact coronary arteries. ECHO also revealed signs of a non-compact myocardium. Cardiac MRI (radiologist S.A. Aleksandrova) confirmed non-compact cardiopathy (Fig.3) while the mass of non-compact part comprised 27.3% of the mass of a compact myocardium. Despite the results the patient was not under medical observation. In 2018, he had cardiological check up at the National Research Center for Preventive Medicine. Blood tests were normal. Holter ECG monitoring revealed atrial fibrillation with an average ventricular rate of 86 beats per minute, VES – 246/day, maximal pause of 2.98 sec. ECHO showed enlargement of left atrium – 4.6 cm, LV EDD – 6.1 cm,



a,b,c – images of a cine MRI, the arrows indicate the thickness of the non-compact layer; d,e,f – phase of delayed contrast. There are no areas of myocardial contrast, which indicates the absence of intramyocardial fibrosis
MRI – magnetic resonance imaging

Figure 3. Cardiac MRI of the proband's father

IVS – 1.0 cm, LVEF – 37%, RV – 4.5 cm. The thickness of the non-compact layer was 2.6 cm in the area of LV apex. After the examination, therapy with antagonists of mineralocorticoid receptors, angiotensin-converting enzyme inhibitors, beta-blockers and anticoagulants was prescribed.

Mother of proband – a 59-year-old female also underwent medical examination (including echocardiography). There were no signs of a non-compact myocardium (IVS thickness – 1.0 cm, LV EDD – 5.0 cm).

Brother of proband – a 28-year-old male with normosthenic constitution (height 189, weight 78 kg) had no medical history of cardiac pathology. A comprehensive cardiological examination was performed. Blood tests were normal. Holter ECG monitoring demonstrated sinus rhythm with an average heart rate of 82 beats/minute, SVE – 5/day. ECHO revealed LV EDD – 4.6 cm, IVS – 1.0 cm, LVEF – 52% with signs of a non-compact myocardium in the apex and lateral wall (Stolberger criterion – two-layer myocardial structure, more than three trabeculae in the LV and intertrabecular spaces connected with LV cavity).

Molecular Genetic Diagnostics

The proband had heterozygous nonsynonymous substitution in exon 30 of the *MYH7* gene *(hg19:chr14:23887575) NM_000257:c.4013*A>C, that was not described before and led to the amino acid substitution *p.His1338Pro*. It is known that mutations in the *MYH7* gene are responsible for a significant proportion of cases of genetically determined LVNC. This variant is not registered in the gnomAD control sample. According to DNA sequence alignment data of 100 vertebrates (multiz100way), the

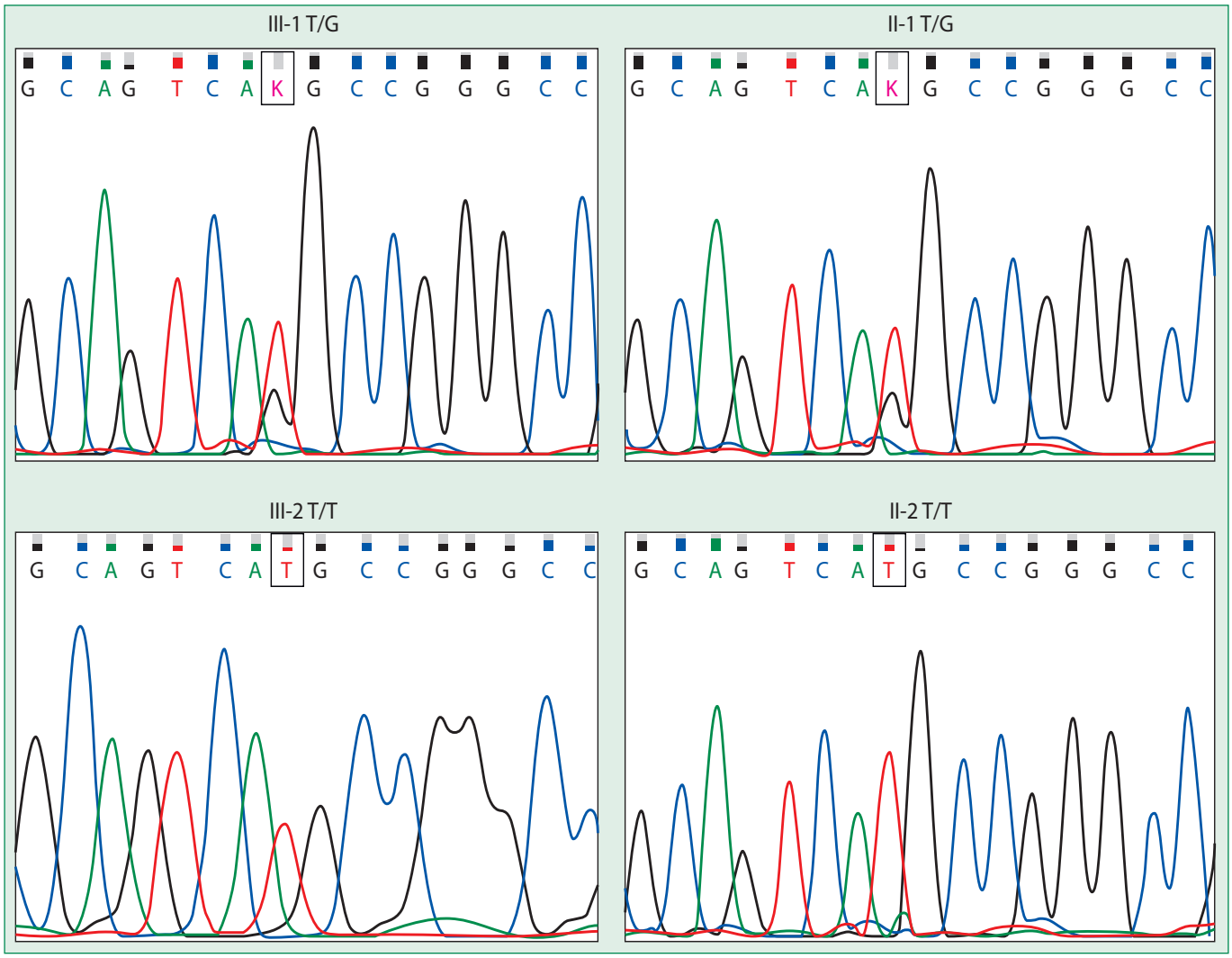


Figure 4. Electrophoregram of proband (III-1) and his relatives (III-2, II-1, II-2) on *MYH7*: c.4013A>C (reference sequence in GenBank: NM_000257).

location where the mutation occurred, was characterized by high conservatism, which could indicate the functional value of this section of the protein. Predictive algorithms for evaluation the pathogenicity of mutations also demonstrated a high probability of protein functions damage as a result of the replacement of *p.His1338Pro* (SIFT: 0.0, PolyPhen-2: 0.95). The identified variant in the *MYH7* gene was present also in the proband's father, but was absent in his mother and brother, who had one ECHO criterion for non-compact myocardium. Cumulatively, the replacement *p.His1338Pro* was classified as an option with uncertain clinical significance.

The revealed variant was confirmed by the Sanger sequencing method (Fig. 4).

Discussion

Currently, the prognosis in patients with LVNC varies from a completely favorable to a fulminant course requiring heart transplantation [8,9]. In the presented case, course of the disease is rather favorable, both in the proband and his father. In the clinical presentation of proband supraventricular cardiac arrhythmias predominate. His father has signs of moderate heart failure (NYHA I functional class) despite reduced LV ejection fraction, dilatation of the cardiac chambers, chronic atrial fibrillation and poor treatment adherence (the patient does not follow medical recommendations, including anticoagulants).

In the study of S. Li et al., the correlation between a positive genetic status and a poor prognosis of the

disease was demonstrated [10]. In a cohort of patients with LVNC, genetic screening was performed, as a result of which 42 pathogenic variants were detected in 38 patients (38%). Most often, mutations were found in the genes: *TTN* (36%), *MYH7* (14%), *MYBPC3* (10%). Initially, atrial fibrillation and positive family history were more often detected in patients with identified mutations, as well as these patients had a lower LV ejection fraction compared to patients without identified mutations. The follow up period was 4.2 years, during which patients with identified mutations more often reached primary endpoints compared to patients without identified mutations (50.0% versus 23.5%; p=0.013). Multivariate analysis showed that patients with identified mutations had a higher risk of death and heart transplantation, regardless of age, gender, and systolic function at the screening stage.

Another author group (J.I. Waning et al.) presented the results of a study that included 327 patients with LVNC [11]. All patients were divided into three groups: genetic 32% (81 adults and 23 children), probably genetic 16% (45 adults and 8 children) and sporadic 52% (149 adults and 21 children). Mutations in the genes *MYH7*, *MYBPC3*, and *TTN* were the most common (71 cases in the genetic group). The risk of LV systolic function impairment was higher in the group of genetic patients compared with other groups (p=0.024). Despite the high risk of complications in the group with identified mutations, it was shown that patients with mutations in the *MYH7* gene had a lower risk of major cardiovascular events (p=0.03), which indicated a more favorable prognosis for these patients compared to participants with other mutations. This conclusion was confirmed in a previously published work by F. Sedaghat-Hamedani et al., who revealed an association between poor prognosis in patients and mutations in the *LMNA* and *RBM20* genes, whereas in patients with mutations in the *TTN* and *MYH7* genes such correlation was not shown [12].

Presented in our case variant of the *MYH7* gene is currently in the category of uncertain significance, however, considering family segregation, we believe that this variant contributed to the disease in proband and his relatives.

In addition to genetic factors, the presence of signs of delayed contrast accumulation (intramyocardial fibrosis) during cardiac MRI correlates with poor prognosis in LVNC patients. Previously, delayed accumulation of gadolinium was considered a predictor of future adverse cardiac events in patients with dilated cardiomyopathy [13-15]. In 2018, the results of a meta-analysis of C. Grigoratos (which included 4 studies) were published [16-19]. In patients with LVNC, included in this meta-analysis [20], delayed accumulation of gadolinium in the myocardium was associated with a prognostically unfavorable course of the disease and was characterized as a predictor of serious adverse cardiovascular events including cardiac death, ischemic stroke, ventricular fibrillation and hospitalization for heart failure progression. This group of patients had a worse prognosis compared to LVNC patients without signs of fibrosis. A multivariate analysis also demonstrated a correlation between LV systolic dysfunction, intramyocardial fibrosis and higher risk of major cardiovascular events. And it was suggested that, with preserved systolic function and in the absence of contrast medium accumulation, cardiovascular complications should not be expected and observational tactics should be chosen.

In the presented family, the proband and his father had moderate symptoms of systolic dysfunction and LV remodeling in the absence of intramyocardial fibrosis, which also allowed us to classify them as patients with a relatively favorable prognosis of the disease.

It should be noted that recently, in connection with the progress of cardiac visualization, there has been an increase in the detection of signs of non-compact myocardium in asymptomatic patients, especially in people of African descent [21], athletes [22], as well as pregnant women [23]. The authors attribute this feature to physiological adaptation, and not to the pathological process. Therefore, it is of great interest to study additional factors that allow us to evaluate the nature of changes in the myocardium. Therefore, the results of molecular genetic

methods may be useful in the differential diagnosis of pathological myocardial trabecularity. So in the case presented, clinically healthy brother of a proband with one ECHO-criterion of non-compact myocardium (Stollberger) had normal cardiac chambers parameters, mild systolic LV dysfunction but without above mentioned variant in the *MYH7* gene, which allowed us to attribute the ECHO findings to morphological features of the normal structure of the heart, and not to a pathological condition.

Conclusion

The variant *p.His1338Pro* revealed in the *MYH7* gene may be related to the development of non-compact left ventricular cardiomyopathy with a benign course.

Disclosures. All authors have not disclosed potential conflicts of interest regarding the content of this paper.

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