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Association of serotonin 2C receptor gene polymorphism with depression and quality of life indicators in patients before coronary artery bypass grafting

Inozemtseva A.A., Pomeshkina S.A., Argunova Yu.A., Barbarash O.L.

Research Institute for Complex Issues of Cardiovascular Diseases
6, Sosnovy Bulv., Kemerovo, 650002, Russian Federation

ABSTRACT

The aim was to study the association of the rs6318 polymorphism of the *HTR2C* gene with the level of depression and quality of life in patients undergoing coronary artery bypass grafting (CABG).

Materials and methods. A total of 116 patients with coronary artery disease (CAD) (age 60 [57; 65] years) were examined before CABG. Depression was assessed in all patients in the preoperative period using the Beck Depression Inventory (BDI). In addition, the quality of life was measured in all patients using the SF-36 questionnaire. Blood samples were collected for the subsequent polymerase chain reaction-based genotyping to detect the rs6318 polymorphism of the *HTR2C* gene. Statistical analysis was performed using the STATISTICA 10.0 software package (StatSoft Inc., USA). The value of $p < 0.05$ was considered statistically significant.

Results. No significant differences were found in the associations between different genotypes of the HTR2C gene and depression levels. However, certain trends have been established ($p = 0.1$). Thus, the pairwise comparison of different genotypes reported that carriers of the CC genotype had higher BDI scores (12 [8; 19]), whereas carriers of the CG genotype ($p = 0.07$) and GG genotype ($p = 0.08$) had lower BDI scores (3.5 [2; 5] and 8 [0; 25], respectively). The quality of life among carriers of the CC, CG and GG genotypes did not differ significantly. Nevertheless, the median values of almost all indicators (GH, PF, RE, VT) were lower in carriers of the CC genotype. Carriers of the CC genotype suffered more from pain limiting their daily activities than carriers of the GG genotype ($p = 0.04$). Homozygous C allele carriers demonstrated poorer mental health than heterozygous carriers (56 [40; 64] vs. 82 [72; 92], $p = 0.04$).

Conclusions. Reliable associations of different genotypes of the rs6318 polymorphism of the *HTR2C* gene with the quality of life parameters have been found in patients with coronary artery disease.

Key words: coronary artery disease, coronary artery bypass grafting, depression, quality of life

Conflict of interest. The authors declare no obvious or potential conflicts of interest related to the publication of this article.

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Conformity with the principles of ethics. All patients signed an informed consent. The study protocol and design were approved by the local Ethics Committee of the Research Institute for Complex Issues of Cardiovascular Diseases (Protocol No. 20 of 25.01.2011).

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✉ *Argunova Yulia A.,* e-mail: argunova-u@mail.ru.

Ассоциация полиморфизма гена рецептора серотонина 2С с депрессией и показателями качества жизни у пациентов перед операцией коронарного шунтирования

Иноземцева, А.А., Помешкина, С.А., Аргунова Ю.А., Барбараш О.Л.

Научно-исследовательский институт комплексных проблем сердечно-сосудистых заболеваний (НИИ КПССЗ) Россия, 650002, г. Кемерово, Сосновый бульвар, 6

РЕЗЮМЕ

Цель. Изучить связи генетического полиморфизма rs6318 гена *HTR2C* с уровнем депрессии и качеством жизни у пациентов перед коронарным шунтированием (КШ).

Материалы и методы. Обследованы 116 пациентов с ишемической болезнью сердца (ИБС) перед КШ (возраст 60 [57; 65] лет). В предоперационном периоде проводилась оценка депрессии с помощью шкалы Бека, качества жизни с применением опросника SF-36, а также проводился забор крови с последующим генотипированием полиморфизма rs6318 *HTR2C* методом полимеразно-цепной реакции. Статистическая обработка осуществлялась с использованием пакета программ Statistica 10.0 (StatSoft Inc., США). Во всех случаях нулевую гипотезу отвергали при $p < 0,05$.

Результаты. При анализе связи различных генотипов гена *HTR2C* с уровнем депрессии значимых различий не найдено, однако установлены определенные тенденции ($p = 0,1$). Так, при попарном сравнении различных генотипов обнаружено, что у носителей генотипа CC балл по шкале Бека был выше и составил 12 [8; 19], тогда как у носителей генотипов CG ($p = 0,07$) и GG ($p = 0,08$) он был ниже и составил 3,5 [2; 5] и 8 [0; 25] соответственно. Показатели качества жизни у носителей генотипов CC, CG и GG значимо не различались, однако, значение медианы практически по всем показателям опросника (GH, PF, RE, VT) было ниже у носителей генотипа CC. У носителей генотипа CC боль ограничивала их повседневную деятельность больше, чем у носителей генотипа GG ($p = 0,04$). У гомозигот по аллелю *C* уровень психического здоровья было также ниже, чем у гетерозигот (56 [40; 64] против 82 [72; 92], $p = 0,04$).

Заключение. В настоящем исследовании обнаружены статистически значимые связи различных генотипов полиморфизма rs6318 гена *HTR2C* у пациентов с ИБС с показателями качества жизни.

Ключевые слова: ишемическая болезнь сердца, коронарное шунтирование, депрессия, качество жизни.

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

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INTRODUCTION

Effectiveness of coronary artery bypass grafting (CABG) for treating patients with coronary artery disease (CAD) has already been proven and is of no doubt [1]. However, despite all recent advances in the CABG surgical strategies, anesthesia and pre- and postoperative management, the proportion of patients becoming disabled after CABG remains very high [2]. However, CABG is aimed at improving the quality of life (QoL), not worsening it. There are

many reasons that might provoke this paradox: a lack of cardiac rehabilitation programs at each phase of rehabilitation, low patients' awareness of cardiac rehabilitation benefits [3], limited ability of patients to participate in these programs, etc. Patients' unwillingness to participate may be explained by depression and anxiety before and after CABG. In addition, cardiac surgery itself is considered as a significant stressful factor for patients [4]. The prevalence of depression and severe anxiety among patients before cardiac surgery ranges from 30 to 40% [5].

Over the past decades, it has been proven that personality traits are largely dependent on genetic factors [6]. Since the serotonergic system is actively involved in the pathogenesis of depression [7], the genes associated with it are currently being actively studied. Particular attention is focused on the serotonin 2c receptor gene (HTR2C), located on the chromosome Xq24 site and responsible for social behavior and cognition.

HT2C receptors are found in the striatum, choroid plexus, cerebral cortex, hippocampus, and substantia nigra. 2C receptors have been shown to control the release of other neurotransmitters, such as norepinephrine and dopamine. HT2C receptors are involved in the regulation of mood, anxiety, sexual functions, sleep, appetite, and the cardiovascular system [8].

Cys23Ser (rs6318) is one of the most well-studied HTR2C gene polymorphisms. The replacement of guanine by cytosine results in the amino acid replacement, and cysteine is then replaced by serine. Binding of the receptors in CC genotype carriers is two times weaker than in homozygous GG carriers. Thus, CC carriers are supposed to be more prone to the onset of depressive disorders [9, 10]. A number of studies have reported the association between this polymorphism and suicidal behavior [11], alcoholism, bipolar mental disorders, schizophrenia [12], and major depressive disorders [13].

However, evidences on the contributive role of this polymorphism in the development of anxiety and depression in somatic patients are limited.

Our study is aimed at determining the relationship of HTR2C (rs6318) gene polymorphism with the level of depression and quality of life in patients undergoing preoperative management for CABG.

MATERIALS AND METHODS

116 patients with stable coronary artery disease undergoing preoperative management for on-pump CABG were enrolled in the study. Of those, 95 (82%) were men and 21 (18%) were women. The median age was 60 [57; 65] years. The exclusion criteria were the presence of severe somatic pathology (acute or chronic renal failure, liver failure, chronic lung diseases, thyroid diseases, autoimmune diseases) and refusal to participate in genotyping.

Two-to-seven days before CABG, all patients underwent depression screening using the Beck Depression Inventory and the quality of life assessment using the SF-36 questionnaire. Eight subscales were assessed (physical functioning (PF), role-physical functioning (RP), bodily pain (BP), general health (GH), vitality (VT), social functioning (SF), role-emotional functioning (RE) and mental health (MH). Blood sampling was performed at days 3–5 before CABG, followed by the genotyping of HTR2C (rs6318) polymorphism. DNA was isolated by phenol-chloroform extraction according to Maniatis et al. The concentration of obtained DNA was measured on the NanoDrop-2000 spectrophotometer. DNA quantification was performed using real-time polymerase chain reaction with the Taqman-probes (a 96-well plate). The Hardy – Weinberg equilibrium was met.

Clinical and demographic data of patients are presented in Table 1.

Half of the patients had myocardial infarction and arterial hypertension in their medical history and a quarter of patients had diabetes mellitus.

All patients had been receiving standard four-component CAD therapy (antiplatelet agents, beta-blockers, statins, ACE inhibitors or angiotensin receptor blockers) for 7 days before surgery.

Statistical analysis was performed using commercially available software package Statistica 10.0 (Statsoft Inc., USA). The data distribution was different from normal. The data are presented as absolute values and percentage, as well as the median and interquartile range. The Kruskal – Wallis test was used to measure the differences between the groups. A p value of ≤ 0.05 was considered statistically significant.

Table 1

Clinical and demographic data of patients before coronary artery bypass grafting

Parameter	Value
Age, years, *Me* [Q_1; Q_3]	60 [57; 65]
BMI, kg/m^2, *Me* [Q_1; Q_3]	28.5 [26.5; 30.7]
EuroScore 2, % , *Me* [Q_1; Q_3]	1.68 [1.27; 1.98]
Duration of coronary artery disease, years, *Me* [Q_1; Q_3]	4 [1;8]
Arterial hypertension, *n* (%)	95 (47)
Duration of arterial hypertension, years, *Me* [Q_1; Q_3]	10 [5; 15]
Angina pectoris, *n* (%): – 0; – I; – II; – III	 6 (5) 6 (5) 79 (68) 25 (22)
Heart failure (NYHA), *n* (%): – I; – II; – III	 12 (10) 95 (82) 9 (8)
Prior myocardial infarction, *n* (%)	64 (55)
Prior stroke, *n* (%)	6 (5)
History of type 2 diabetes mellitus, *n* (%)	29 (25)
Left ventricular ejection fraction, %, *Me* [Q_1; Q_3]	60 [51; 65]

Note. BMI – body mass index, NYHA – New York Heart Association.

RESULTS

At the first stage of the study, the prevalence of depression was assessed in the studied group of patients. According to the Beck Depression Inventory, most patients (64%) did not have depression (0–9 points), 20% of patients had minimal depression (10–15 points), 9% – mild (16–19 points) and 7% – moderate (20–29 points). There were no patients with severe depression (30–63 points) in the studied group. The distribution of patients depending on the genotype of rs6318 polymorphism is presented in Table 2.

Table 2

Depression level measured by the Beck Depression Inventory in the carriers of different genotypes of the rs6318 polymorphism of the *HTR2C* gene

Beck Depression Inventory, depression level	Genotype, *n* (%)		
	GG	CG	CC
None	68 (59)	2 (2)	3 (3)
Minimal	22 (19)	0 (0)	2 (1)
Mild	10 (8)	0 (0)	1 (1)
Moderate	7 (6)	0 (0)	1 (1)
Severe	0 (0)	0 (0)	0 (0)

The analysis of the relationships of different *HTR2C* genotypes with the level of depression measured by the Beck Depression Inventory did not show any significant differences. However, some trends were established (p = 0.1). The pairwise comparison of different genotypes reported that CC genotype carriers had higher BDI score of up to 12 [8; 19], while in CG genotype carriers (p = 0.07) and GG genotype carriers (p = 0.08) it was up to 3.5 [2; 5] and 8 [0; 25], respectively. Then, we analyzed the presence of the relationships between the quality of life and various genotypes of the *HTR2C* gene. There were no significant differences in PF, RP, GH, VT, SF, and RE between CC, CG and GG genotype carriers. The obtained data are presented in Table 3.

CC genotype carries reported lower mean score of GH, PF, RE, and VT, indicating the worst physical and mental health. The absence of reliable differences might be associated with a small sample size.

Table 3

The mean SF-36 score, depending on the different genotypes of polymorphism rs6318, *Me* [Q_1; Q_3]

SF-36 scale	*HTR2C* rs6318, *Me* [Q_1; Q_3]			*p*
	GG	CG	CC	
SF	50 [38; 50]	56.5 [50; 63]	50 [38; 63]	0.09
GH	50 [40; 62]	68.5 [55; 82]	40 [35; 52]	0.34
PF	55 [35; 80]	62.5 [30; 95]	50 [30; 60]	0.56
RP	0 [0; 50]	25 [0; 50]	25 [0; 50]	0.99
RE	34 [0;67]	83.5 [67; 100]	0 [0; 34]	0.42
VT	55 [40; 70]	67.5 [55; 80]	45 [30; 55]	0.36

Pain in CC genotype carriers interfered with their daily activities more than in GG genotype carriers (p = 0.04). The mean score was 41 [31; 62], and it was significantly lower than that of homozygotes for the G 51 allele [41; 74]. Moreover, homozygotes for the C allele had poorer mental health. Patients with this genotype had lower MH score than heterozygotes (p = 0.04): 56 [40; 64] vs. 82 [72; 92] (Fig. 1).

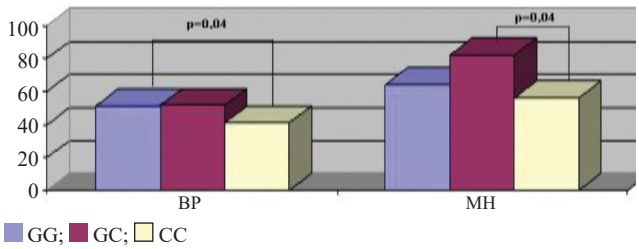

Figure 1. Distribution of mental health scores and bodily pain scores depending on the genotypes of the rs6318 polymorphism of the *HTR2C* gene

DISCUSSION

To date, the effects of depression and anxiety on the development and adverse course of coronary artery disease has been proven. The Framingham study has reported the correlation of depression with the onset of CAD [14].

Over the past decade, both pilot and large-scale studies have shown that not only depression, but also a high level of anxiety affect the course of coronary artery disease. Sumin et al. have found that CAD patients with polyvascular disease have higher depression and anxiety levels than patients with isolated coronary artery disease [15]. The Russian multicenter study COORDINATE performed in 37 cities from 2007 to 2009 demonstrated that a high level of anxiety in patients with arterial hypertension and coronary artery disease increases the risk of death during 1.5 years by 45% [16].

CAD patients undergoing CABG are a special group of patients. These patients undergo massive cardiac surgery with the extracorporeal circulation, while the surgery itself is aimed at improving their quality of life in the future and should not result in disability. Thus, this group of patients has long attracted the attention of researchers from the perspective of studying depression and anxiety and their cumulative impact on the postoperative period, as well as on the short- and long-term prognoses. The presence of anxiety in the preoperative period significantly increases the probability of death in the postoperative hospital period, as well as the development of atrial fibrillation, stroke, myocardial infarction and renal failure [17, 18].

The serotonergic system plays an important role in the regulation of social behavior. Given the fact that polymorphic loci of genes determine the activity of the product that they encode, various polymorphic variants of genes responsible for exchange of serotonin, including *HTR2C* gene, can cause the development of depression and high anxiety [19].

The rs6318 polymorphism of the *HTR2C* gene is located in the position affecting the coding region of the gene, and, therefore, may affect expression. It is hypothesized that CC genotype carriers synthesize the protein that may reduce affinity for serotonin [20].

Alfimova M.V. et al. have demonstrated that the level of anxiety in C allele carriers is higher than in G allele carriers of the rs6318 polymorphism of the *HTR2C* gene among patients with schizophrenia (n = 337) and mentally healthy individuals (n = 333) [12]. Levchuk et al. compared the distribution of genotypes of the rs6318 polymorphism in 22 men with depression and 29 somatically and mentally healthy men. They reported that the GG genotype in men with depression was significantly less common than in somatically healthy men [10].

We have not found any associations between the genotypes and depression. However, patients with the CC genotype have shown a higher level of depression according to the Beck Depression Inventory. The absence of statistically significant associations of any genotype with the presence of depression might be explained by the absence of depression in the majority of the studied patients (64%).

Quality of life indicators are a more subtle marker for anxiety-depressive disorders; they allow to identify a group of patients who are at high risk of adverse events in the postoperative period and those who will be less compliant with drug therapy and rehabilitation.

CC genotype carriers have demonstrated lower mean SF-36 score than other genotype carriers. Statistically significant differences were found for mental health and bodily pain. Similar findings were reported in the study of Golimbet et al. Out of 167 CAD patients, C allele carriers of the rs6318 polymorphism of the *HTR2C* gene were more likely to have a painful form of coronary artery disease and hostility, i.e. factors predisposing to the development of depression [21].

Thus, there is a close relationship between genetic polymorphisms and the development of depression. The impact of genes on the development of schizophrenia, suicidal behavior and major depressive disorders is widely studied both in the world and in Russia. However, the relationship of genes with subclinical depression and a high level of anxiety in patients with somatic pathology, including coronary artery disease, requires further detailed studies.

CONCLUSION

The obtained findings suggest the presence of the association between the rs6318 genetic polymorphism of the *HTR2C* gene and low quality of life in patients undergoing CABG, which can be considered as an

unfavorable prognostic factor in the postoperative period. This polymorphism seems to be promising in screening of patients prone to depression, giving the opportunity to early diagnose and timely prevent anxiety and depression (patient education, sessions with psychologists, and educational consultations with cardiologists).

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Authors information

Inozemtseva Anastasia A., Cand. Sci. (Med.), Researcher, Rehabilitation Laboratory, Research Institute for Complex Issues of Cardiovascular Diseases, Kemerovo, Russian Federation. ORCID 0000-0002-6868-4205.

Pomeshkina Svetlana A., Dr. Sci. (Med.), Head of the Rehabilitation Laboratory, Research Institute for Complex Issues of Cardiovascular Diseases, Kemerovo, Russian Federation. ORCID 0000-0003-3333-216X.

Argunova Yulia A.,* Cand. Sci. (Med.), Researcher, Rehabilitation Laboratory, Research Institute for Complex Issues of Cardiovascular Diseases, Kemerovo, Russian Federation. ORCID 0000-0002-8079-5397.

Barbarash Olga L., Dr. Sci. (Med.), Corresponding Member of the RAS, Professor, Director of Research Institute for Complex Issues of Cardiovascular Diseases, Kemerovo, Russian Federation. ORCID 0000-0002-4642-3610.

(✉) **Argunova Yulia A.,** e-mail: argunova-u@mail.ru.

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