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Brugada syndrome: variability of clinical and genetic characteristics

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ABSTRACT

AIM: To evaluate the clinical characteristics of patients with diverse genetic variants of Brugada syndrome.

MATERIALS AND METHODS: 24 patients (17 male and 7 female) aged 18 to 55 years (median age 32.5 [20; 42] years) with a pattern of Brugada syndrome on electrocardiogram were observed for 3 years. From their ECGs, a type 1 pattern was found in 9 (37.5%) of these patients, type 2 pattern in 14 (58.3%) and type 3 pattern only in 1 patient. The clinical and instrumental study included 12-lead electrocardiogram, 24-hour Holter electrocardiogram monitoring, provocative drug testing with intravenous administration of sodium channel blockers (novocainamide), electrophysiologic study according to indications, genealogical history collection and family history of sudden cardiac death, transthoracic echocardiography and cardiac magnetic resonance imaging to detect structural myocardial changes. High-throughput sequencing was utilized to search for mutations in genes linked to the onset of channelopathies and other inherited rhythm disorders.

RESULTS: In 15 (62.5%) of the 24 probands included in the study, variants of the nucleotide sequence of pathogenicity classes III–V according to The American College of Medical Genetics and Genomics criteria (2015) were found in genes encoding sodium (*SCN5A*, *SCN10A*) and potassium (*KCNE3*, *KCNJ2*, *KCNJ8*, *KCNA5*) channels, as well as in *HCN4* and *SNTA1* genes linked with these channels. Moreover, 3 variants were identified in *ANK2* gene associated with ankyrinopathies, and 3 variants in *DSP* and *DES* genes connected with arrhythmogenic right ventricular cardiomyopathy. Four genetic variants in *SCN5A* gene were of pathogenicity classes IV and V, the rest were variants of uncertain clinical significance (class III). Six (40.0%) of the 15 genotype-positive patients had several genetic variants. The most severe form of the disease, manifested by the development of ventricular fibrillation with successful resuscitation and subsequent cardioverter-defibrillator implantation, was observed in patients with mutations in *SCN5A*, *SCN10A* genes. Recurrent syncope, polymorphic ventricular tachycardia induced by programmed ventricular stimulation during electrophysiologic study, followed by cardioverter-defibrillator implantation were observed in patients with variants *KCNJ8* and *HCN4*, *DES* and *MYH11*. In 2 patients with clinical manifestations, no mutations were identified. 13 (54.2%) patients were asymptomatic, while 3 of them had pathogenic and likely pathogenic mutations in *SCN5A* gene, as well as variants of uncertain clinical significance.

CONCLUSION: Thus, this study examined various genetic variants in patients with Brugada syndrome based on their clinical manifestation. The impact of the genotype on the Brugada syndrome phenotype is not unambiguous. The most severe form of the disease with the development of ventricular fibrillation and successful resuscitation with subsequent cardioverter-defibrillator implantation was observed mainly in patients with variants in several genes (*SCN5A* and *JUP*, *KCNJ8* and *HCN4*, *DES* and *MYH11*). This substantiate the idea that Brugada syndrome, along with monogenic, may also have a polygenic nature of the disease, in which the clinical phenotype is determined by variants in respective genes linked to the onset of cardiovascular disorders.

Keywords: Brugada pattern; genotypic and phenotypic diversity; provocative drug tests.

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Синдром Бругада: вариабельность клинических и генетических характеристик

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АННОТАЦИЯ

Цель исследования — оценить клиническую характеристику у пациентов с различными генетическими вариантами синдрома Бругада.

Материалы и методы. Обследовано 24 пациента (17 мужского и 7 женского пола) в возрасте от 18 до 55 лет (медиана возраста 32,5 [20; 42] года) с паттерном синдрома Бругада на электрокардиограмме, наблюдаемых в течение 3 лет. У 9 (37,5 %) пациентов зарегистрирован спонтанный паттерн электрокардиограммы 1 типа, у 14 (58,3 %) — паттерн электрокардиограммы 2 типа, у 1 — паттерн электрокардиограммы 3 типа. Клинико-инструментальное исследование включало регистрацию электрокардиограммы в 12 отведениях, суточное мониторирование электрокардиограммы, проведение провоцирующего теста с блокатором натриевых каналов новокаинамидом, выполнение эндокардиального электрофизиологического исследования по показаниям, сбор генеалогического анамнеза с оценкой электрокардиограмм всех членов семьи с выявлением случаев внезапной сердечной смерти в семье или наличия семейной формы заболевания, эхокардиограммы и магнитно-резонансной томографии сердца для исключения структурных изменений миокарда. Поиск мутаций в кодирующих последовательностях генов, ассоциированных с развитием каналопатий и других наследственных нарушений ритма, проводили методом высокопроизводительного секвенирования.

Результаты. У 15 (62,5 %) из 24 включенных в исследование пробандов выявлены варианты нуклеотидной последовательности III–V классов патогенности согласно критериям Американского общества медицинской генетики (2015) в генах, кодирующих натриевые (*SCN5A*, *SCN10A*) и калиевые (*KCNE3*, *KCNJ2*, *KCNJ8*, *KCNA5*) каналы, а также в генах *HCN4* и *SNTA1*, ассоциированных с этими каналами. Кроме того, выявлено 3 варианта в гене *ANK2*, ассоциированном с анкиринопатиями, и 3 варианта в генах *DSP* и *DES*, ассоциированных с аритмогенной кардиомиопатией правого желудочка. Четыре генетических варианта в гене *SCN5A* были IV и V классов патогенности, остальные являлись вариантами с неопределенной значимостью (VUS, III класс). Шесть (40,0 %) из 15 генотип-положительных пациентов имели несколько генетических вариантов. Наиболее тяжелая форма заболевания, манифестирующая развитием фибрилляции желудочков с успешным проведением реанимационных мероприятий и последующей имплантацией кардиовертера-дефибриллятора, наблюдались у пациентов с мутациями в генах *SCN5A*, *SCN10A*. Рецидивирующие синкопальные состояния, полиморфная желудочковая тахиаритмия/фибрилляция желудочков, индуцированная программируемой стимуляцией желудочков при эндокардиальном электрофизиологическом исследовании, с последующей имплантацией кардиовертера-дефибриллятора наблюдались у пациентов с вариантами *KCNJ8* и *HCN4*, *DES* и *MYH11*. У 2 пациентов с клиническими проявлениями мутаций не выявлено. 13 (54,2 %) пациентов были бессимптомными, при этом у 3 из них обнаружены патогенные и вероятно патогенные мутации в гене *SCN5A*, а также вариант VUS в этом же гене.

Заключение. Изучены клинические проявления у пациентов с различными генетическими вариантами синдрома Бругада. Влияние генотипа на фенотип синдрома Бругада не однозначно. Наиболее тяжелая форма заболевания с развитием фибрилляции желудочков и успешным проведением реанимационных мероприятий с последующей имплантацией кардиовертера-дефибриллятора наблюдалась преимущественно у пациентов с вариантами в нескольких генах (*SCN5A* и *JUP*, *KCNJ8* и *HCN4*, *DES* и *MYH11*). Полученные данные подтверждают идею о том, что синдром Бругада наряду с моногенным может иметь и полигенный характер заболевания, при котором клинический фенотип обусловлен вариантами в нескольких генах, ассоциированных с сердечно-сосудистой патологией.

Ключевые слова: паттерн синдрома Бругада; генотипическое и фенотипическое разнообразие; провокационные пробы.

Как цитировать

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ЭКО•ВЕКТОР

BACKGROUND

Brugada syndrome (BrS), an inherited cardiac channelopathy first diagnosed in 1992, is still considered a complex disorder in terms of diagnostics, arrhythmia risk prediction, pathophysiology, and treatment. It is electrophysiologically characterized by the typical electrocardiogram (ECG) pattern of BrS type 1, demonstrating *ST*-segment elevation by 2 mm, followed by a negative *T*-wave in at least one or two right precordial leads, and a high incidence of life-threatening arrhythmic events in the absence of structural heart diseases [1]. BrS may be the cause of 4%–12% of all sudden cardiac death (SCD) cases and up to 20% of SCD cases due to polymorphic ventricular tachyarrhythmias (VTs) or ventricular fibrillation (VF) [2]. The prevalence of BrS ranges from 1:5000 to 1:2000, with the highest incidence in Asians [3].

The onset of symptoms often occurs at a young age, and SCD or SCD with successful resuscitation may be the first clinical manifestation of BrS. Although BrS appears to occur equally in men and women, most patients with clinically significant BrS are men [4]. Patients more often experience fever or conditions that increase vagal tone, including sleep. The diagnosis is made by identifying the BrS type 1 ECG pattern, which can be noted either spontaneously or over the course of provocative testing with a sodium channel blocker such as ajmaline, flecainide, pilsicainide, or novocainamide [5]. These antiarrhythmic drugs, by inhibiting the fast sodium current (INa), increase the imbalance between inward and outward currents during the early phases of the action potential (AP), thereby eliciting the phenotypic expression of BrS. However, the disease is asymptomatic in most patients. Owing to the fact that the inducibility of VT/VF during the endocardial electrophysiological study (EEPS) is associated with the high risk of future ventricular arrhythmias, patients with BrS and induced VT/VF in the course of EEPS, consequently, have an implantable cardioverter defibrillator (ICD) inserted [6].

Clinical variability in BrS may be primarily due to genetic heterogeneity. BrS is most commonly caused by changes in *SCN5A* gene, which is responsible for the synthesis of the alpha subunit of the myocardial sodium channel Nav1.5. It accounts for 15%–30% of confirmed BrS cases. Genes encoding subunits of other sodium channels, as well as potassium and calcium channels, including *SCN10A*, *SCN1B-3B*, *GPD1L*, *RANGRF*, *SLMAP*, *ABCC9, KCNH2*, *KCNE3*, *KCNJ8*, *KCNE5*, *KCND3*, *HCN4*, *CACNA1C*, *CACNB2B*, *CACNA2D1*, *TRPM4*, and *PKP2,* are also associated with this syndrome. A plethora of identified variants in these genes are registered in individual families and cause < 5% of BrS cases.

Polymorphic variants of other genes, as well as nongenetic factors such as fever and intake of certain drugs, contribute to the phenotypic implementation of the main mutations. Therefore, the same genetic variant can lead to different phenotypes even among members of the same family [7]. BrS may represent a group of diseases with common ECG changes that are characterized by different clinical manifestations and inheritance patterns [8]. The reason is that the BrS phenotype may be due to variants in genes associated with other diseases. Thus, the so-called overlap syndrome of BrS with other heart diseases, such as arrhythmogenic cardiomyopathy, hypertrophic cardiomyopathy, and long *QT* syndrome (LQTS), was noted. Desmosomal proteins, including plakophilin-2, encoded by *PKP2*, and desmoglein-2, encoded by *DGC2*, have been implicated in arrhythmogenic right ventricular cardiomyopathy (ARVC) and BrS by interacting with the NaV1.5 sodium channel [9]. However, the role of desmosomal proteins in the etiology of BrS is still debated.

These issues emphasize the need for a better understanding of the molecular genetic causes of BrS and more accurate genotype–phenotype correlations.

This study evaluated the clinical characteristics of patients with different BrS genetic variants.

MATERIALS AND METHODS

The study included 24 patients (17 men and 7 women) aged 18–55 years (median age, 32.5 [20; 42] years) with an ECG pattern of BrS. The median follow-up period was 3 years.

The clinical and instrumental study included recording a standard 12-lead electrocardiogram (ECG-12), 24-h ECG monitoring (24H ECG), provocative testing with the sodium channel blocker novocainamide, EEPS according to indications, and gathering a complete and accurate medical history with ECG assessment of all family members with identified SCD, or the family history of the disease.

According to ECG-12, the following parameters were assessed: heart rate (HR), corrected *QT* interval (*QT*c), *T*-wave morphology and alternans (negative, positive, or biphasic), *J*-point elevation, configuration (coved or saddle-shaped), and terminal part (smooth descending or elevation) of the ST-segment in the right precordial leads, presence of right bundle branch block, and intermittent prolongation of the *PR* interval.

In intensive care unit at the Republican Scientific and Practical Center "Cardiology", patients underwent a diagnostic testing with novocainamide (10 mg/kg for 10 min) under constant monitoring of ECG and blood pressure (BP). BrS was diagnosed if the patient had ECG changes in the right precordial leads (V1 and/or V2), characterized by *ST*-segment elevation from the *J*-point of >2 mm in a "coved" configuration along with a negative *T*-wave. For patients with BrS type 1 pattern, provocative testing was not performed due to no additional diagnostic value.

To rule out structural myocardial disorders, an echocardiographic study (EchoCG) was performed using an IE-33 device Philips (USA), as well as magnetic resonance imaging (MRI) using a Magnetom Aera 1.5 T tomograph (Siemens, Germany) according to relevant recommendations.

ECG was performed on the Intecard-3 hardware and software complex (Republic of Belarus). 24H ECG was performed using an Oxford Medilog AR12 recorder (UK). EEPS was performed on Siemens (Germany) and Bard (USA) systems.

During the 24H ECG, the average HR per day, QRS fragmentation, early repolarization pattern, prominent *S*-wave in lead *I*, diverse ventricular arrhythmias and sustained VT and VF), BrS ECG pattern (intermittent or permanent), and *ST*-segment and *T*-wave alterations were assessed. The ventricular genesis of the arrhythmia was confirmed by 24H ECG data, ECG registration during the arrhythmia episode and EEPS in some cases. Eleven patients underwent EEPS to screen for arrhythmic risk by examining the area and size of the arrhythmogenic substrate causing the arrhythmia burden. This method corresponded to an internationally recognized protocol using stimulation of two segments, namely, the region of the right ventricular apex and the right ventricular outflow tract, with a cycle length of 600, 430, and 330 ms, application of 1, 2, or 3 extrastimuli, and a progressive decrease in the coupling interval to minimum values (200 ms) [10]. Programed electrical stimulation was performed in accordance with a standard protocol. If sustained VT or VF lasting > 30 s was induced or cardioversion was required, patients were classified as having an inducible arrhythmia.

Mutations in the coding sequences of genes associated with the development of channelopathies and other inherited heart rhythm disorders were identified using high-throughput sequencing on a MiSeq genetic analyzer (Illumina, USA). Sample preparation was performed using the TruSight Cardio Sequencing Kit (Illumina, USA). Annotation of the sequencing results was performed using ANNOVAR software [11]. The pathogenicity of the new and previously described genetic variants was interpreted according to the recommendations of the American College of Medical Genetics and Genomics (ACMG, 2015) [12]. Pathogenic (class V) and likely pathogenic (class IV) genetic variants were considered diagnostically significant. The analysis also included variants of uncertain clinical significance (VUS, class III), pathogenic according to in silico predictors, whose incidence in population databases (GnomaD) did not exceed 0.01%.

This study was approved by the ethics committee of the Institute of Genetics and Cytology of the National Academy of Sciences of Belarus (Minutes No. 2 of the meeting of the Bioethics Committee dated 06/08/2021). All patients provided informed voluntary consent to participate in the study.

RESULTS

Twenty-four probands from unrelated families in whom the BrS pattern was recorded on ECG were examined (Table 1). The majority of patients were men (n = 17; 70.8%), with a median age of 32.5 (20; 42) years. Nine (37.5%) patients had a spontaneous type 1 ECG pattern, 14 (58.3%) represented with type 2, and 1 patient with type 3. Four (16.7%) patients had a family history of SCD among their close relatives. Seven (29.2%) patients had clinical manifestations of BrS (syncope, spontaneous or induced polymorphic VT/VF, with resuscitation after SCD). Of these patients, 4 probands (16.7%) had VF with successful resuscitation and subsequent ICD implantation, and 3 (12.5%) had recurrent syncope, polymorphic VT/VF induced by programed ventricular stimulation during EEPS, followed by ICD implantation. EEPS revealed sick sinus syndrome (SSS) that required pacemaker implantation in one patient, sinus node dysfunction in two patients, and loop recorder implantation in one patient. Supraventricular paroxysmal tachycardia was recorded in two patients. In one patient, premature ventricular contractions (PVCs) and episodes of second-degree atrioventricular (AV) block, type I, were registered. A loop recorder was implanted in a patient with a single syncope episode and a BrS type 3 ECG pattern. The remaining 13 (54.2%) patients were asymptomatic.

To determine the risks of arrhythmic events, 11 (45.8%) patients underwent EEPS with programed ventricular stimulation. In 3 (12.5%) patients, VT was induced, and an ICD was implanted. However, in 8 (33.3%) patients, VTs were not triggered. The clinical characteristics of the patients are presented in Table 1.

While genotyping, in 15 (62.5%) out of 24 probands included in the study, nucleotide sequence variants of pathogenicity classes III–V were identified according to the criteria of the ACMG (2015) in the genes encoding sodium (*SCN5A* and *SCN10A*) and potassium (*KCNE3, KCNJ2, KCNJ8,* and *KCNA5*) channels, as well as in *HCN4* and *SNTA1* genes associated with these channels (Table 1). In addition, three variants in *ANK2*, which are associated with ankyrinopathies, and variants in *DSP* and *DES*, which are mutations that lead to ARVC, were determined. Only four variants belonged to pathogenicity classes IV and V, two of which were new, and the rest were VUS, class III). All pathogenic and likely pathogenic variants were defined in *SCN5A*. Six (40.0%) out of 15 genotype-positive patients had several genetic variants, and predominantly they affected genes linked to cardiomyopathies.

In seven patients, variants were identified in the genes encoding sodium channels and associated proteins (Table 2). Five patients carried *SCN5A* variants.

The most severe clinical manifestations of the disease were registered in proband 799 (41 years old), in whom the disease manifested with VF with resuscitation measures, which required ICD implantation. His father died suddenly at the age of 28 years. The proband experienced syncope during the day, which clearly has not been related to exercise, and eventually cardiac arrest occurred at night. ECG showed a spontaneous BrS type 1 pattern. Upon further monitoring, the BrS pattern was not registered on the ECG; sinus rhythm was recorded with an HR of 68 beats/min, the *PQ* interval duration was 110 ms, the *QT*c interval was 380 ms, and

Table 1. Clinical and genetic characteristics of patients with Brugada syndrome
Таблица 1. Клинико-генетическая характеристика пациентов с синдромом Бругада

Patient code	Age	Sex	History of SCD	Syncope	Brugada pattern	EEPS	Test with novocainamide	Gene mutation	Pathogenicity class	Events/outcomes
611	26	F	+	+	Type 1	Not performed	Not performed	*SCN5A*	P	Refusal of ICD therapy
799	41	M	+	+	Type 1	Not performed	Not performed	*SCN5A* *JUP*	P VUS	VF and ICD
717	20	M	–	–	Type 1	Not performed	Not performed	*SCN5A*	LP	Transient SA block deg. 2 type 1
716	18	M	–	–	Type 2	Not performed	+	*SCN5A* *TPM1*	LP VUS	–
668	31	M	–	–	Type 1	Not performed	Not performed	*SCN5A*	VUS	–
732	55	F	–	+	Type 1	Not performed	Not performed	*SCN10A*	VUS	VF and ICD
641	38	M	–	–	Type 2	VT not induced	+	*SNTA1*	VUS	PVCs, AV block deg. 2 type I
638	37	F	+ #	+	Type 2	Induced polymorphic VT	+	*KCNJ8* *HCN4*	VUS VUS	ICD, PVT, and SVT
606	44	M	–	–	Type 2	VT not induced	+	*KCNJ2*	VUS	SVT
580c	36	M	+ *	+	Type 2	Induced VT	+	*DES* *MYH11*	VUS VUS	PVT/ICD
598	29	M	–	–	Type 1	VT not induced	Not performed	*DSP* *MYOZ2*	VUS VUS	–
788	26	M	–	–	Type 2	Not performed	Not performed	*DSP* *RBM20*	VUS VUS	–
796	25	M	–	–	Type 2	VT not induced	+	*ANK2*	VUS	SSS and PM
756c	19	M	_	+	Type 3	Not performed	+	*ANK2*	VUS	ILR
12м	19	M	–	–	Type 2	Not performed	+	*ANK2*	VUS	–
626	46	F	–	+	Type 1	Not performed	Not performed	Not detected	–	VF and ICD
789	34	F	–	+	Type 2	Induced PVT	+	Not detected	–	PVT/VF and ICD
667	47	F	–	–	Type 1	Not performed	Not performed	Not detected	–	–
605	55	M	–	–	Type 1	VT not induced	Not performed	Not detected	–	–
806	20	M	–	–	Type 2	VT not induced	+	Not detected	–	SND and ILR
792	18	M	–	–	Type 2	VT not induced	+	Not detected	–	SND
730	40	M	–	–	Type 2	VT not induced	+	Not detected	–	–
779	48	F	–	–	Type 2	Not performed	+	Not detected	–	–
2м	20	M	–	–	Type 2	Not performed	+	Not detected	–	–

Note: SCD — sudden cardiac death; SND — sinus node dysfunction; VT — ventricular tachycardia; ICD — implantable cardioverter defibrillator; PVT — polymorphic ventricular tachycardia; SVT— supraventricular tachycardia; SA — sinoatril; PVCs — premature ventricular contractions; SSS — sick sinus syndrome; VF — ventricular fibrillation; PM — pacemaker; EEPS — endocardial electrophysiological study; # — in 4 relatives; * — in 2 relatives.

Примечание: ВСС — внезапная сердечная смерть; ДСУ — дисфункция синусового узла; ЖТ — желудочковая тахикардия; ИКД — имплантируемый кардиовертер-дефибриллятор; ПЖТ — полиморфная желудочковая тахикардия; СВТ — суправентрикулярная тахикардия; СА — синоатриальная; ЖЭС — желудочковая экстрасистолия; СССУ — синдром слабости синусового узла; ФЖ — фибрилляция желудочков; ЭКС — электрокардиостимулятор; ЭЭФИ — эндокардиальное электрофизиологическое исследование; # — у 4 родственников; * — у 2 родственников.

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Table 2. Genetic characteristics of patients with variants in genes encoding sodium channels and associated proteins
Таблица 2. Генетическая характеристика пациентов с вариантами в генах, кодирующих натриевые каналы и ассоциированные с ними белки

Patient code	Gene	Nucleotide substitution/Rs	Amino acid substitution	Variant class	MAF (GnomaD)
799	*SCN5A*	c.142G > A, rs199473048	p.Glu48Lys	P	0.000039
	JUP	c.427G > A, rs375788626	p.Ala143Thr	VUS	0.000098
611	*SCN5A*	c.3840 + 1G > A rs1366120635	–	P	0.0000048
716	*SCN5A*	c.4055G > A	p.Gly1352Asp	LP*	–
	TPM1	c.76G > C	p.Glu26Gln	VUS	–
717	*SCN5A*	c.2572dupA	p.Met858Asnfs*73	LP*	–
668	*SCN5A*	c.5360G > A, rs199473316	p.Ser1787Asn	VUS	0.000495
732	*SCN10A*	c.5216 A > T, rs760863009	p.Asp1739Val	VUS	0.000014
641	*SNTA1*	c.787G > T, rs150576530	p.Ala263Ser	VUS	0.00026

Note: * — new variant; P — pathogenic variant; LP — likely pathogenic variant; VUS — variant with uncertain significance; MAF — minor allele frequency.
Примечание: * — новый вариант; P — патогенный вариант; LP — вероятно патогенный вариант; VUS — вариант с неопределенной значимостью; MAF — частота минорного аллеля.

the *QRS* was 120 ms. Genotyping revealed a p. Glu48Lys pathogenic variant in *SCN5A* and an additional substitution in *JUP* associated with ARVC. Cardiac MRI revealed no changes in myocardial structure and no evidence of ARVC.

In patient 611 (26 years old) with a family history of SCD in a relative (elder brother aged 30 years) and a spontaneous BrS type 1 pattern on ECG, no clinical manifestations of BrS were observed, and, ultimately, she refused further EEPS and ICD implantation. Genotyping revealed a pathogenic mutation, c.3840 + 1G > A, affecting a splice site in *SCN5A*.

Patients 668, 716, and 717 also had an asymptomatic disease course. ECG of proband 717 (20 years old) showed a BrS type 1 pattern. Genotyping revealed a new probably pathogenic duplication of one nucleotide c.2572dupA, leading to a reading frame shift and the appearance of a premature stop codon (p. Met858Asnfs*73) in *SCN5A*. The patient refused EEPS. Patient 716 (18 years old) had a BrS type 2 pattern on ECG, and the novocainamide test was positive. In this patient, a new variant was detected, which was pathogenic according to the in silico predictors, c.4055G > A (p. Gly1352Asp) in exon 23 of *SCN5A*. Patient 668 (31 years old) had a BrS type 1 pattern on ECG. Genotyping revealed a p. Ser1787Asn substitution of unknown clinical significance in *SCN5A*.

Proband 732 (female, 55 years old), who had no known risk factors for the development of coronary heart disease and no family history of SCD, was admitted to the intensive care unit by reason of cardiac arrest with documented VF and underwent ICD implantation; a BrS type 1 pattern was detected on serial ECG. Genotyping revealed p. Asp1739Val substitution in *SCN10A*, which encodes the neuronal sodium channel (Nav1.8) and is associated with BrS, which was proven in recent genome-wide association studies (GWAS) [13]. A study demonstrated similarities in phenotypes between patients with a *SCN10A* variant and those with *SCN5A* variants, including family history, presence of syncope, and spontaneous ECG patterns [14]. In our cohort, a *SCN10A* substitution was also associated with disease manifestation, VF development, and cardiac arrest, followed by ICD implantation. D. Hu et al. [15] identified *SCN10A* mutations in 25 of 150 probands (17%) with BrS, emphasizing the crucial role of this gene in this disease. Its significance was confirmed by studies on the influence of *SCN10A* on both cardiac conduction [16] and the autonomic nervous system [17]. In proband 641 (male, 38 years old), a BrS type 2 pattern was recorded for the time of a routine ECG (Fig. 1).

The novocainamide test was positive. In the course of EEPS, ventricular arrhythmias were not induced. Holter ECG monitoring recorded frequent PVCs and episodes of second-degree AV block, type 1. Antiarrhythmic drug treatment was prescribed. Genotyping revealed p. Ala263Ser substitution in *SNTA1*, which encodes syntrophin, a scaffold protein of the cytoplasmic peripheral membrane and a component of the dystrophin-associated protein complex. This gene is a member of the syntrophin gene family and encodes the most abundant syntrophin isoform detected in cardiac tissue. The N-terminal PDZ domain of this syntrophin protein interacts with the C-terminus of the pore-forming alpha subunit (*SCN5A*) of the cardiac sodium channel Nav1.5. This gene is associated with LQTS and sudden infant death syndrome (SIDS). This protein also binds to dystrophin and dystrophin-related proteins at neuromuscular junctions and alters intracellular calcium ion levels in muscles [18].

In two patients with BrS, variants were identified in the genes encoding potassium channels (Table 3), and their clinical manifestations were analyzed.

Patient 638 (female, 34 years old) had a family history of SCD via parental lineage in her closest relatives (a second cousin aged 24 years and three paternal uncles aged 36, 47, and 52 years), and a BrS type 2 pattern was registered on the ECG (Fig. 2). The proband has experienced rapid heart palpitation accompanied by shortness of breath and dizziness since the age of 16 years. Several months before

Table 3. Genetic characteristics of patients with variants in potassium channels
Таблица 3. Генетическая характеристика пациентов с вариантами в калиевых каналах

Patient code	Gene	Nucleotide substitution/Rs	Amino acid substitution	Mutation class	MAF (GnomaD)
638	*KCNJ8*	c.980T > C rs1940609307	p.Ile327Thr	VUS	0.0000034
	HCN4	c.415C > T	p.Pro139Ser	VUS*	–
606	*KCNJ2*	c.845T > G rs758092571	p.Leu282Trp	VUS	0.00001735

Note: * — new variant; VUS — variant with uncertain significance; MAF — minor allele frequency.
Примечание: * — новый вариант; VUS — вариант с неопределенной значимостью; MAF — частота минорного аллеля.

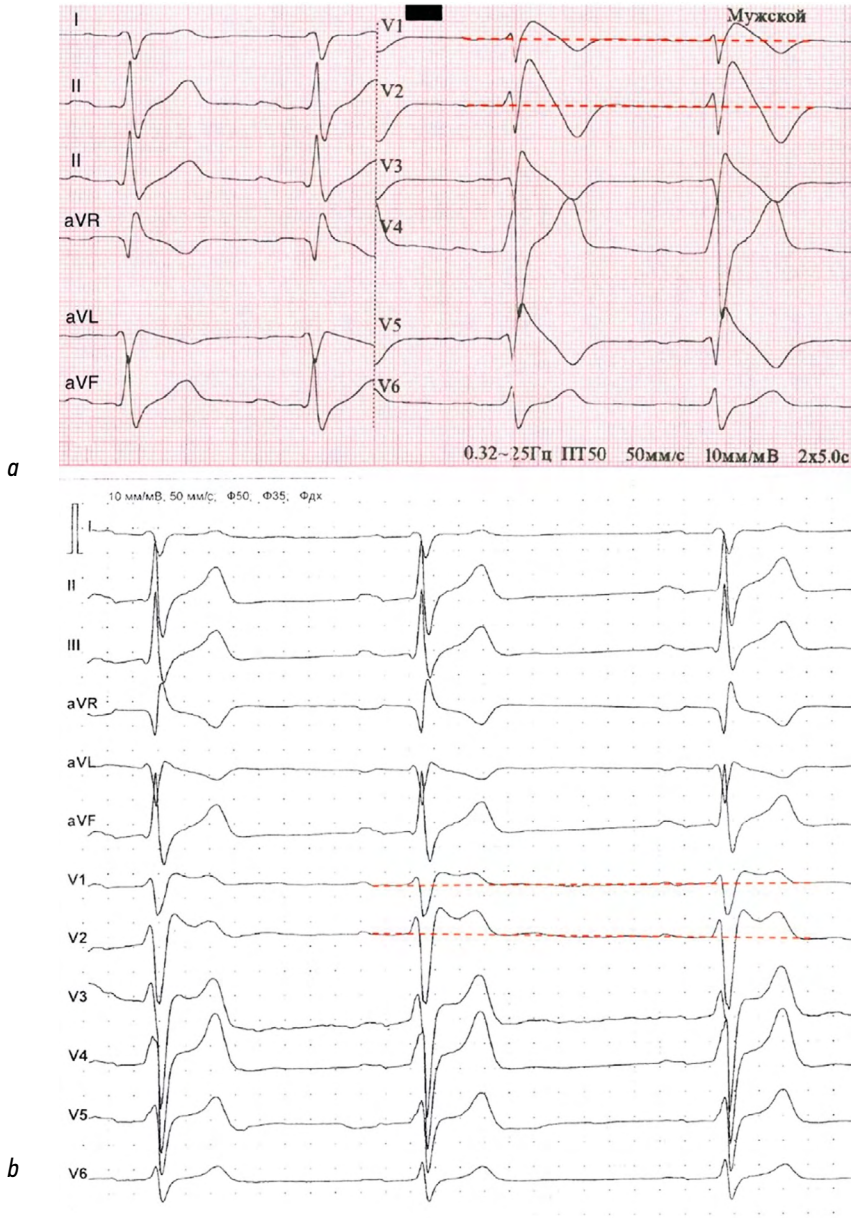

Fig. 1. 12-lead electrocardiogram of patients (598 and 641) with distinct Brugada patterns: *a* — Brugada pattern type 1 (coved), showing a "vaulted" elevation of the *ST* segment of more than 2 mm in more than one right precordial lead, followed by a negative *T*-wave; *b* — Brugada pattern type 2 (saddle-back), showing a "saddle-shaped" elevation of the *ST* segment of more than 2 mm in more than one right precordial lead, followed by a positive *T*-wave
Рис. 1. Электрокардиограмма в 12 отведениях пациентов № 598 и 641 с разными паттернами Бругада: *a* — паттерн Бругада тип 1 (coved), показывающий «сводчатый» подъем сегмента *ST* более 2 мм в более чем одном правом прекордиальном отведении, за которым следует отрицательный зубец *T*; *b* — паттерн Бругада типа 2 (saddle-back), показывающий «седловидный» подъем сегмента *ST* более 2 мм в более чем одном правом прекордиальном отведении, за которым следует положительный зубец *T*

hospitalization, the patient endured three episodes of syncope. Changes were recorded in the analysis of a series of ECGs, namely, abnormalities of intraventricular conduction (widening of the *QRS* complex up to 130 ms), or R-wave progressionin leads V1–V3, slowing of AV conduction with transient first-degree AV block, transient second-degree SA block type I, and pauses lasting 1495 ms.

During a novocainamide testing (10 mg/kg body weight intravenously for 10 min) at the tenth minute, changes were recorded in leads V1–V2, such as a coved-type ST-segment elevation (Fig. 3), characteristic of a BrS type 1 pattern (amplitude > 2 mm, width > 4 mm, Corrado index > 1).

During EEPS, programed stimulation of the ventricles with extrastimuli (coupling intervals of 220 and 230 ms) provoked a sustained paroxysm of polymorphic VT with a cycle of 224–176 ms, which was terminated spontaneously, and a characteristic BrS pattern with 2–3 mm *ST* elevation. Considering the presence of BrS, recurrent syncope, induced polymorphic ventricular tachycardia during EEPS, and a high SCD risk, a single-chamber ICD was implanted for urgent indications. During treatment (metoprolol 12.5 mg twice a day under HR and BP control), the patient's medical state improved, and she was discharged in a satisfactory condition. Genotyping

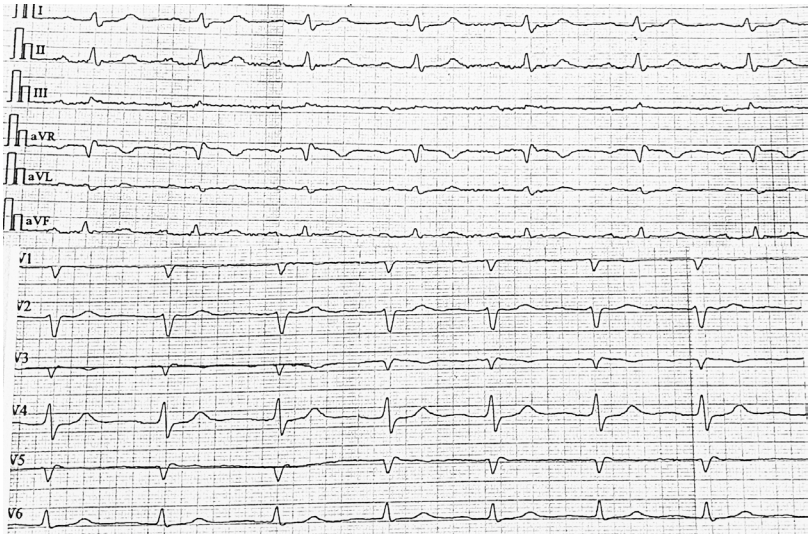

Fig. 2. 12-lead electrocardiogram of patient 638 at rest, 10 mm/mV, 50 mm/s
Рис. 2. Электрокардиограмма в 12 отведениях пациентки № 638 в покое, 10 мм/мВ, 50 мм/с

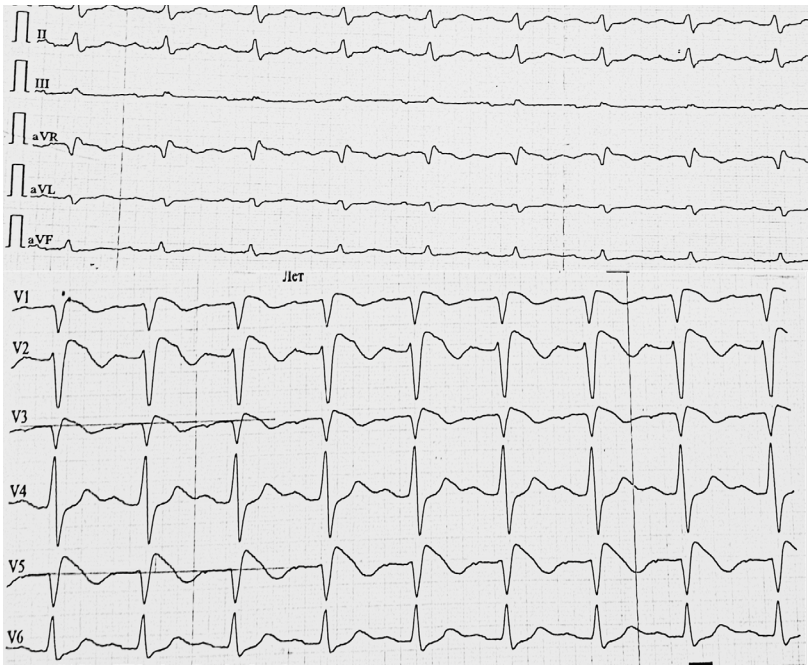

Fig. 3. 12-lead electrocardiogram of patient 638, 10 min of the novocainamide testing, 10 mm/mV, 50 mm/s
Рис. 3. Электрокардиограмма в 12 отведениях пациентки № 638 на 10-й минуте проведения новокаинамидовой пробы, 10 мм/мВ, 50 мм/с

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revealed two new allelic variants: the p. Ile327Thr mutation in *KCNJ8*, which encodes a subunit of the ATP-sensitive potassium channel Kir6.1, and the p. Pro139Ser mutation in *HCN4*, which is responsible for the synthesis of one of the family members controlled by cyclic nucleotides in hyperpolarization-activated potassium channels.

In patient 606 (44 years old) with a BrS type pattern on ECG and asymptomatic disease course, the novocainamide testing was positive. While conducting EEPS, VT was not induced. Antiarrhythmic drug therapy was prescribed. Genotyping revealed a variant of unknown clinical significance of p. Leu282Trp in *KCNJ2*, encoding the alpha subunit of the influent potassium current channel Kir2.1.

Genetic variants leading to BrS in one of the potassium channels usually result in increased channel function. Rare *KCNJ8* variants, by increasing the throughput of the ATP-sensitive potassium channel (IK-ATP), reduce the AP as well as plateau depression, causing the ECG changes registered in BrS [19]. The severe clinical presentation in proband 638 was conceivably due to the presence of another, also not previously described, mutation c.415C > T (p. Pro139Ser) in *HCN4*, which encodes the protein of hyperpolarization-activated cyclic nucleotide-dependent potassium channel 4.

KCNJ2 variants are associated with LQTS type 7 and short *QT* syndrome type 3. This gene is related to *KCNJ8*, which is associated with BrS type 8, and its variants presumably cause this syndrome.

In patients 598, 788, and 580c (male) with the BrS pattern on ECG were revealed desmosomal gene substitutions (Table 4).

Proband 580c (36 years old) with recurrent syncope and BrS type 2 ECG pattern and SCD in two family members (father and brother aged 32 years) underwent a novocainamide

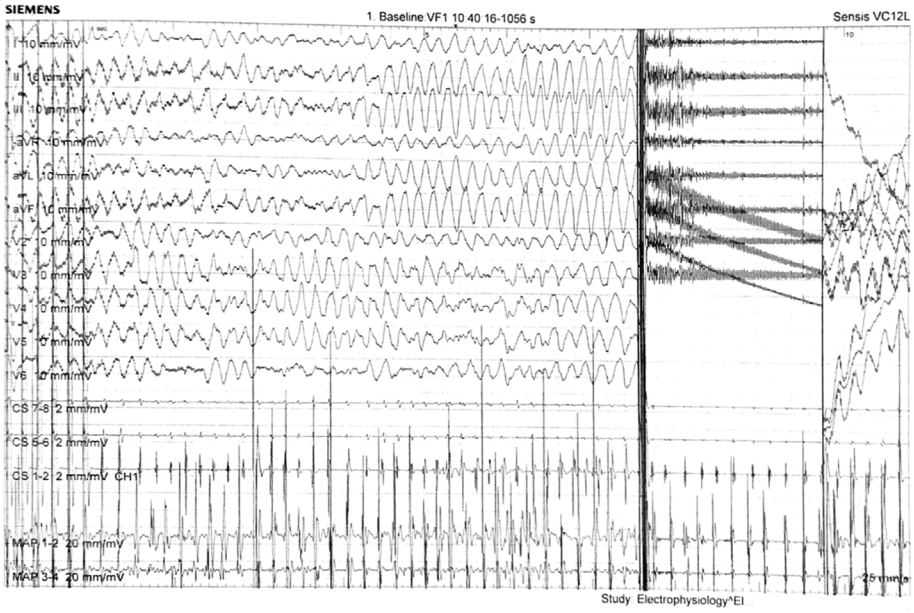

Fig. 4. Endoelectrogram of proband 580c, representing the paroxysm of ventricular fibrillation
Рис. 4. Эндоэлектрограмма пробанда № 580с, представляющая пароксизм фибрилляции желудочков

Table 4. Genotyping results of patients with Brugada syndrome (overlapping phenotypes with right ventricular arrhythmogenic cardiomyopathy)
Таблица 4. Результаты генотипирования пациентов с синдромом Бругада (перекрывающие фенотипы с аритмогенной кардиомиопатией правого желудочка)

Patient code	Gene	Nucleotide substitution/Rs	Amino acid substitution	Mutation class	MAF (GnomaD)
580c	*DES*	c.752A > C	p.Gln251Pro	VUS*	–
	MYH11	c.3925G > C	p.Asp1309His	VUS*	–
598	*DSP*	c.6188G > A rs142927608	p.Arg2063Gln	VUS	0.00001115
	MYOZ2	c.674C > T rs200428820	p.Pro225Leu	VUS	0.0001289
788	*DSP*	c.6014C > T rs749925817	p.Ala2005Val	VUS	0.000007
	RBM20	c.1244G > A rs748133931	p.Ser415Asn	VUS	0.000035

Note: * — new variant; VUS — variant with uncertain significance; MAF — frequency of the minor allele.
Примечание: * — новый вариант; VUS — вариант с неопределенной значимостью; MAF — частота минорного аллеля.

testing (positive) and EEPS. During EEPS, VF paroxysm was induced and was successfully terminated by cardioversion, and the arrhythmia substrate was ablated (Fig. 4). Considering the persistently high SCD risk, an ICD was implanted as a next step. Genotyping revealed two new variants that were pathogenic according to in silico predictors, precisely, p. Gln251Pro in *DES*, which encodes desmin and is associated with ARVC [20], and p. Asp1309His in *MYH11*, which is linked to SCD and familial aortic aneurysm.

In patient 598 (29 years old), without clinical disease manifestations and family history, a BrS type 1 pattern was recorded on ECG (Fig. 1). Throughout the EEPS, VT was not induced, and the patient was followed up. A VUS p. Arg2063Gln was identified in *DSP*, which encodes desmoplakin.

Patient 788 (26 years old) without clinical manifestations had a BrS type 2 pattern on ECG. Novocainamide testing and EEPS were not performed. The patient refused further examination. Cardiac MRI did not reveal any evidence of cardiac structural alterations. Genotyping revealed p. Ala2005Val substitution in *DSP.*

In patients 580c, 598, and 788, genetic testing revealed rare variants in *MYOZ2, RBM20*, and *MYH11* associated with changes in myocardial structure.

Genetic variants in desmosomal genes in patients with BrS ECG patterns specify an overlap between BrS and ARVC phenotypes. Genes encoding desmosomal proteins, known as ARVC susceptibility genes [21], have also been described in several patients with signs of BrS in the absence of evident structural disease manifestations. In vitro functional studies in HL-1 cells and human cardiomyocytes derived from induced pluripotent stem cells showed that desmosomal gene mutations can reduce sodium ion (INa) current by disrupting the interaction between desmosomal proteins and the Nav1.5 channel in the cardiac muscle [22]. These data enabled us to hypothesize that ARVC and BrS are not completely different conditions and could thereby be considered final stages of the same disease, i.e., cardiac connexome disease [9].

In patients 12m, 756c, and 796, genotyping revealed *ANK2* substitutions (Table 5).

Patients 12m and 756c (both male, 19 years old) with BrS type 2 and 3 ECG patterns that transformed into type 1 during the novocainamide testing were asymptomatic. In patient 796 (25 years old), VT was not induced during EEPS; however, SSS was detected, and an PM was implanted.

Ankyrin is a multifunctional protein involved in the functioning of ion channels and transporters in various tissues [23]. Despite their common basis, these proteins have different functions. The genes encode three different ankyrin proteins, namely, ankyrin-R (ANK-1), ankyrin-B (ANK-2), and ankyrin-G (ANK-3). ANK-2, like ANK-3, controls the functioning of the sodium channel Nav1.5 and is associated with BrS [24]. In case ANK-B is impaired, other arrhythmia phenotypes are distinguished, including SSS, atrial fibrillation, and life-threatening ventricular arrhythmias with SCD risk [25]. Hence, this phenotypic diversity of rhythm disorders was combined and presented as Ankirin B syndrome. In a Japanese cohort of 535 probands with inherited rhythm disorders, 12 (2.2%) had *ANK2* mutations, with 8 out of 12 probands having bradycardia, 2 having BrS phenotypes, and 7 having malignant VTs [26]. Thus, *ANK2* variants are potential candidates for BrS. Further functional and molecular studies of the detected variants should clarify the mechanisms associated with the *ANK2* variants underlying BrS.

DISCUSSION

In this paper, we characterized the clinical aspects, including adverse arrhythmic events, and analyzed the phenotypic manifestations depending on the genotype in patients with BrS ECG patterns. In the study cohort, the clinical diagnosis of BrS was confirmed by genetic testing in 7 (29.2%) patients; most patients (20.8%) were carriers of *SCN5A* variants, which is considered the most clinically significant in relation to this syndrome [27]. A patient with severe clinical presentation of BrS had a variant in *SCN10A*, which encodes another sodium channel, Nav1.8. Recent studies have highlighted that the Nav1.8 channel is a modulator of cardiac conduction and that *SCN10A* variants may be associated with atrial fibrillation and BrS [28]. *SCN10A* variants affect *PR* interval duration, *QRS*, HR, and arrhythmia risk [14].

In another female patient, two rare variants of *KCNJ8* and *HCN4*, which encode potassium channels and are

Table 5. Genotyping results of patients with Brugada syndrome associated with ankyrin
Таблица 5. Результаты генотипирования пациентов с синдромом Бругада, ассоциированные с анкирином

Patient code	Gene	Exon	Nucleotide substitution/Rs	Amino acid substitution	Mutation class	MAF (GnomaD)
12м	*ANK2*	38	c.6097A > G	p.Lys2033Glu rs756877862	VUS	0.0000032
756с	*ANK2*	38	c.9841C > G	p.Gln3281Glu rs372534074	VUS	0.00017
796	*ANK2*	26	c.2890A > G	p.Ile964Val rs750129234	VUS	0.00001055

Note: VUS — variant with uncertain significance; MAF — frequency of the minor allele.
Примечание: VUS — вариант с неопределенной значимостью; MAF — частота минорного аллеля.

associated with BrS, were identified. *KCNJ8* is responsible for the synthesis of the membrane protein of the inward rectifying potassium channel (Kir and IRK), through which positive ions easily pass into the cell. The flow of ions into the cell may play an important role in the regulation of neuronal activity, helping to stabilize the resting membrane potential of the cell. Defects in this gene may also cause *J*-wave syndrome and SIDS. *HCN4* encodes the hyperpolarization-activated cyclic nucleotide-gated potassium channel 4 protein. This gene is expressed primarily in cardiac cells with high automaticity. Through the HCN4 channel, potassium and sodium ions enter the cells of the sinoatrial node, generating electrical impulses that trigger each heartbeat and maintain a regular heart rhythm. Moreover, the HCN4 protein is responsible for slow kinetic activation and inactivation and is essential in cardiac excitation and for the proper functioning of the cardiac conduction system [29]. Accordingly, mutations in this gene are also associated with SSS.

In 8 (33.3%) patients, rare substitutions were identified in *SNTA1, KCNJ2, ANK2, DSP,* and *DES*, which are associated primarily with LQTS and ARVC. Currently, growing evidence shows that some allelic variants of these genes may also cause BrS. Furthermore, this phenomenon is associated with the overlap syndrome of several diseases, namely, BrS and LQTS and BrS and ARVC.

Remarkably, 6 out of 15 patients with a positive genetic analysis had several nucleotide variants, which most often affected genes associated with changes in myocardial structure, specifically, *MYOZ2, RBM20, JUP, TPM1,* and *MYH11*. Although BrS was initially described as a monogenic autosomal dominant disorder with incomplete penetrance, it is increasingly evident that it may follow a more complex genetic model. Indeed, it can be considered an oligogenic or polygenic disease in which more than one causative gene contributes to the clinical phenotype [30].

On the other hand, no genetic changes were observed in 7 (29.2%) patients. No significant relationship was noted between the disease course and the patient's genotype. The most severe clinical course with cardiac arrest due to VF development at the age of 36–55 years was registered in patients 799, 732, and 580, who had *SCN5A* and *SCN10A* variants, and patient 789 who had no genetic changes. Polymorphic VT/VF induced by EEPS followed by ICD implantation was identified in patient 638 (female) with rare *KCNJ8* and *HCN4* variants, in patient 580s with *DES* and *MYH11* variants, and in a patient without mutations. Moreover, 13 (54.2%) patients were asymptomatic, whereas three of them (patients 611, 716, and 717) had pathogenic and likely pathogenic mutations in *SCN5A*, and a variant of uncertain clinical significance in the same gene was found in patient 668. However, BrS symptoms were more common in patients with mutations because out of 9 patients without genetic changes, 5 (55.6%) were asymptomatic, accounting for 33.3% (5 of 15) of those with rare genetic variants. SCD among close relatives with a family history was acclaimed in 50% of probands with pathogenic *SCN5A* mutations, implying a poor prognosis in carriers of pathogenic variants in this gene and the need for scrupulous examination of such patients.

The impact of genetic variants on the risk of developing cardiac arrhythmias and their prognosis is still debated. The extent to which different gene variants increase the risk of arrhythmic events and SCD remains unclear and is therefore not yet considered in risk stratification. However, genetic data can be another tool for risk stratification in genotype-positive patients, and if it does not result in an active treatment strategy, this could at least contribute to a lifestyle change (avoidance of drugs that may induce ST-segment elevation in right precordial leads and excessive alcohol intake).

CONCLUSION

This study substantiates the idea that BrS, along with monogenic inheritance, may also have a polygenic nature, in which the clinical phenotype is caused by variants in several genes associated with cardiovascular diseases. Mutations in patients with the BrS pattern have been associated with an increased likelihood of clinical manifestations of the disease. Nevertheless, the impact of genotype on the BrS phenotype is not entirely clear. The most severe form of the disease with VF development and successful resuscitation followed by ICD implantation was predominantly registered in patients with variants in several genes (*SCN5A* and *JUP; KCNJ8* and *HCN4; DES* and *MYH11*).

STUDY LIMITATIONS

The study limitations include the small number of patients with different genetic variants of BrS on grounds of its low prevalence. Nevertheless, the data presented are consistent with those described in the literature.

ADDITIONAL INFORMATION

Ethics approval. The protocol of the study was approved by Institute of Genetics and Cytology of Belarus National Academy of Sciences Ethics Committee, protocol No. 2, 08.06.2021.

Author contribution. All authors made significant contributions to the preparation of the article and read and approved the final version before publication.

Contribution of each author. S.M. Komissarova — concept and design of the study, writing — original draft, patient follow-up; N.N. Chakova — conducting and interpreting the results of genetic analysis, writing — original draft; N.M. Rineiska — data curation, diagnostic studies, writing — original draft, review and editing, literature review; S.S. Niyazova — conducting and interpreting the results of the genetic analysis; T.V. Dolmatovich — conducting and interpreting the results of the genetic analysis; V.Ch. Barsukevich — patient follow-up; L.I. Plaschinskaya — diagnostic studies.

Competing interests. The authors declare that they have no competing interests.

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Вклад авторов. Все авторы внесли существенный вклад в подготовку статьи, прочли и одобрили финальную версию перед публикацией.

Вклад каждого автора. С.М. Комиссарова — концепция и дизайн исследования, написание текста, динамическое наблюдение за пациентами; Н.Н. Чакова — проведение и интерпретация результатов генетического анализа пациентов, написание текста; Н.М. Ринейская — анализ полученных данных, диагностические исследования, написание текста, обзор литературы; С.С. Ниязова — проведение и интерпретация результатов генетического анализа пациентов; Т.В. Долматович — проведение и интерпретация результатов генетического анализа пациентов; В.Ч. Барсукевич — динамическое наблюдение за пациентами; Л.И. Плащинская — диагностические исследования.

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Источник финансирования. Авторы заявляют об отсутствии внешнего финансирования при проведении исследования.

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