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Association of rs1061657 single nucleotide polymorphism of the *TBX3* gene with Wolff–Parkinson–White syndrome

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ABSTRACT

BACKGROUND: Wolff–Parkinson–White syndrome is one of the most well-known heart rhythm disorders characterized by pre-excitation of the ventricles. This phenomenon occurs because the electrical impulse passes through an additional conduction pathway between the atria and the ventricles. The syndrome is most commonly associated with the likelihood of supraventricular tachycardia. Numerous studies indicate the presence of a genetic component in the pathogenesis of the Wolff–Parkinson–White syndrome, which confirms its complex nature.

AIM: The study aimed to investigate the association of the rs1061657 single nucleotide polymorphism of the *TBX3* gene with the Wolff–Parkinson–White syndrome.

METHODS: Patients diagnosed with the Wolff–Parkinson–White syndrome, manifesting in various clinical forms, including the Wolff–Parkinson–White phenomenon, were recruited over five years for a study based at the Professor V.F. Voino-Yasenetsky Krasnoyarsk State Medical University. A total of 200 patients with the Wolff–Parkinson–White syndrome, encompassing those with the Wolff–Parkinson–White phenomenon, were examined for this paper. This group included 97 males (48.5%) and 103 females (51.5%) with a mean age of 31.9 ± 15.8 years and 38.8 ± 20.0 years, respectively. All patients underwent standard clinical, laboratory, and instrumental examinations (electrocardiography, Holter monitoring, echocardiography), as well as molecular genetic testing.

All patients were divided into the following groups by the clinical variants of the disease: 90 patients (45%) with the manifest Wolff–Parkinson–White syndrome; 60 patients (30%) with the intermittent Wolff–Parkinson–White syndrome; 46 patients (23%) with the latent Wolff–Parkinson–White syndrome; and 4 patients (2%) with the Wolff–Parkinson–White phenomenon. Excel, Statistica for Windows 10.0 (StatSoft, USA), and SPSS 20 (IBM, USA) were used for the statistical data processing.

RESULTS: A statistically significant predominance of the homozygous GG genotype was observed in the distribution of genotypes of the rs1061657 polymorphism of the *TBX3* gene in patients with the Wolff–Parkinson–White syndrome compared with the control group (12.5% vs 5.5%, respectively). Furthermore, a statistically significant predominance of the G allele carriers was observed in patients with the Wolff–Parkinson–White syndrome (31.75%) compared with the control group (24.5%). The estimated risk based on odds ratio for the Wolff–Parkinson–White syndrome in the GG genotype of the *TBX3* gene was 1.323-fold higher (95% confidence interval: 0.866–2.023; $p = 0.04$) compared with the GA and AA genotypes. In the G allele carriers, the odds ratio for the Wolff–Parkinson–White syndrome was 1.434-fold higher (95% confidence interval: 1.051–4.127; $p = 0.028$) compared with the A allele.

CONCLUSION: The study results confirmed that the rs1061657 polymorphism of the *TBX3* gene contributes to the development of the Wolff–Parkinson–White syndrome.

Keywords: single nucleotide polymorphism; genetic predictors; *TBX3* gene; Wolff–Parkinson–White syndrome.

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Ассоциативная роль однонуклеотидного полиморфизма rs1061657 гена *TBX3* в развитии синдрома Вольфа–Паркинсона–Уайта

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АННОТАЦИЯ

Обоснование. Синдром Вольфа–Паркинсона–Уайта (Wolf–Parkinson–White, WPW) является одним из наиболее известных нарушений сердечного ритма. Он проявляется в преждевременном возбуждении желудочков сердца. Причина этого явления заключается в том, что электрический импульс проходит через дополнительный путь проведения между предсердиями и желудочками. Чаще всего данный синдром может быть связан с вероятностью развития наджелудочковых тахикардий. Многочисленные исследования указывают на наличие генетического компонента в патогенезе синдрома WPW, что подтверждает его сложную природу.

Цель. Изучение ассоциативной роли однонуклеотидного полиморфизма rs1061657 гена *TBX3* в развитии синдрома WPW.

Методы. На протяжении пяти лет на клинических базах Красноярского государственного медицинского университета имени профессора В.Ф. Войно-Ясенецкого проводили набор пациентов с синдромом WPW различных клинических форм, в том числе с феноменом WPW. В настоящей работе обследовано 200 пациентов с синдромом WPW, в том числе и с феноменом WPW. Среди них 97 мужчин (48,5%), 103 женщины (51,5%). Средний возраст мужчин составил 31,9±15,8 года, средний возраст женщин — 38,8±20,0 года. Всем пациентам выполнены стандартные клинические, лабораторные, инструментальные исследования (электрокардиограмма, холтеровское мониторирование электрокардиограммы, эхокардиография), а также молекулярно-генетическое исследование.

Все пациенты были разделены по клиническим вариантам синдрома WPW: *n*=90 (45%) — манифестирующего типа; *n*=60 (30%) — интермиттирующего типа; *n*=46 (23%) — скрытого типа и всего 4 пациента (2%) с феноменом WPW. Статистическую обработку данных проводили с использованием пакета прикладных программ Excel; Statistica для Windows 10.0 (StatSoft, США); SPSS 20 (IBM, США).

Результаты. При распределении генотипов полиморфизма rs1061657 гена *TBX3* наблюдалось статистически значимое преобладание гомозиготного генотипа GG у больных с синдромом WPW в сравнении с лицами контрольной группы (12,5 и 5,5% соответственно). Установлено также статистически значимое преобладание носителей аллеля G в группе больных с синдромом WPW (31,75%) по сравнению с лицами контрольной группы (24,5%). Оценённый по отношению шансов риск развития синдрома WPW у носителей генотипа GG гена *TBX3* оказался в 1,323 раза выше (95% доверительный интервал 0,866–2,023; *p*=0,04) по сравнению с генотипами GA и AA, а у носителей аллеля G — в 1,434 раза выше (95% доверительный интервал 1,051–4,127; *p*=0,028) по сравнению с аллелем A.

Заключение. Результаты исследования подтвердили вклад полиморфизма rs1061657 гена *TBX3* в развитие синдрома WPW.

Ключевые слова: однонуклеотидный полиморфизм; генетические предикторы; ген *TBX3*; синдром WPW.

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BACKGROUND

Wolff–Parkinson–White (WPW) syndrome is one of the best-known heart rhythm disorders. It is characterized by pre-excitation of the ventricles. This phenomenon occurs because the electrical impulse passes through an additional conduction pathway between the atria and the ventricles. The syndrome is most commonly associated with an increased likelihood of supraventricular tachycardia [1–3].

According to the published evidence, the cardiac conduction system disorder described above may be hereditary, and its prevalence ranges from 1 to 3 cases per 1000 population [4]. One of the most likely and dangerous consequences of this disease is an increased risk of sudden cardiac death [5]. This may result from the transition of atrial fibrillation to ventricular fibrillation [6].

The etiology of the cardiac conduction anomaly, which contributes to the formation of additional pathways between the atria and ventricles, is multifactorial [7, 8]. Numerous studies indicate the presence of a genetic component in the pathogenesis of WPW syndrome, which confirms its complex nature [9].

The scientific literature provides information about several genetic predictors of WPW syndrome. These encompass groups of genes that regulate the energy balance in cells, such as the gene encoding protein kinase adenosine monophosphate-activated non-catalytic subunit gamma 2 (*PRAKG2*) [10] and genes involved in the activation of ion channels and intercellular contacts, including the gene for voltage-gated sodium channels (*SCNA5A*) [11]. In addition to the previously studied gene polymorphisms, the association of the *TBX3* gene rs1061657 polymorphism with the development of WPW syndrome is of particular interest.

The *TBX3* gene rs1061657 polymorphism belongs to the T-box family of transcription factor genes, which are characterized by a highly conserved DNA-binding domain, known as the T-box, located at locus (12q24.21) on chromosome 12. The *TBX3* gene consists of seven exons, which upon splicing result in a protein comprised of 723 amino acids [4].

A large-scale study was conducted by a team of Chinese researchers at the Cardiology Center of the First Hospital of Lanzhou University (Lanzhou, China) from January 2013 to March 2020. The hypothesis proposed by the researchers was that, given the involvement of this gene in the formation of the fibrous ring and myocardial development of the atrioventricular canal in transgenic mice, its single nucleotide polymorphisms (SNPs) are likely to be associated with sporadic WPW syndrome in humans. The aim of this study was to investigate whether SNPs in the *TBX3* and *TBX2* genes affect the susceptibility to WPW syndrome in the Han Chinese population. A total of 230 patients with WPW syndrome (148 men and 82 women; mean age: 46.0 ± 15.2 years) were included in the study. A control group of 231 patients (143 men and 88 women, mean age 47.6 ± 14.4 years) without cardiovascular diseases was recruited for comparison. All patients underwent molecular genetic testing. The frequencies of the C allele and the CC rs1061657 genotype were higher in patients in the study group compared with the control group (odds ratio [OR] = 1.41, 95% confidence interval [CI] 1.09–1.83, p = 0.010 vs. OR = 2.24, 95% CI 1.25–3.99, p = 0.006, respectively). Conversely, the C allele and the CC rs8853 genotype exhibited higher frequency among individuals in the control group (OR = 0.70, 95% CI 0.54–0.92, p = 0.010 vs. OR = 0.44, 95% CI 0.23–0.83, p = 0.011, respectively) [12].

Remarkably, the *TBX3* gene is pleiotropic and may be associated with dilated cardiomyopathy and congenital heart defects (tetralogy of Fallot) in addition to WPW syndrome. The published sources describe studies in a British population sample of 40,000 individuals who underwent genetic testing and right ventricular structure and function. The whole-genome association studies revealed 130 different loci located in proximity to genes previously associated with congenital heart disease: *WNT9B*, *GATA4*, *NKX2-5*, and *TBX5/TBX3* [13, 14].

The present study used a candidate gene approach to select the gene polymorphism based on its function in the pathogenesis of the disease. This approach was based on data suggesting that the *TBX3* gene is involved in the regulation of fibrous ring formation and the development of the atrioventricular canal. Abnormal development of the atrioventricular annulus may lead to a bypass pathway between the atria and ventricles, resulting in WPW syndrome.

AIM

The aim of this study was to investigate the association between the rs1061657 SNP of the *TBX3* gene and the development of WPW syndrome.

METHODS

Study Design

A case–control study was conducted.

Eligibility Criteria

Inclusion criteria: subjects of both sexes, aged 18 years or older; residents of Krasnoyarsk or Krasnoyarsk Krai; patients with a confirmed diagnosis of WPW syndrome; and the ability to undergo the necessary procedures.

Exclusion criteria: unspecified diagnosis; patients unwilling to comply with the study protocol or procedures; inability of the subject to perform the necessary procedures; residence of the subject outside Krasnoyarsk Krai; age under 18 years.

Study Setting

The study was conducted at the Federal Center for Cardiovascular Surgery (Krasnoyarsk), Berzon Krasnoyarsk Interdistrict Clinical Hospital No. 20, and Professorial Clinic (Krasnoyarsk).

Study Duration

The study was conducted in 2012–2017 at the Prof. Voyno-Yasenetsky Krasnoyarsk State Medical University.

Intervention

All patients underwent clinical, laboratory, and instrumental examinations, including electrocardiography (ECG), Holter monitoring, and echocardiography. In addition, all patients in the study group underwent radiofrequency ablation.

Molecular genetic testing was conducted at the Laboratory of Molecular Genetic Studies for Internal Diseases of the Federal Research Center "Institute of Cytology and Genetics" at the Siberian Branch of the Russian Academy of Sciences (Novosibirsk). Venous blood samples, with a volume ranging from 5–10 mL, were obtained from all subjects. Standard phenol-chloroform extraction was used to isolate deoxyribonucleic acid. Subsequently, genotyping was performed using the polymerase chain reaction, where restriction fragment length polymorphism was assessed. For this purpose, primers specific to the corresponding regions of the genome were used [15].

For the evaluation of polymorphic allelic variants of the studied genes in patients with WPW syndrome, a population sample of healthy individuals (n = 200, including 97 men and 103 women) was used as a control group.

Main Study Outcome

A comprehensive analysis of the patients was performed, including clinical, laboratory, instrumental and molecular genetic testing.

Subgroup Analysis

A total of 200 patients with WPW syndrome of the following clinical forms were selected at the Krasnoyarsk State Medical University:

1) Manifest WPW, in which a constant delta wave is recorded on ECG, with antegrade and retrograde excitation through additional atrioventricular connections;

2) Intermittent WPW, which is characterized by transient symptoms of pre-excitation on ECG;

3) Latent WPW, characterized only by retrograde conduction through additional pathways;

4) WPW phenomenon, in which ECG shows evidence of conduction along the additional atrioventricular connections, but without clinical manifestations.

Outcomes Registration

A comprehensive analysis of the source documentation of the patients was conducted. This analysis included clinical, instrumental, and molecular genetic testing, and the results were subsequently entered into the database.

Statistical Analysis

Sample size calculation principles: The sample size was not pre-calculated.

Methods of statistical data analysis: The statistical data processing was performed using Excel, Statistica for Windows 10.0 (StatSoft, USA), and SPSS 20 (IBM, USA) software packages. The distribution of allele and genotype frequencies of the *TBX3* gene was evaluated between groups using the χ^2 test. In the case of the 2×2 contingency tables, the two-sided Fisher's exact test was used to compare samples by genotype and allele frequencies. The relative risk of disease for a specific allele or genotype was calculated as OR (given with 95% CI). Differences were considered statistically significant at $p < 0.05$.

RESULTS

Participants

The study group consisted of patients with WPW syndrome and WPW phenomenon (n = 200), including 97 men (48.5%) and 103 women (51.5%) with a mean age of 31.9 ± 15.8 and 38.8 ± 20.0 years, respectively. The control group was represented by a population-based sample of healthy individuals without cardiovascular disease (n = 200), including 97 men (48.5%) and 103 women (51.5%) with a mean age of 44.57 ± 16.65 and 45.47 ± 15.35 years, respectively.

Primary Results

The patients included in the study were divided into groups by clinical forms of WPW syndrome: manifest WPW (n = 90, 45%; 40 men and 50 women), intermittent WPW (n = 60, 30%; 27 men and 33 women), latent WPW (n = 46, 23%; 27 men and 19 women), and WPW phenomenon (n = 4, 2%; 3 men and 1 woman) (Table 1).

When analyzing the results of ECG and Holter monitoring in patients with WPW syndrome, the following cardiac rhythm and conduction disorders were registered:

- Paroxysmal supraventricular tachycardias (n = 39; 19.5%), including atrioventricular reciprocal tachycardia (n = 3; 1.3%)
- Paroxysms of ventricular tachycardia (n = 6; 2.8%)
- Paroxysms of atrial fibrillation (n = 8; 4.1%)
- Conduction disturbances due to incomplete right bundle branch block (n = 9; 4.3%)
- Conduction disturbances due to complete right bundle branch block (n = 25; 12.5%)
- Sinus arrhythmia (n = 33; 16.6%)
- Pacemaker migration (n = 11; 5.7%).

In the distribution of the genotypes of rs1061657 polymorphism of the *TBX3* gene, there was a statistically significant predominance of the homozygous GG genotype in patients with WPW syndrome compared with the control group (12.5% vs. 5.5%, respectively; Table 2). In addition, a statistically significant predominance of G allele carriers was found in the group of patients with WPW syndrome (31.75% vs. 24.5% in the control group; Table 3). The OR-estimated risk of WPW syndrome for the GG genotype of the *TBX3*

Table 1. Distribution of patients with Wolff–Parkinson–White syndrome by clinical variants (*n* = 200), *n*/%

Clinical variant	Men	Women	Total
Manifest (*n* = 90)	40/20.0	50/25.0	90/45.0
Intermittent (*n* = 60)	27/13.5	33/16.5	60/30.0
Latent (*n* = 46)	27/13.5	19/32.5	46/46.0
Wolff–Parkinson–White phenomenon (*n* = 4)	3/1.5	1/0.5	4/2.0

Table 2. Distribution of the rs1061657 genotype frequencies of the *TBX3* gene in patients with Wolff–Parkinson–White syndrome and controls

Gene polymorphism	Study group, *n*/%	Control group, *n*/%	*p*
GG	25/12.5	11/5.5	<0.001
GA	77/38.5	76/38.0	
AA	98/49.0	113/56.5	
Total	200/100	200/100	

Table 3. Distribution of rs1061657 allele frequencies of the *TBX3* gene in patients with Wolff–Parkinson–White syndrome and controls

Gene polymorphism	Study group, *n*/%	Control group, *n*/%	*p*
G allele	127/31.75	98/24.50	0.028
A allele	273/68.25	302/75.50	
Total	400/100	400/100	

gene was 1.323-fold higher (95% CI 0.866–2.023; $p = 0.04$) compared with the GA and AA genotypes (See Table 3). In carriers of the G allele, the risk of WPW syndrome was 1.434-fold higher (95% CI 1.051–4.127; $p = 0.028$) compared with the A allele (See Table 3).

Adverse Events

No adverse events were recorded during the study.

DISCUSSION

Summary of Primary Results

A comprehensive study of patients with WPW syndrome was conducted for the first time in Krasnoyarsk. The study was based on clinical, instrumental, and molecular genetic testing of genotypic and allelic frequencies of the *TBX3* gene for patient-oriented medical examination.

Interpretation

The hypothesis suggests that the *TBX3* gene polymorphism plays a pivotal role in the formation of the fibrous ring and the development of the atrioventricular canal. Disturbances in this gene's functionality may result in the onset of WPW syndrome, a serious cardiovascular condition that may lead to life-threatening arrhythmias and, most critically, sudden cardiac death. A comprehensive understanding of the role of this gene in the pathogenesis of WPW syndrome is therefore paramount for the development of new diagnostic and therapeutic methods for this condition.

The study of the clinical characteristics of patients with WPW syndrome revealed that it occurs in all age groups, has no specific signs, and may be asymptomatic. WPW syndrome frequently leads to the development of supraventricular tachycardia. The latter may significantly increase the risk of sudden cardiac death by transforming into life-threatening arrhythmias. According to Chinese and British studies, the *TBX3* gene has a pleiotropic effect. In addition to WPW syndrome, it may be associated with other cardiovascular diseases such as dilated cardiomyopathy and congenital heart defects (tetralogy of Fallot).

The results of the molecular genetic testing demonstrate the crucial role of the *TBX3* gene rs1061657 polymorphism in the pathogenesis of WPW syndrome. The study adds to our knowledge of the clinical and genetic markers of this syndrome and associated cardiac rhythm and conduction disorders. The study of genetic predictors has the potential to facilitate the timely and early diagnosis of latent and asymptomatic forms of the disease in individuals at risk. The investigation into genetic associations with this syndrome serves as a foundation for a personalized approach to its diagnosis and treatment.

CONCLUSION

The present study focused on the clinical and genetic characteristics of WPW syndrome. The study confirmed the contribution of rs1061657 SNP of the *TBX3* gene to the development of WPW syndrome in the population of Krasnoyarsk Krai.

Genotyping of *TBX3* may reveal the molecular basis of WPW syndrome. However, further studies are warranted to fully understand the functional role of rs1061657 SNP of the *TBX3* gene in the pathogenesis of this syndrome. The problem of establishing the genetic mechanisms of manifestation of WPW syndrome, multifactorial by nature, is currently relevant. Clinical and genetic studies of the whole complex of nosological units may be effective in diagnosis.

ADDITIONAL INFORMATION

Author contributions. Yu.A. Tolstokorova — recruitment of patients, maintaining statistical data; S.Yu. Nikulina — supervision, preparation and writing of the article; A.A. Chernova — analysis of literary sources, writing the text and editing the article; D.A. Sarkisyan — literature review, processing of literary data; A.A. Dyakonova — literature review; A.A. Lobastova — literature review. All authors have approved the manuscript (version for publication) and have also agreed to be responsible for all aspects of the work, ensuring that issues related to the accuracy and integrity of any part of it are properly addressed and resolved.

Ethics approval. The study was approved by the Local Ethics Committee Professor V.F. Voino-Yasenetsky Krasnoyarsk State Medical University (protocol No. 109 by 16.11.2021). All study participants signed a voluntary informed consent form prior to enrollment.

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