Russian Journal of Cardiology 2021;26(10):4707
doi:10.15829/1560-4071-2021-4707
https://russjcardiol.elpub.ru

ORIGINAL ARTICLES
ISSN 1560-4071 (print)
ISSN 2618-7620 (online)

RBM20 gene variants associated with left atrial dilatation in patients with old myocardial infarction and heart failure with reduced ejection fraction

Vakhrushev Yu. A., Kuular A. A., Lebedeva V. K., Kozyreva A. A., Kostareva A. A., Sitnikova M. Yu., Lyasnikova E. A.

Aim. To study the prevalence of *RBM20* gene polymorphisms and their relationship with the structural and functional left atrial (LA) characteristics in patients with coronary artery disease and heart failure with reduced ejection fraction (HFrEF).

Material and methods. The study included 138 men aged 55,8±6,6 years with prior myocardial infarction ≥12 months ago and HFrEF (class II-IV heart failure, left ventricular ejection fraction (Simpson's methods), 25,1±7,2%). The control group consisted of 384 healthy donors. Genotyping of two *RBM20* polymorphic variants (rs942077 and rs35141404) was performed by real-time polymerase chain reaction.

Results. The prevalence of *RBM20* polymorphisms did not differ in the HFrEF cohort and the control group. The GA rs35141404 genotype was more common among patients with a less pronounced increase in LA volume index (LAVI) (p=0,034). The minor A allele rs35141404 was associated with a protective effect on severe LA remodeling. However, this association did not reach the level of significance.

Conclusion. For the rs942077 and rs35141404 polymorphic variants of the *RBM20* gene, no significant associations were found with the LA size and atrial fibrillation presence in patients with HFrEF and old myocardial infarction. There was a tendency towards the association of the A allele and the GA rs35141404 genotype with a protective effect on LA remodeling. The data obtained confirm the need for further search for genotype-phenotype relationships of a wider population of patients with heart failure and coronary artery disease.

Keywords: heart failure with reduced ejection fraction, left atrium, polymorphic variants, *RBM20*.

Relationships and Activities. The study was financially supported and carried out within the state assignment of the Almazov National Medical Research Center (№ AAAA-A19-119070490034-4).

Almazov National Medical Research Center, St. Petersburg, Russia.

Vakhrushev Yu. A.* ORCID: 0000-0001-8911-1927, Kuular A. A. ORCID: 0000-0002-8869-8655, Lebedeva V. K. ORCID: 0000-0002-0507-096X, Kozyreva A. A. ORCID: 0000-0003-0656-7967, Kostareva A. A. ORCID: 0000-0002-9349-6257, Sitnikova M. Yu. ORCID: 0000-0002-0139-5177, Lyasnikova E. A. ORCID: 0000-0003-0613-829X.

*Corresponding author: thevakhr@gmail.com

Received: 01.09.2021
Revision Received: 22.09.2021
Accepted: 29.09.2021

For citation: Vakhrushev Yu. A., Kuular A. A., Lebedeva V. K., Kozyreva A. A., Kostareva A. A., Sitnikova M. Yu., Lyasnikova E. A. *RBM20* gene variants associated with left atrial dilatation in patients with old myocardial infarction and heart failure with reduced ejection fraction. *Russian Journal of Cardiology*. 2021;26(10):4707. doi:10.15829/1560-4071-2021-4707

The influence of polymorphic genetic variants on development and course of various cardiovascular diseases has been noted and actively studied for many years, but the volume of study in this area has increased significantly after development of new methods of molecular biology and genetics. The application of genome-wide studies and the use of next-generation sequencing allowed to detect new determinants associated with the risk of development and adverse outcome of chronic heart failure (CHF) of various etiologies. At the same time, the influence of genetic factors on some structural and functional parameters of the cardiac muscle in CHF development and myocardial remodeling remained poorly studied.

In recent years, many studies have been published analyzing the association of various genetic determinants with myocardial structural parameters and cardiac chamber sizes. The greatest number of works was devoted to the search of genotype-phenotypic associations in development of pathological myocardial remodeling of predominantly dilated phenotype. At the same time, single works were devoted to the analysis of genetic variants associated with structural atrial remodeling. Thus, in 2010, the relationship between genetic variants of polymorphic loci in the genes *NTN1*, *MYH10*, *COX10* and *MYOCD* with left atrium (LA) size was demonstrated [1]. In 2015, Mints Y, et al. confirmed the association of the polymorphism rs10033464, located near the gene *PITX2* in locus 4q25, with LA dilatation development [2]. The gene *PITX2* encodes the protein Pitx2, which is a transcription factor that is a member of the RIEG/Pitx family of homeodomain transcription factors that play an essential role in embryonic development. It is important to note that this transcription factor undergoes alternative splicing, resulting in four isoforms (Pitx2A, Pitx2B, Pitx2C, PitxD) in the body and is connected to LA formation and structural and morphological features of pulmonary venous mouths [3]. This transcription factor is expressed asymmetrically during different stages of cardiac development and plays an integral role in cardiogenesis, and insufficiency of its function leads to development of structural and electrophysiological abnormalities in atrium [4].

Another foreign study demonstrated the association of the above-described polymorphism rs10033464 with early recurrence of atrial fibrillation (AF) after cardioversion and larger LV size in a meta-analysis of 7034 patients with this rhythm disorder [5]. The mechanism of structural and functional interconnections of the LA tissue remains incompletely understood. Atrium dilation is thought to cause activation of signal-dependent extracellular kinase Erk1/ERk2, causing further progression of atrium tissue fibrosis, formation of re-entry foci and contributing to arrhythmogenesis [6]. There is also an inverse relationship: LA dilation can occur due to AF in patients without its primary expansion. Currently, the search for genotype-phenotypic associations with regard to structural and functional remodeling of cardiac chambers is actively continuing [5, 6].

The development of dilatational remodeling is associated with multiple genetic determinants of myocardial structural proteins, including the gene *RBM20*, pathogenic variants in which lead to development of arrhythmogenic cardiomyopathy in aggressive form [7]. The gene *RBM20* encodes the protein RBM20, which is a transcriptional splicing factor for many genes expressed in cardiac muscle and involved in maintaining sarcomere structure, diastolic function and ion transport, such as: *TTN*, *CaMKII*, *CACNA1C*, *LDB3*, *LMO7*, *FHOD3*, *PDLIM3*, *RTN4*, *TRDN*, *OBSCN*, *RYR2* [7, 8]. The main target of *RBM20* is the gene *TTN* encoding the giant protein taytin, which acts as a spring that provides sarcomere stiffness and plays an important role in passive relaxation of the cardiomyocyte [9]. It is noteworthy that 2 above-mentioned genes, *TTN* and *RBM20*, are predominantly associated with the development of dilated cardiomyopathy (DCM), and in the last 3 years much attention has been paid to studying the role of their genetic variants in development of arrhythmic events in patients with CHF and DCM, including AF, both in inherited forms of cardiomyopathies and in the general population [1, 9].

It seems relevant to study the relationship of genetic determinants, such as polymorphic variants of the gene *RBM20* (rs942077 and rs35141404), with structural and functional characteristics of LA in patients with heart failure (HF) with low ejection fraction (HFrEF) of predominantly non-monogenic nature.

Material and methods

This study is a single-center study including 138 men with coronary heart disease, postinfarction cardiosclerosis, and stable HFrEF of II-IV functional class, aged 40-68 years, on standard drug therapy, who were treated at the V.A. Almazov Federal State Medical Research Center in 2012-2018. The control group was represented by practically healthy people who constituted the donor control base of the V.A. Almazov Scientific Research Center (384 people), comparable in age to the studied cohort. The criteria for non-inclusion in the study were: primary and postmyocardial DCM, hypertrophic cardiomyopathy, hemodynamically significant organic heart valve lesions, cardiac chamber dilata-

tion due to accumulation disease, secondary arterial hypertension (AH), extensive cardiac surgery or percutaneous coronary intervention or valvuloplasty, and electrophysiology intervention within 12 months before randomization, acute or decompensated HF less than 3 months prior to inclusion.

The study was approved by the ethical committee of the V. A. Almazov Scientific Research Center and was conducted in accordance with good clinical practice and the ethical standards of the Declaration of Helsinki. All respondents signed an informed consent for the necessary examination methods.

Patients' status was assessed, and routine laboratory and instrumental diagnostic methods were performed. Echocardiography was performed according to the standard protocol of the center. The LA volume (LAV) was indexed to the body surface area (BSA) and the degree of severity of growth (in meters). Normative values of the LA size: LAV (ml)/BSA (m^2) and LAV (ml)/(height, $m)^2$ specific for gender was determined in accordance with the recommendations of the American and European associations of echocardiographic (ASE/EAE) — 2015 for echocardiography in adults and the European communities on cardiology and hypertension (ESC/ESH) — 2018 for treatment of hypertensive patients (⩽40 mm, ⩽34 ml/BSA $(m)^2$ and ⩽18,5 ml/(height in $m)^2$, respectively) [10, 11]. The ejection fraction (EF) of the left ventricle (LV) was calculated using the Simpson method. The study included patients with LV EF <35%.

Characteristics of patients. The main characteristics of the cohort under study are given in Table 1. The average age of patients was 55,8±6,6 years. Most respondents had undergone myocardial revascularization and had HFrEF of functional class II. AH, diabetes mellitus and obesity were observed in 96%, 17%, and 23% of cases, respectively. Implanted devices, including permanent pacemaker, implanted cardioverter defibrillator, cardiac resynchronization therapy device, cardiac contractility modulator had 60% of patients. According to the anamnesis and programming results, AF (constant, persistent or paroxysmal form) was registered in 27% of cases. LV EF was 25,1±7,2%. An increase in LA volumes was detected in more than 90% of cases.

To study polymorphic variants of *RBM20* (rs942077 and rs35141404), DNA was isolated from whole blood using the FlexiGene DNA Kit (Catalog No.51206). These polymorphic variants were identified by real-time polymerase chain reaction using allele-specific primers from Applied Biosystems on an Applied Biosystems 7500 RealTimePCRSystem amplifier and Syntol reagent kit.

Statistical processing was performed using the Statistica 10 package. Data are presented as: mean ± standard deviation (M±SD) in case of normal distribution, medians (Me) and 25% (Q25) and 75% (Q75) quartiles, frequencies, and percentages of the total number of follow-up n (%). Continuous values with a normal distribution were compared with each other using a t-test. The nonparametric Mann-Whitney test for independent samples was used to compare continuous values with a distribution other than normal. Independent categorical data were compared using Fisher's two-sided test and chi-square (χ^2) test with Yates continuity correction at statistical significance p<0,05.

Table 1

Characteristics of patients

Indicator	n=138
Gender (men), n (%)	138 (100%)
Age, years, M±SD	55,8±6,6
Minimum/maximum range, years	40-68
Q-myocardial infarction, n (%)	138 (100%)
Q-myocardial infarction of anterior LV wall, n (%)	131 (95%)
Myocardial revascularization, n (%)	94 (68%)
Arterial hypertension, n (%)	132 (96%)
Duration of arterial hypertension, years	11,6±10,6
Obesity, n (%)	32 (23%)
Diabetes mellitus, n (%)	23 (17%)
Atrial fibrillation, n (%)	36 (26%)
PCP/ICD/CPT, n (%)	9 (7%)/56 (41%)
Cardiac contractility modulator, n (%)	18 (13%)
Functional class of CHF II/III/IV, n (%)	94 (68%)/36 (26%)/ 8 (6%)
LV ejection fraction (Simpson), M±SD	25,1±7,2%
Minimum/maximum range, %	14-35%
End-diastolic volume of LV, ml, M±SD	249,8±78,8
End-systolic volume of LV, ml, M±SD	185,0±65,4
LA size, mm M±SD	49,8±6,6
LA volume/(height, $m)^2$, ml/m^2, M±SD	36,5±11,8
LA volume/BSA, ml/m^2, M±SD	55,8±17,5

Note: the values are given in %, absolute values (indicated in parentheses), as the average value ± standard deviation.

Abbreviations: LA — left atrium, LV — left ventricle, BSA — body surface area, PCP — permanent cardiac pacing, ICD — implanted cardioverter defibrillator, CRT — cardioresynchronizing therapy, CHF — chronic heart failure.

Results

The occurrence of alleles and genotypes of the polymorphic variants of *RBM20* (rs942077 and rs35141404) in the presented sample of patients with HFrEF did not differ compared with the control group (Table 2). There were also no differences in

Table 2

Distribution of genotypes and alleles of polymorphic variants *RBM20* (rs942077 and rs35141404) in the study groups

Genotypes and alleles of polymorphic variants		CHF group, n=138	Control group, n=384	Distribution according to dbSNP
rs942077	CC	83% (114)	79% (304)	79%
	CG	17% (24)	19% (72)	17%
	GG	0% (0)	2% (8)	4%
	C	91% (252)	88,5% (680)	87%
	G	14% (24)	11,5% (88)	13%
rs35141404	GG	75,4% (104)	80,4% (309)	77%
	GA	23,2% (32)	18,8% (72)	22%
	AA	1,4% (2)	0,8% (3)	1%
	G	86,9% (240)	89,8% (690)	86%
	A	13,1% (36)	10,2% (78)	14%

Note: the values are given in %, absolute values.

Table 3

Distribution of genotypes and alleles of polymorphic variants rs942077 and rs35141404 of the gene *RBM20* in groups of patients with HFrEF, depending on the presence of AF

Genotypes and alleles of polymorphic variants		Group without AF, n=102	Group with AF, n=36	All patients, n=138	Control group, n=384
rs942077	CC	80% (82)	86% (31)	83% (114)	79% (304)
	CG	20% (20)	14% (5)	17% (24)	19% (72)
	GG	0% (0)	0% (0)	0% (0)	2% (8)
	C	90% (184)	93% (67)	91% (252)	88,5% (680)
	G	10% (20)	7% (5)	14% (24)	11,5% (88)
rs35141404	GG	76,5% (78)	72,2% (26)	75,4% (104)	80,4% (309)
	GA	22,5% (23)	25% (9)	23,2% (32)	18,8% (72)
	AA	1% (1)	2,7% (1)	1,4% (2)	0,8% (3)
	G	88% (179)	85% (61)	87% (240)	90% (690)
	A	12% (25)	15% (11)	13% (36)	10% (78)

Note: the values are given in %, absolute values.
Abbreviation: AF — atrial fibrillation.

the prevalence of the studied *RBM20* gene polymorphisms depending on the presence of AF (Table 3).

Given the high detectability of LA dilatation in this cohort of patients, the analysis of the relationship between SNP rs942077 and rs35141404 of the gene *RBM20* with the degree of gender-specific increase in LA size according to ASE/EAE recommendations was carried out [11]. As a result of this analysis, no statistically significant difference in the frequency of genotypes and alleles of *RBM20* polymorphic variants was obtained (Table 4).

It is known that among different parameters of LA there is more prognostic value with regard to adverse cardiovascular outcomes in the index of LAV/BSA regardless of the presence of AF, HF and its etiology [12]. The values of LAV index (LAVI) of >50 ml/m^2 and >40 ml/m^2 had the same predictive ability with LV EF in relation to hospitalizations due to HF and mortality in patients with coronary heart disease [13]. Therefore, we attempted to analyze the prevalence of the studied *RBM20* SNPs in patients with varying degrees of LAVI enlargement.

When analyzing alleles and genotypes rs942077 and rs35141404 *RBM20* in the study groups, depending on the presence of severe LA dilatation according to LAVI indicator, significant differences in the representation of the GA genotype rs35141404 were detected. In patients with LAVI <40 ml/m^2, corresponding to less pronounced LA dilatation according to ASE/EAE classification, was dominated by GA genotype and allele A rs35141404 compared with patients with LAVI 50 ml/m^2 (38%:16%, p=0,034% and 19%:11%, p>0,05). At the same time,

Table 4

Distribution of genotypes and alleles of polymorphic variants rs942077 and rs35141404 of the gene *RBM20* in groups of patients with HFrEF depending on the size of LA

Genotypes and alleles of polymorphic variants		Subgroups of patients			
		LA* ⩽40 mm, n=11	LA 41-51 mm, n=79	LA* ⩽40 mm, n=11	All patients, n=138
rs942077	CC	72,7% (8)	86% (68)	77% (37)	83% (114)
	CG	27,3% (3)	14% (11)	22% (11)	17% (24)
	C	86,4% (19)	93% (147)	88,5% (85)	91% (252)
	G	13,6% (3)	7% (11)	11,5% (11)	14% (24)
rs35141404	GG	72,7% (8)	75,9% (60)	77% (37)	75,4% (104)
	GA	27,3% (3)	22,8% (18)	21% (10)	23,2% (32)
	AA	0% (0)	1,3% (1)	2% (1)	1,4% (2)
	G	86% (19)	87,3% (138)	87,5% (84)	87% (240)
	A	14% (3)	12,7% (20)	12,5% (12)	13% (36)

Note: the values are given in %, absolute values, * — left atrium, antero-posterior size in parasternal position.
Abbreviation: LA — left atrium.

Table 5

Distribution of genotypes and alleles of polymorphic variants rs942077 and rs35141404 of the gene *RBM20* in groups of patients with HFrEF depending on LAVI

Genotypes and alleles of polymorphic variants		Group with LAVI <40 ml/m², n=21	Group with LAVI ⩾40 ml/m², n=96	Group with LAVI 50 ml/m², n=75	All patients, n=138
rs942077	CC	81% (17)	81,3% (78)	80% (59)	83% (114)
	CG	19% (4)	18,7% (18)	21% (16)	17% (24)
	GG	0% (0)	0% (0)	0% (0)	0% (0)
	C	90% (38)	91% (174)	89% (134)	91% (252)
	G	10% (4)	9% (18)	11% (16)	14% (24)
rs35141404	GG	62% (13)	79% (76)	81% (61)	75,4% (104)
	GA	38% (8)	19% (18)	16% (12)	23,2% (32)
	0,034				
	AA	0% (0)	2% (2)	3% (2)	1,4% (2)
	G	81% (34)	88,5% (170)	89% (134)	87% (240)
	A	19% (8)	11,5% (22)	11% (16)	13% (36)

Note: the values are given in %, absolute values.
Abbreviation: LAVI — left atrium volume index, reduced to body surface area.

there was a higher prevalence of GG genotype among patient groups with LAVI ⩾40 ml/m² and >50 ml/m² when the threshold of significance was not reached (79%:62% and 81%:62%, respectively, all p>0,05). Patients with LAVI <40 ml/m² had less pronounced clinical manifestations of CHF and greater LV EF compared with patients in the reference group with LAVI >50 ml/m². AF was observed more frequently among the contingent with more pronounced LA dilatation (p>0,05). Having said so, the subgroups of patients did not differ in age, body mass index, AH frequency and its duration, prevalence of diabetes mellitus, obesity (all p>0,05). Data on subgroups of patients are given in Tables 5 and 6.

Discussion

Currently, much attention is paid to the study of molecular determinants associated with the development of various HF phenotypes and myocardial remodeling, the so-called molecular epidemiology of CHF, in which an important place is given to genetic predictors [14].

The gene *RBM20* regulates the splicing of many cytoskeletal protein genes, including *TTN*, *CAMK2D*, *LDB3*, *LMO7*, *PDLIM3*, *RTN4*, and *RYR2*, and is also connected to sarcomere assembly, ion transport and posttranslational splicing of a number of calcium signaling and calcium homeostasis protein genes [7]. The listed functions of the gene *RBM20* largely

Table 6

Clinical characteristics of groups of patients with HFrEF depending on LAVI

Indicator	Group with LAVI <40 ml/m², n=21	Group with LAVI 50 ml/m², n=75
Age, years, Me [Q25;Q75]	56 [53;62]	57 [53;62]
AH, % (n)	76 (16)	68 (50)
AH duration, years, Me [Q25;Q75]	14 [0;15]	11 [0;18]
BMI, kg/m², Me [Q25;Q75]	27,1 [20,9;29,4]	25,8 [20,1;28,1]
Obesity, % (n)	24 (5)	21 (16)
Diabetes mellitus, % (n)	43 (9)	27 (20)
AF, % (n)	19 (4)	35 (26)
LV FV, %, Me [Q25;Q75]	32 [30;34]	27 [21;31]*
CHF FC, Me [Q25;Q75]	2 [2;2]	2 [2;3]*

Note: the values are given in %, absolute values (indicated in parentheses), in the form of median and quartiles; * — p<0,01.
Abbreviations: AH — arterial hypertension, BMI — body mass index, LAVI — left atrium volume index, LV EF — left ventricular ejection fraction, FC — functional class, AF — atrial fibrillation, CHF — chronic heart failure.

determine the high frequency of arrhythmological events in patients carrying pathogenic variants of *RBM20* [1]. In this regard, it can be assumed the presence of genotype-phenotypic associations of polymorphic variants of this gene with regard to structural remodeling, in particular, of atrium tissue in CHF of noninherited genesis.

In our study, the occurrence of genotypes and alleles of polymorphic variants rs942077 and rs35141404 of the gene *RBM20* in patients in the narrow phenotypic HFrEF group with postinfarct cardiosclerosis did not differ from data obtained in controls and dbSNP genetic database data, but SNP rs35141404 was associated with LA dilatation. The GA rs35141404 genotype was significantly more common in patients with a less pronounced increase in LAVI. A similar association was seen for the prevalence of minor allele A (rs35141404), although the significance threshold was not reached. It is important to note that the group of patients with the highest occurrence of this genotype and allele did not differ in age and cardiometabolic factors contributing to LA dilatation from the reference group with more pronounced LA remodeling and, naturally, a higher incidence of AF, which largely agrees with the work of Refaat MM, et al. (2012) [15]. When studying the associations of SNP rs942077 and rs35141404 of the gene *RBM20* with arrhythmic events and outcomes in a sample of patients with HFrEF of coronary etiology and DCM, the authors demonstrated the association of rs35141404 polymorphism of the gene *RBM20* with AF regardless of the CHF causative factor. It is worth noting that in this work, similar to the data we obtained, it was the rs35141404 A allele that was associated with a protective effect in relation to the risk of developing AF (odds ratio 0,59, 95% confidence interval 0,40-0,84, p=0,006) [15].

The results of several recent studies demonstrate the association of rare, shortening variants of the gene *TTN* (*TTNtv*) with AF, CHF and lower LV EF in patients even without the diagnosis of DCM [16]. Taking into account these data and the key role of *RBM20* in the *TTN* splicing process, further investigation of the molecular mechanisms of pathogenesis and structural and functional myocardial remodeling in CHF of ischemic etiology associated with *RBM20* and shortening variants and/or pathogenic SNPs of the tetin gene seems relevant, providing a potential opportunity to develop a personalized medical approach.

Study limitations. An important limitation of this study was the relatively small sample size of the study group (138 patients), the presence of possible additional causal factors potentially influencing myocardial remodeling, including the ongoing drug and non-drug therapy, which may have an effect on the LA dilatation development. Only male patients were included in the work, while the control group had no gender restrictions. The above predetermines the cohort expansion of the studied patient population and the application of multivariate statistical methods for a more complete understanding of genotype-phenotypic associations.

Conclusion

The polymorphic variant and rs35141404 of the gene *RBM20* is associated with the severity of LA dilatation in patients with HFrEF and pronounced postinfarction myocardial remodeling. Our preli-

minary data support the need to further search for genotype-phenotypic associations in the broader population of patients with CHF of coronary etiology in the focus of personalized medicine.

Relationships and Activities. The study was performed at the expense and within the framework of the state assignment of the V.A. Almazov Scientific Research Center Reg. No. AAAA19-119070490034-4.

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