INTERNAL DISEASE

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New frameshift mutation found in *PKP2* gene in arhythmogenic right ventricular cardiomyopathy/dysplasia: a family case study

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Arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVC) is a progressive myocardial disease that primarily affects the right ventricle. It develops predominantly at young age, and the first symptom is often sudden cardiac death (SCD) associated with malignant ventricular arrhythmia. Diagnosis using standard cardiac assessment may be hampered due to slight and nonspecific clinical signs at early stage of the disease, particularly in relatives of the patient. Molecular genetic testing can provide more information for clinical decision making. Here we report a patient with a clinical diagnosis of ARVC who was found to have a new frame shift mutation in the *PKP2* gene through molecular genetic testing using Next Generation Sequencing methods. Subsequent family assessment showed that all three of the proband's children also carried this mutation. The results of molecular diagnostics allowed us to assess the risk of developing ARVC and SCD in relatives of the proband, as well as to set up individual cardiac assessment protocols. Results obtained emphasize the importance of family screening when a pathogenic mutation is detected in the primary patient, and demonstrate the efficiency of genetic testing in cardiological practice.

Keywords: arrhythmogenic right ventricular cardiomyopathy/dysplasia, sudden cardiac death, Next Generation Sequencing, new frame shift mutation, *PKP2* gene, Russian family.

Introduction

Arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVC) is a hereditary progressive cardiac muscle disease characterized by fibro fatty myocardial dysplasia, ventricular arrhythmia, and sudden cardiac death (SCD) [1]. Predominantly the right ventricular myocardium is affected; left ventricular and biventricular forms are less common [2]. The mode of inheritance is autosomal dominant. Thirty to fifty percent of cases have a familial distribution, with typical varying expressivity and incomplete age-dependent penetrance [1]. The general population frequency is reported to be 1/1000 to 1/10,000 in different references [3; 4]. ARVC is a primary cause of SCD among athletes and young people [1; 5]. The diagnosis is established according to the Task Force Criteria of the European Society of Cardiology revised in 2010 (TFC2010) [6].

To date, 14 genes have been reported to be associated with the development of ARVC (*PKP2, DSP, FLNC, DSC2, DSG2, JUP, TGFB3, TMEM43, LMNA, DES, TTN, PLN, CTNNA3, RYR2)* [7; 8]. The most frequently found mutations were mutations in the *PKP* gene, which were detected in 10 % to 78 % of patients according to different reports [7; 9; 10]. "Radical" mutations (in-frame and frame shift insertions/deletions, splice junction, and nonsense mutations) constitute up to 75 % of all pathogenic variants identified in ARVC patients [7; 10]. Genetic testing should be recommended to patients with definite or potential diagnosis of ARVC (TFC 2010 criteria), as well as to their relatives if a pathogenic mutation was detected [11]. The use of conventional methods such as PCR-RFLP and Sanger sequencing is time consuming and cost-ineffective compared with Next Generation Sequencing (NGS). In Russia, most studies are targeted at hypertrophic and restrictive cardiomyopathy [15–17], with insufficient data on ARVC. More detailed informationon the etiology, pathogenesis, and clinical course characteristics of the ARVC, depending on the genetic variant present, can be found in the previous review article [18; 21; 22].

Case report

A 56-year-old man (proband) presented with episodes of rapid, uneven heartbeat, repeated episodes of general weakness, dizziness, insomnia, death anxiety, and a decline in ability to perform daily activities. These symptoms concerned him for many years, and over the last few months his general state became worse. The patient had no history of arterial hypertension, ischemic heart disease, or hypercholesterolemia. Since the age of 19 he was experiencing weakness, episodes of dizziness, and recurrent syncope during physical exertion. The family medical history indicated that the eldest son of the proband died suddenly at the age of 20 during exercise (sports activity). Ventricular fibrillation during cardiopulmonary resuscitation (CPR) resulted in asystole, CPR was ineffective. His second son, a 17-year-old, complaints of rapid heartbeat, weakness, and lightheadedness associated with stress, but physical exercise is well tolerated. Holter electrocardiogram (ECG) monitoring showed no arrhythmias, despite his complaints of rapid heartbeat. Other routine methods of cardiological assessment [ECG, echocardiograph (echo-CG),

and signal averaged ECG (SAECG)] did not show any deviations from normal values. Two younger children of the proband, a daughter (6 years old) and son (4 years old), do not have any complaints, and their development and health status indicators are normal for their age; the results of cardiological assessment (ECG, echo-CG) did not show any significant deviations. The proband's parents, 86-year-old mother and 88-year-old father, are alive, their state of health is consistent with their age, and neither had anyclinically proven cardiovascular diseases. The proband's sister and her children are healthy, as well.

The proband underwent a cardiological assessment. Physical examination showed right heart dilation and muffled arrhythmic heart tones on auscultation.

Fig. 1 shows the ECG of the proband, with signs of right (RV) and left (LV) ventricular myocardial hypertrophy, as well as with specific findings of epsilon wave in leads V1-V2 and negative T-wave in right-sided chest leads.

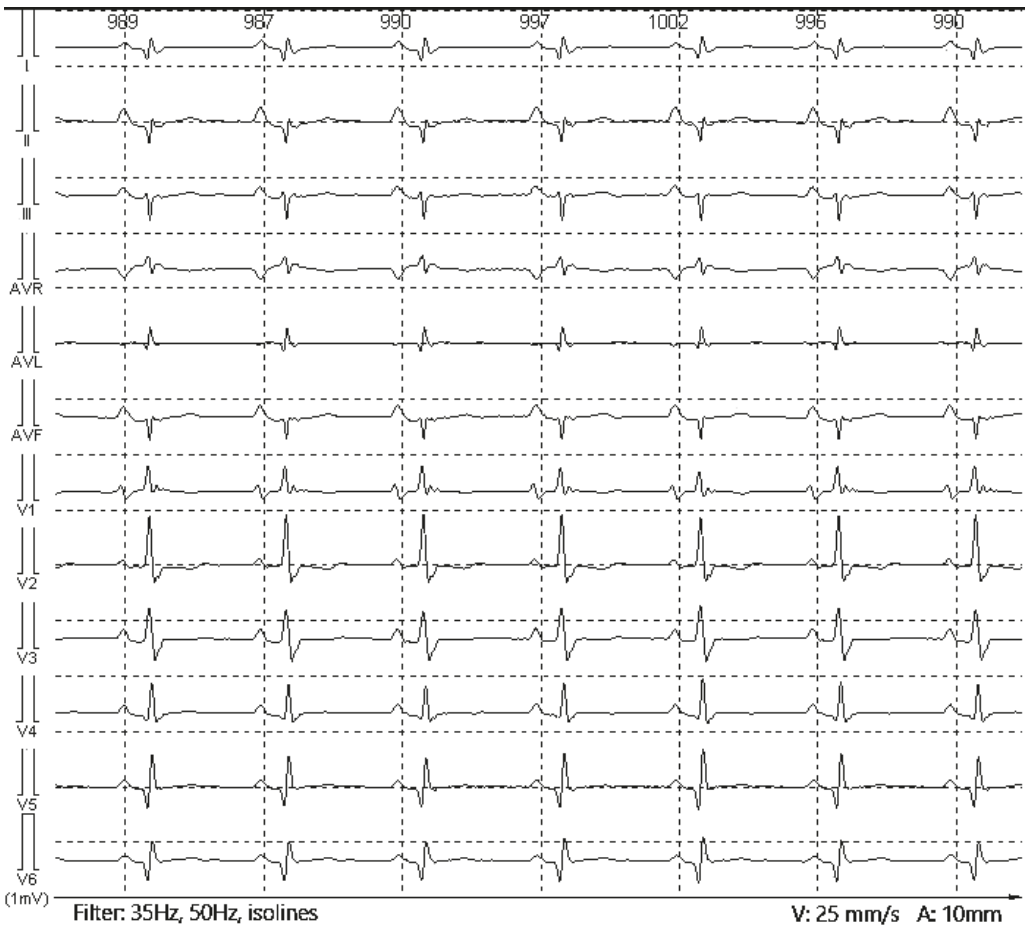

Fig. 1. 12-lead ECG of the patient. The epsilon wave is present in chest leads, and best visualized in the lead V1.

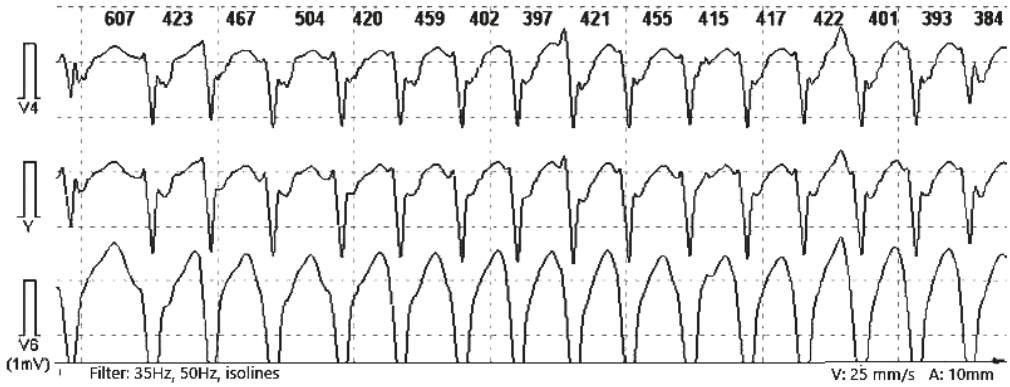

Fig. 2. 24-hour Holter monitoring. Paroxysmal monomorphic ventricular tachycardia with a heart rate of 141 beats per minute (bpm).

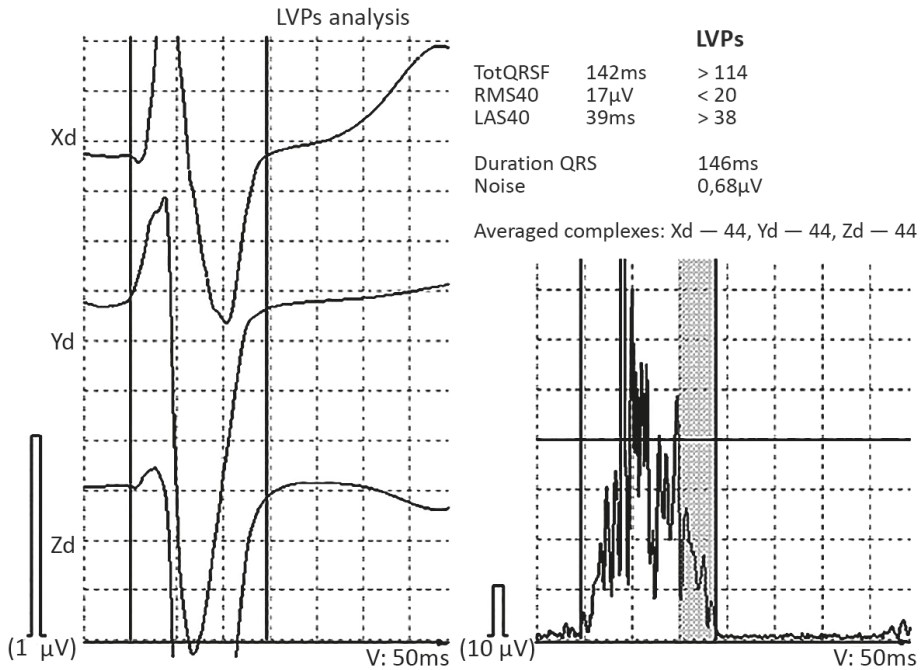

Fig. 3. Signal averaged ECG in the patient. Positivity criteria for late ventricular potentials (LVPs) are present.

In the course of 24-hour Holter monitoring (HM) following findings were recorded: 2653 polymorphic ventricular extrasystoles for a period of 24 hours with regular intraday distribution, three short episodes of unstable ventricular tachycardia lasting up to 5 seconds with a wide QRS-complex morphologytypical for complete left bundle branch block, and 3451 isolated supraventricular extrasystoles. The HM record fragment containing the episode of unstable ventricular tachycardia is presented in Fig. 2.

The results of signal averaged ECG analysis showing late ventricular potentials (LVPs) are shown in Fig. 3. The duration of the filtered QRS complex (tot QRSf) is 142 ms.

Root mean square voltage of the terminal 40 ms of the filtered QRS complex (RMS40) is 17 μV. Duration of low-amplitude signals in the terminal filtered QRS complex (LAS40) is 39 ms. The presence of all three positivity criteria definitively indicates that the proband has LVPs. LVPs reflect delayed myocardial repolarization and often correspond to epsilon wave on the standard ECG.

Transthoracic echo-CG indicates a dilation of all cardiac chambers, predominantly of the right ventricular chamber, mild eccentric hypertrophy of the LV myocardium, and a decrease in the global left ventricular contractility; LV ejection fraction (EF) by Simpson is 31 %. No LV local contractility impairment zones were found. A decrease in the RV contractility [tricuspid annular plane systolic excursion (TAPSE) is 13 mm], thinning of the RV wall, and aneurysmal bulging of the RV free wall at the apex were observed. Doppler examination showed increased pressure in the right chambers of the heart, stage 2 pulmonary hypertension (calculatedsystolic pressurein thepulmonary arterywas 45 mm Hg), and tricuspid regurgitation due to over distension of the tricuspid annulus bydilated RV. Fig. 4 shows the echocardiographic scan with changes in the RV.

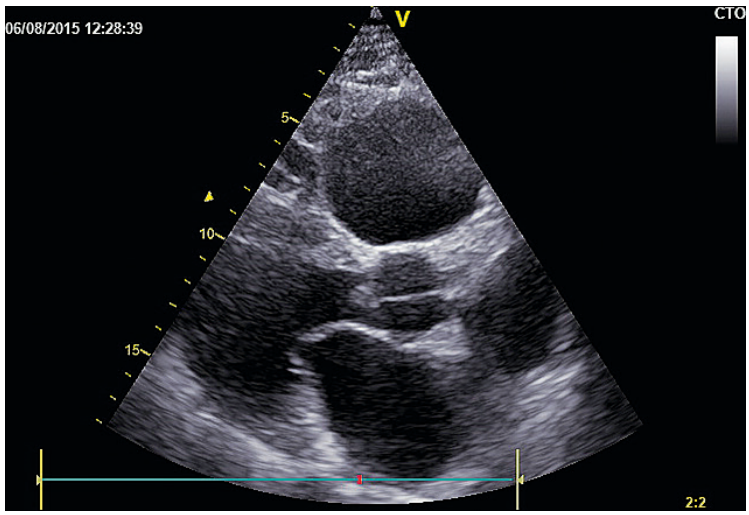

Fig. 4. Echocardiogram of the patient. Parasternal long axis view. Significant dilation and spherical configuration of the right ventricle; thinning and heterogeneity of its walls are clearly seen.

Contrast enhanced magnetic resonance imaging (MRI) (contrast agent, Gadovist) with fat suppression function showed RV dilation, free wall deformation, and no visible moderator band. End-diastolic volume of the RV was 347 mL. End-systolic volume of the RV was 315 mL. RV ejection fraction constituted 9 %. Significant uneven fat infiltration of all of the RV walls, particularly in its basal and apical segments, can be seen. Multiple, various in area, occasionally confluent regions of transmural fibrosis of the RV wall are visualized. Concordant with detected fibrotic foci, the patient had hypokinesia of all of the RV walls with kinetic and dyskinetic zones. Wall aneurysm up to 40 mm in size is clearly seen in the basal RV segments, as shown in Fig. 5. In other RV segments, single small aneurysms up to 5 mm in size were seen. Double cardiac apex due to enlarged RV is visible, as well as dilated LV, but to a lesser extent. End-diastolic volume of the LV is 265 mL. End-

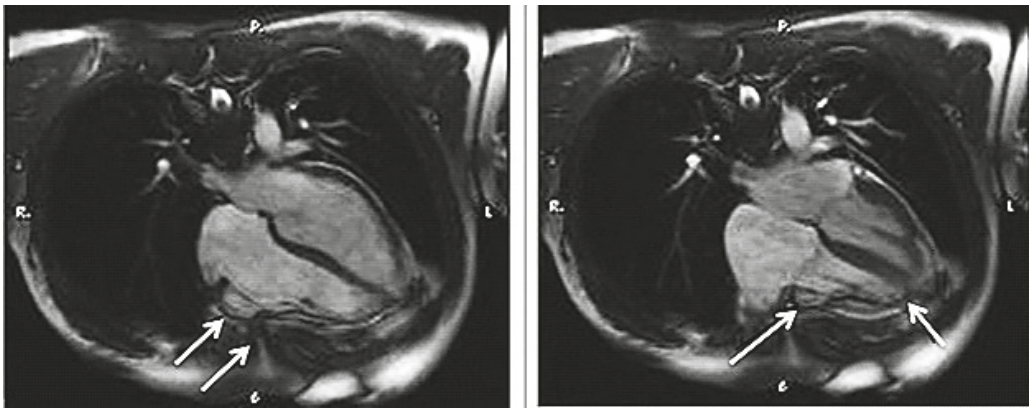

Fig. 5. Cardiac MR-tomogram. End-diastolic phase. Dilation of the right ventricular cavity. Aneurysmis seen inbasalsegments of the right ventricular wall, as well as basal segment hypokinesia (arrows).

systolic volume of the LV is 177 mL. LV ejection fraction constituted 33 %. No LV local contractility impairment zones were found.

Ischemic heart disease was excluded by coronary angiography: rightcoronary circulation and right coronary artery are visible along the entire length, and the artery is large in caliber. The left main coronary artery is seen without defects and is short (up to 5 mm in length), and the anterior interventricular artery is visible along the entire length up to distal segments and is large in caliber. The circumflex artery is medium in caliber and visualized along the entire length with no signs of stenotic lesions. The diagonal branch is medium in caliber with no visible stenosis.

Endocardial electrophysiological examination showed no evidence of atrioventricular dissociation or the presence of an additional atrioventricular connection; no induction of atrial arrhythmia was observed. Programmed stimulation of theRV was performed, inducing stable ventricular tachycardia from the RV outflow tract with conversion to ventricular flutter. Sinus rhythm was restored by electrical cardioversion.

According to current criteria [6], the patient was diagnosed with ARVC. Three major criteria were present (the epsilon wave, inverted T waves on body-surface ECG, and aneurysms and RV dilation registered with cardiac MRI and Echo-CG). Moreover, minor criteria were also present (family history of sudden death, LVPs, unstable ventricular tachycardia with characteristic morphology of RV outflow tract, and more than 500 ventricular extra systoles per day).

SCD risk estimation was performed. Due to ventricular tachycardia episodes, syncopal conditions, SCD in a first-degree relative under 40 years old, and RV wall aneurysm, SCD risk was regarded as very high. Taking all these factors into account, the patient was implanted with a cardioverter defibrillator (ICD). Sotalol was prescribed as an antiarrhythmic therapy in a daily dose of 160 mg. The patient was recommended to avoid significant physical activity, and his children were advised to refrain from competitive sports.

The well-being of the patient remained satisfactory during the 4-year follow-up period, with no registered syncopal conditions. Over this period, ICD internal memory registered three events of paroxysmal ventricular tachycardia with a heart rate of 150 to 160 bpm. All three paroxysmal ventricular tachycardia events were terminated by effective antitachycardia pacing (ATP) therapy without ICD shocks.

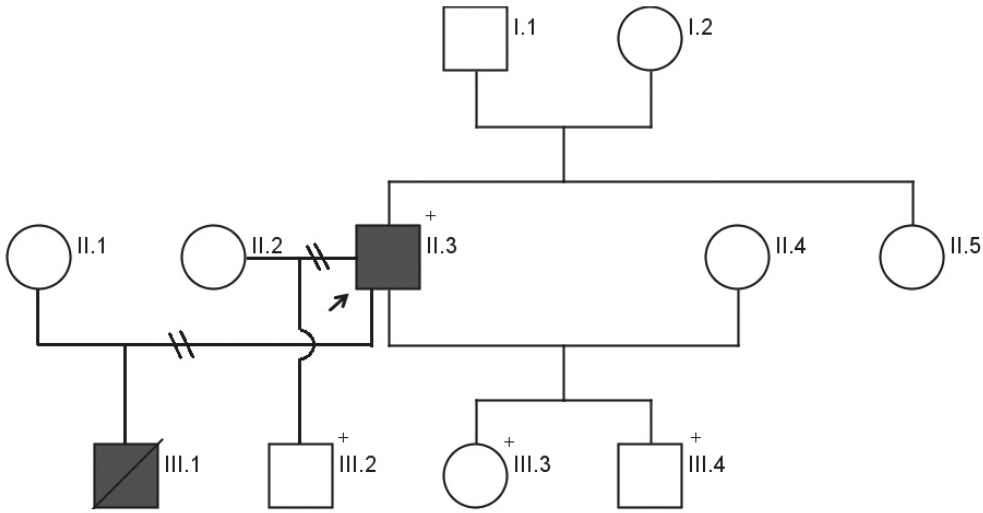

Fig. 6. Pedigree. The proband is indicated by the arrow; solid black-filled shapes represent patients with ARVC TFC+; + represents individuals with c.355delT mutation.

Considering the autosomal dominant inheritance of the disease and the high probability of SCD, we decided to perform molecular genetic testing of the proband and his family. The pedigree is shown in Fig. 6. DNA was isolated using phenol/chloroform extraction from patients' peripheral blood leukocytes [12]. The assay was performed on the MiSeq (Illumina, USA) Next-Generation sequencer using paired-end reads (2×150bp). The sample preparation involved selective capture of DNA fragments comprising coding regions of 46 genes associated with the development of inherited cardiomyopathies, including genes *PKP2, PLN, DSP, DSC2, DSG2, JUP, TMEM43, DES, TTN, LMNA* associated with the development of the hereditary form of ARVC. A complete list of genes tested is presented on the manufacturer's website: http://support.illumina.com/downloads/trusight_cardiomyopathy_product_files.html. The annotation of identified variants was performed against all known transcripts of each gene found in the RefSeq database. Clinically relevant variants were confirmed by an alternative method, Sanger sequencing.

A heterozygous deletion c.355delT (NM_004572.3) in the *PKP2* gene (Fig. 7) was identified in the proband. This variant was not reported to date in databases or scientific literature; it was also absent from the Exome Aggregation Consortium, the Exome Variant Server, and the 1000 Genomes Project. The *PKP2* gene encodes a protein, plakophilin-2, which is involved in desmosome formation. Desmosomes are major components of intercellular interactions and are particularly abundant in epidermis and myocardium. Defects inintercellular junctions are a major factor leading to ARVC [19]. Thymine deletionat cDNA position 355 results in a frame shift, causing premature chain termination p.Y119fs*23 (and eventually leads to non sense-mediated transcript decay or truncated protein formation). According to ACMG criteria [13], the identified mutation was classified as "likely pathogenic."

Subsequent cascade screening of the family members showed that all three of the proband's children carried this mutation. Cardiological assessment (examination, ECG, Echo-CG, and HM ECG) showed no abnormalities, which does not rule out the possi-

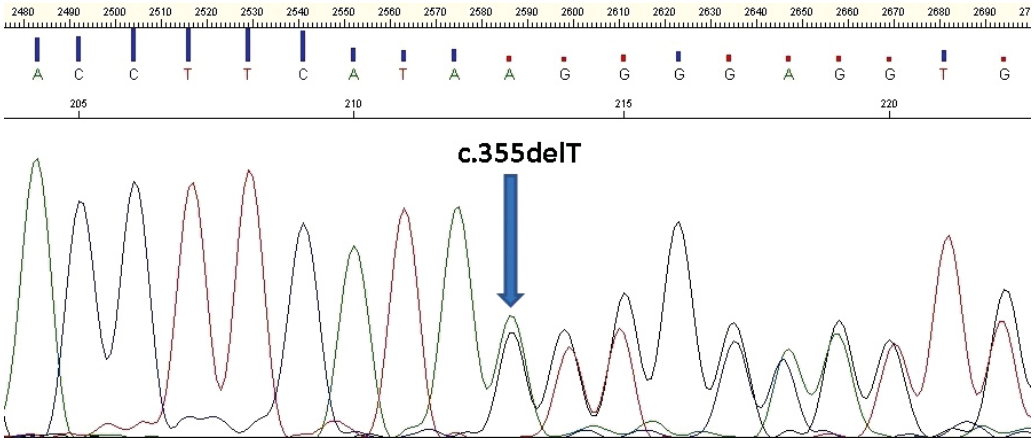

Fig. 7. Electropherogram. Frame shift mutation c.355delT (p.Y119fs*23) in the *PKP2* gene (for the R-primer).

bility of future disease development, as the average age at diagnosis of ARVC is 31 (±13; range of 4–64 years) [4]. Based on information obtained, we selected the following monitoring algorithm for children of the proband: visiting a cardiologist for standard assessment (including children/parents interviews about events of syncopes, paroxysms, and tachyarrhythmias; ECG, echo-CG, 24-hour ECG monitoring) every 2 to 3 years until the age of 10 years, and annually after 10 years (screening protocol should include SAECG). If any abnormalities are detected, then contrast-enhanced cardiac MRI is indicated. Recommendations also include life style modification (avoiding heavy physical exertions, restriction from competitive sports).

Discussion and conclusion

ARVC is a hereditary progressive myocardial disease with incomplete age-related penetrance and variable expressivity. It is inherited in an autosomal dominant pattern, often with the first symptom being SCD. We examined a family in whichthe father (with a clinical diagnosis of ARVC) and his children (currently asymptomatic) are heterozygous carriers of the novel frame shift mutation c.355delT in the *PKP2* gene. At the time of this study, the proband has a definite clinical diagnosis of ARVC in advanced stage, and he was implanted with a cardioverter defibrillator for life-saving reasons. Accordingly, the detection of a pathogenic mutation will not influence prognosis and treatment modality. Nevertheless, determination of the carrier state is necessary for asymptomatic relatives, because it has diagnostic, prognostic, and the rapeutic value. According to existing criteria, identification of a pathogenic mutationis is a major criterion for ARVC diagnosis [6]. Moreover, according to data reported in the literature, relatives, who inherited the mutation, have two times the risk of developing ARVC in their lifetime, and eight times the risk of developing stable ventricular tachycardia compared with non-carriers [14]. Patients carrying this mutation have an increased risk of SCD; therefore, they have a greater need for ICD [14]. All children in the studied family inherited the pathogenic mutation from their father, which indicates a high risk of ARVC and SCD. Accordingly, preventive meas-

ures are taken (regular cardiological assessment and life style changes) that help to avoid the development of the disease, as well as related complications.

Despite global trends, genetic testing for inherited cardiomyopathy in Russia is rare. There were no detailed reports in the literature about molecular genetic confirmation of ARVC diagnosis in Russian families. Systemic approach is valuable in diagnostics of cardiologic pathology [20]. The family case described here proves the efficiency of molecular genetic analysis (in particular by Next Generation Sequencing methods) in the practice of cardiology.

Ethics and informed consent

The patient and his relatives gave their signed informed consent for participation in this research study. A copy of the consent form is available for review by the Editor of this journal.

Abbreviations

ARVC — arrhythmogenic right ventricular cardiomyopathy/dysplasia; SCD — sudden cardiac death; *PKP2* — plakophilin-2; DSP — desmoplakin; FLNC — filamin C; DSC2 — desmocollin 2; DSG2 — desmoglein 2; JUP — junction plakoglobin; TGFB3 — transforming growth factor beta 3; TMEM43 — transmembrane protein 43; LMNA — lamin A/C; DES — desmin; TTN — titin; PLN — phospholamban; CTNNA3 — catenin alpha 3; RYR2 — ryanodine receptor 2; NGS — next generation sequencing; CPR — cardiopulmonary resuscitation; ECG — electrocardiogram; echo-CG — echocardiography; SAECG — signal averaged electrocardiogram; MRI — magnetic resonance imaging; HM — Holter monitoring; TAPSE — tricuspid annular plane systolic excursion; ATP — antitachycardiapacing therapies; ICD — implantable cardioverter defibrillator;VT — ventriculartachycardia; RV — rightventricle; LV — left ventricle; LVPs — late ventricular potentials; EF — ejection fraction.

Authors' contributions

VOE, RSD, SYV carried out family recruitment, clinical analysis, provided clinical consultation. SNY, ROV, ITE performed the experiments. FMA, VOE, GOS analyzed the data. FMA, VOE, GOS wrote the paper. SYV, SAM, SSG, GOS helped to draft and revised the manuscript. All authors read and approved the final manuscript.

Competing interests

None of the authors have any competing interests to declare.

Consent for publication

Written consent was obtained from the patient or their relatives for publication of study.

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