https://doi.org/10.22416/1382-4376-2025-35-2-105-118
UDC 616.36-097-07:577.21

Occurrence of Alleles of the *HLA-A/B/C/DPB1/DQB1/DRB1* Genes in Autoimmune Hepatitis (Results of a Single-Center Study)

Mikhail D. Chanyshev[1]*, Yulia G. Sandler[2], Natalia V. Vlasenko[1], Natalia A. Bodunova[2], Albina G. Glushchenko[1], Anzhelika S. Chegodar[2], Anastasiia V. Vykhodtseva[1], Elena V. Vinnitskaya[2], Kamil F. Khafizov[1], Vasiliy G. Akimkin[1]

[1] *Central Research Institute of Epidemiology of the Federal Service for Surveillance on Consumer Rights Protection and Human Wellbeing, Moscow, Russian Federation*
[2] *Loginov Moscow Clinical Scientific Center, Moscow, Russian Federation*

Aim: determination of alleles of *HLA* genes associated with autoimmune hepatitis (AIH) and overlap syndrome (OS) in the Russian population.
Materials and methods. The study included 160 adult patients with a verified diagnosis of AIH or OS. The control group consisted of 320 conditionally healthy participants. A custom NGS panel was used to type the alleles of the *HLA* class I and II genes. The statistical analysis was carried out using Pearson's χ^2 test with multiple FDR correction ($p < 0.05$). A logistic regression model was used to evaluate *HLA* alleles as predictors of the disease.
Results. Alleles and haplotypes which frequencies have statistically significant difference in the study and control groups were identified. In the study group, alleles HLA-A*01:01:01 (OR = 2.15; 95 % CI: 1.43–3.23), HLA-B*08:01:01 (OR = 3.38; 95 % CI: 2.10–5.44), HLA-C*07:01:01 (OR = 1.90; 95 % CI: 1.30–2.78), HLA-DPB1*01:01:01 (OR = 3.22; 95 % CI: 1.58–6.55), DQB1*02:01:01 (OR = 3.11; 95 % CI: 2.06–4.70), HLA-DRB1*03:01:01 (OR = 3.03; 95 % CI: 2.02–4.55) were more common. Frequency of occurrence of the DQB1*03:01:01 allele in the study group was lower than in the control group (OR = 0.49; 95 % CI: 0.34–0.71). A logistic regression model was built, which was characterized by an accuracy of 0.688, a sensitivity of 0.487, and a specificity of 0.887.
Conclusion. Alleles and haplotypes of *HLA* genes associated with AIH and OS were identified in a representative sample of the Russian population.
Key words: autoimmune hepatitis, human leukocyte antigen, *HLA* class I and II, alleles, haplotype
Conflict of interest: the authors declare no conflict of interest.

For citation: Chanyshev M.D., Sandler Yu.G., Vlasenko N.V., Bodunova N.A., Glushchenko A.G., Chegodar A.S., Vykhodtseva A.V., Vinnitskaya E.V., Khafizov K.F., Akimkin V.G. Occurrence of Alleles of the *HLA-A/B/C/DPB1/DQB1/DRB1* Genes in Autoimmune Hepatitis (Results of a Single-Center Study). Russian Journal of Gastroenterology, Hepatology, Coloproctology. 2025;35(2):105–118. https://doi.org/10.22416/1382-4376-2025-35-2-105-118

Встречаемость аллелей генов *HLA-A/B/C/DPB1/DQB1/DRB1* при аутоиммунном гепатите (результаты одноцентрового исследования)

М.Д. Чанышев[1]*, Ю.Г. Сандлер[2], Н.В. Власенко[1], Н.А. Бодунова[2], А.Г. Глущенко[1], А.С. Чегодарь[2], А.В. Выходцева[1], Е.В. Винницкая[2], К.Ф. Хафизов[1], В.Г. Акимкин[1]

[1] *ФБУН «Центральный научно-исследовательский институт эпидемиологии» Федеральной службы по надзору в сфере защиты прав потребителей и благополучия человека, Москва, Российская Федерация*
[2] *ГБУЗ «Московский клинический научно-практический центр им. А.С. Логинова» Департамента здравоохранения города Москвы, Москва, Российская Федерация*

Цель работы: определение аллелей генов *HLA*, ассоциированных с аутоиммунным гепатитом (АИГ) и перекрестным синдромом (ПС), в российской популяции.
Материалы и методы. Исследование включало 160 взрослых пациентов с верифицированным диагнозом АИГ или ПС. Контрольная группа — 320 условно здоровых участников. Для типирования аллелей генов *HLA* класса I и II использовали разработанную нами панель NGS. Статистический анализ проводился с использованием критерия согласия Пирсона χ^2 с множественной поправкой FDR при исходном заданном $p < 0,05$. Для оценки аллелей *HLA* как предикторов заболевания применялась модель логистической регрессии.
Результаты. Были определены аллели и гаплотипы, частота встречаемости которых статистически достоверно различалась в исследуемой и контрольной группах. В исследуемой группе чаще встречались аллели HLA-A*01:01:01 (ОШ = 2,15; 95 % ДИ: 1,43–3,23), HLA-B*08:01:01 (ОШ = 3,38; 95 % ДИ: 2,10–5,44), HLA-C*07:01:01 (ОШ = 1,90; 95 % ДИ: 1,30–2,78), HLA-DPB1*01:01:01 (ОШ = 3,22; 95 % ДИ: 1,58–6,55),

DQB1*02:01:01 (ОШ = 3,11; 95 % ДИ: 2,06–4,70), HLA-DRB1*03:01:01 (ОШ = 3,03; 95 % ДИ: 2,02–4,55). Частота встречаемости аллеля DQB1*03:01:01 в исследуемой группе была ниже, чем в контрольной (ОШ = 0,49; 95 % ДИ: 0,34–0,71). Была построена модель логистической регрессии, которая характеризовалась точностью 0,688, чувствительностью 0,487, специфичностью 0,887.

Выводы. На репрезентативной выборке российской популяции были определены аллели и гаплотипы генов *HLA*, ассоциированные с АИГ и ПС.

Ключевые слова: аутоиммунный гепатит, человеческий лейкоцитарный антиген, *HLA* I и II класса, аллели, гаплотип

Конфликт интересов: авторы заявляют об отсутствии конфликта интересов.

Для цитирования: Чанышев М.Д., Сандлер Ю.Г., Власенко Н.В., Бодунова Н.А., Глущенко А.Г., Чегодарь А.С., Выходцева А.В., Винницкая Е.В., Хафизов К.Ф., Акимкин В.Г. Встречаемость аллелей генов *HLA-A/B/C/DPB1/DQB1/DRB1* при аутоиммунном гепатите (результаты одноцентрового исследования). Российский журнал гастроэнтерологии, гепатологии, колопроктологии. 2025;35(2):105–118. https://doi.org/10.22416/1382-4376-2025-35-2-105-118

Introduction

Autoimmune diseases represent a broad group of pathological conditions characterized by the immune system's loss of tolerance to self-antigens and tissues. Autoimmune hepatitis (AIH) is one such disorder. In general, autoimmune liver diseases are relatively rare. According to a meta-analysis by J.W. Hahn et al. (2023), the global pooled incidence and prevalence of AIH are 1.28 cases per 100,000 population per year and 15.65 cases per 100,000 population, respectively [1]. Specifically, the incidence of AIH is reported to be 1.68 cases per 100,000 population per year in Denmark [2] and 4 cases per 100,000 per year in the United States [3]. Notably, the global prevalence of AIH is steadily increasing, affecting individuals across all age groups from pediatric to elderly. The disease exhibits a marked female predominance, with a female-to-male ratio averaging 4 : 1 [4–6]. The etiology of AIH remains incompletely understood; however, genetic predisposition, environmental factors, infections, and pharmacological agents are presumed to play significant roles in disease development [7, 8].

One of the key diagnostic markers of AIH is the presence of autoantibodies (AAbs). Although the International Autoimmune Hepatitis Group has not endorsed classifying AIH based on autoantibody profiles [9], historically, patients have been categorized into type 1 and type 2 AIH according to their serological profiles. Type 1 AIH is associated with positivity for antinuclear antibodies (ANA) and/or smooth muscle antibodies (SMA). Type 2 AIH, which is significantly less common, is defined by the presence of circulating anti-liver kidney microsomal type 1 antibodies (anti-LKM1), anti-LKM3, and/or anti-liver cytosol type 1 antibodies (anti-LC1) [10]. Among adult patients, neither the autoantibody titer nor profile at disease onset or during therapy reliably reflects disease severity or prognosis [11]. Multiple autoantibodies may coexist in a single patient, and their spectrum can evolve over time; specific antibodies may disappear and be replaced by others. The loss of autoantibodies may correlate with improvements in laboratory and histological activity markers but does not reliably predict therapeutic success [12]. In genetically predisposed individuals, AIH may be accompanied by autoimmune-mediated bile duct destruction, resulting in a mixed clinical phenotype of AIH and primary biliary cholangitis (PBC). The coexistence of two autoimmune liver diseases in a single patient is referred to as autoimmune overlap syndrome (OS), or a variant form of AIH with PBC features (AIH/PBC). This condition is considered a distinct hybrid form or atypical AIH phenotype, characterized by the presence of laboratory, immunological, and/or histological features of PBC in addition to the clinical and morphological picture of AIH. Identifying OS phenotypes is clinically significant, as these patients often require combination therapy including both immunosuppressive agents and ursodeoxycholic acid (UDCA), which may result in more favorable biochemical and histological outcomes [13, 14].

Among genetic factors, the greatest focus has been on *HLA* genes, which encode components of the major histocompatibility complex (MHC). These genes, located on chromosome 6, exhibit high polymorphism. Numerous studies have demonstrated associations between specific *HLA* alleles and haplotypes with various diseases, including autoimmune disorders [15, 16]. Associations between *HLA* alleles and AIH susceptibility have been established, with considerable inter-population variation in risk and protective alleles. In North American and Danish populations, AIH has been linked to HLA-DRB1*03:01 and HLA-DRB1*04:01 [17, 18]. HLA-DRB1*04:01 has also been identified as a high-risk allele in the Japanese population [19]. In Argentine cohorts, HLA-DRB1*04:05 and HLA-DRB1*13:01 were

found to be high-risk alleles, whereas HLA-DRB1*13:02 was associated with reduced risk [20]. DRB1*08:02 and DRB1*08:03 have been associated with increased risk in Japan; DRB1*04:05 — in Korea; DRB1*13 and DRB1*14 — in Pakistan; and DRB1*04:05, DRB1*13:01, DQB1*02, and DQB1*06:03 — in Latin America [8]. Among Chinese AIH patients positive for anti-SLA/LP antibodies, elevated frequencies of B*35:01 and C*08:01 alleles have been reported [21]. To our knowledge, only one study investigating AIH and *HLA* has been published in Russia. This study included 54 patients with autoimmune liver diseases (18 with AIH and 14 with OS) and 100 control samples. It reported an increased frequency of HLA-A*24, B*27, DRB1*04, DQB1*02:01, and DQB1*03:02 alleles in AIH patients, and B*35, DRB1*14, and DQB1*06:03 in patients with OS [22].

It should be noted that most of the aforementioned *HLA* studies employed serological or PCR-based methods, which are considered less precise [23]. The only Russian study involved a very limited AIH patient sample. We developed an NGS-based panel for rapid and reliable typing of *HLA-A/B/C/DPB1/DQB1/DRB1* alleles and determined their frequencies in 160 patients samples with AIH or OS, and 320 control samples.

Materials and methods

Patients

The study group included 160 adult patients with AIH (n = 124) and PS (n = 36), predominantly women (91 %). The general characteristics of the patients are presented in Table 1.

The diagnosis was established according to the simplified diagnostic criteria [24]. All patients underwent liver biopsy with histopathological verification. The study also included 36 patients with overlap syndrome (AIH with features of PBC), who, in addition to the clinical, immunological, and morphological features of AIH (elevated IgG levels, presence of autoantibodies typical of AIH such as ANA, ASMA, SLA/LP, LKM-1, LC-1, and interface hepatitis with lymphoplasmacytic infiltration and moderate or high histological activity), also exhibited certain features characteristic of PBC. Among these patients, 15 out of 36 tested positive for PBC-specific autoantibodies (AMA or sp100, gp210), 20 out of 36 had alkaline phosphatase (ALP) levels ranging from 1.5 to 3.0 times the upper limit of normal, and 17 out of 36 showed mild histological signs of bile duct injury. All patients received immunosuppressive therapy (IST): systemic glucocorticosteroids (topical forms were used less frequently, n = 14) and azathioprine. Patients with AIH/PBC also received ursodeoxycholic acid (UDCA) as part of combination therapy.

The control group consisted of 320 conditionally healthy adult participants. Figure 1 presents the age and sex distribution of the study and control groups. The Mann — Whitney U test was used to compare the groups. There were no statistically significant differences in age ($p < 0.05$) between the study and control groups, either when stratified by sex (females: $p = 0.54$; males: $p = 0.81$) or when considered as a whole ($p = 0.6$).

HLA sequencing

Genomic DNA was extracted from peripheral blood samples using the "RIBO-prep" reagent kit (AmpliSens, Russia). DNA concentration was measured with the Quantum kit (Evrogen, Russia). Exons of the *HLA-A/B/C/DPB1/DQB1/DRB1* genes were amplified using a custom-designed primer panel. Multiplex PCR amplification was performed in two separate reactions, each containing 10 ng of template DNA, 10 μL of PCR-mix-2-blue (AmpliSens, Russia), 1.4 μL of 4.4 mM dNTP mix (AmpliSens, Russia), primers, and sterile water to a final volume of 25 μL. The PCR conditions were as follows: 1) initial denaturation at 95 °C for 3 minutes; 2) 16 cycles of amplification: 95 °C for 30 seconds; 55 °C for 30 seconds; and 72 °C for 20 seconds; 3) final extension at 72 °C for 3 minutes. Pooled PCR products were purified using AMPure XP magnetic beads (Beckman Coulter, USA) at a bead-to-sample ratio

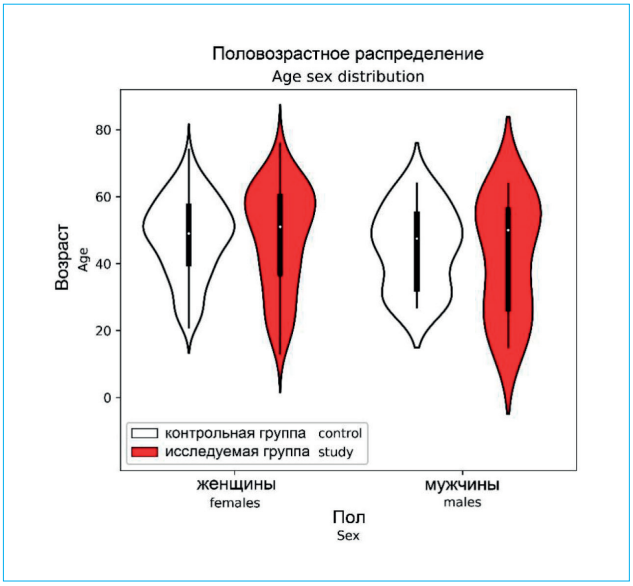

Figure 1. Age and gender diagram of the study (n = 160; 145 women and 15 men) and control (n = 320; 290 women and 30 men) groups

Рисунок 1. Половозрастная диаграмма исследуемой (n = 160; 145 женщин и 15 мужчин) и контрольной (n = 320; 290 женщин и 30 мужчин) групп

Table 1. Overall characteristics of patients
Таблица 1. Общая характеристика пациентов

Characteristics ***Характеристика***	**Patients included in the study** ***Включенные пациенты n = 160***
Demographics / *Демографические данные*	
Age, years / *Возраст, лет; Me (IQR)*	51.0 (36.0–60.0)
Women; *n* (%) / *Женщины, n (%)*	145 (91 %)
BMI / *ИМТ; Me (IQR)*	25.0 (20.5–27.0)
Biochemical parameters / *Биохимические показатели, Me (IQR)*	
Alanine aminotransferase, U/L / *Аланинаминотрансфераза, Ед./л*	610.0 (260–1100)
Aspartate aminotransferase, U/L / *Аспартатаминотрансфераза, Ед./л*	450.0 (190.0–965.0)
Gamma-glutamyltranspeptidase, U/L *Гамма-глутамилтранспептидаза, Ед./л*	83.0 (39.0–175.0)
Total bilirubin, umol/L / *Общий билирубин, мкмоль/л*	19.7 (14.0–49.0)
Alkaline phosphatase, U/L / *Щелочная фосфатаза, Ед./л*	121 (105–230)
Immunoglobulin G, g/L / *Иммуноглобулин G, г/л*	21.5 (17.0–29.0)
Presence of antibodies / *Наличие антител*	
ANA, *n*	159/160
ASMA, *n*	53/139
LKM-1, *n*	9/130
AMA / sp100, gp210, *n*	15/160
Seronegative, *n* / *Серонегативные, n*	1/160
Morphological verification, *n* (%) / *Морфологическая верификация, n (%)*	
Autoimmune hepatitis / *Аутоиммунный гепатит*	125 (78.1)
Autoimmune hepatitis with signs of primary biliary cholangitis *Аутоиммунный гепатит с признаками первичного билиарного холангита*	25 (21.9)
Histological features: activity and fibrosis (according to METAVIR) *Гистологические признаки: активность и фиброз (по METAVIR)*	
F0, *n* (%)	18 (11.2 %)
F, *n* (%)	36 (22.5 %)
F2, *n* (%)	30 (18.8 %)
F3, *n* (%)	39 (24.4 %)
F4, *n* (%)	37 (23.1 %)
Severe fibrosis ≥ F3, *n* (%) / *Тяжелый фиброз ≥ F3, n (%)*	76 (47.5 %)
Liver cirrhosis F4, *n* (%) / *Цирроз печени F4, n (%)*	37 (23.1 %)
A0, *n* (%)	0 (0 %)
A1, *n* (%)	41 (25.6 %)
A2, *n* (%)	60 (37.5 %)
A3, *n* (%)	59 (36.9 %)
Activity ≥ A2, *n* (%) / *Активность ≥ A2, n (%)*	119 (74.4 %)
Presence of immune-mediated diseases, *n* (%) *Наличие иммуноопосредованных заболеваний, n (%)*	64 (40 %)
Autoimmune thyroid diseases, *n* *Аутоиммунные заболевания щитовидной железы, n*	21 / 64
Autoimmune connective tissue disease, *n* *Аутоиммунное заболевание соединительной ткани, n*	15 / 64
Inflammatory bowel diseases, *n* / *Воспалительные заболевания кишечника, n*	10 / 64
Others, *n* / *Другие, n*	18 / 64

Note: *F — stage of fibrosis according to the METAVIR scale; A — degree of histological activity according to the METAVIR scale.*
Примечание: *F — стадия фиброза по шкале METAVIR; A — степень гистологической активности по шкале METAVIR.*

of 0.8 : 1, with an elution volume of 15 μL. PCR indexing was performed in a 25 μL reaction mixture containing 10 μL of PCR-mix-2-blue (AmpliSens, Russia), 1.4 μL of 4.4 mM dNTP mix (AmpliSens, Russia), 5 μL of purified PCR products, sterile water, and Nextera Illumina index adapters, with a final primer concentration of 200 nM. The PCR conditions were as follows: 1) denaturation at 95 °C for 1 minute; 2) 25 cycles of amplification: 95 °C for 20 seconds; 55 °C for 30 seconds; and 72 °C for 20 seconds; 3) final extension at 72 °C for 3 minutes. PCR products were visualized via electrophoresis in a 1.7 % agarose gel. Indexed libraries were pooled and purified using AMPure XP magnetic beads (Beckman Coulter, USA) at a bead-to-sample ratio of 0.8 : 1. The concentration of the purified library was measured using the Qubit dsDNA HS Assay Kit and Qubit 4.0 fluorometer (Invitrogen, USA). High-throughput sequencing was performed on the Illumina MiSeq platform using the MiSeq Reagent Kit v3 (600 cycles).

Bioinformatics: HLA allele typing

Sequencing data quality was assessed using FastQC. Adapter sequences were removed with Trimmomatic, and primer sequences were trimmed using Cutadapt. Bowtie2 was used to align the reads to the reference genome. Allele typing was performed using the SpecHLA software [25]. SpecHLA results were further validated using a custom Python script.

Statistics

All statistical analyses were conducted in the Python programming environment using the Numpy, Pandas, SciPy, and Stats libraries. Data visualization was carried out with Seaborn and Matplotlib. Pearson's chi-squared test was used to compare allele and haplotype frequencies. Multiple comparisons were corrected using the false discovery rate (FDR) method; *p*-values with FDR < 0.05 were considered statistically significant.

Results

Frequency of HLA alleles

Initially, we analyzed the frequency of individual *HLA* alleles in the study and control groups. The results are shown in Figures 2–7. The HLA-A*01:01:01 allele was significantly more frequent in the study group (OR = 2.15; 95 % CI: 1.43–3.23; p_{FDR} = 0.0128), with a more pronounced effect in patients with AIH than those with OS. The frequency of HLA-B*08:01:01 was also significantly higher in the study group compared to the control group (OR = 3.38; 95 % CI: 2.10–5.44; p_{FDR} < 0.01). HLA-B*08:01:01 was equally prevalent among patients with both AIH and OS. The HLA-C*07:01:01 allele was significantly more frequent in the study group (OR = 1.90; 95 % CI: 1.30–2.78; p_{FDR} = 0.0391), again with a more pronounced effect in patients with AIH. The frequency of HLA-DPB1*01:01:01 was significantly higher in the study group (OR = 3.22; 95 % CI: 1.58–6.55; p_{FDR} = 0.0433), with a stronger effect in patients with AIH than OS. The frequency of the DQB1*02:01:01 allele was increased in the study group compared to the control group (OR = 3.11; 95 % CI: 2.06–4.70; p_{FDR} < 0.01), with this allele being equally common among patients with AIH and OS. Conversely, the frequency of the DQB1*03:01:01 allele was reduced in the study group (OR = 0.49; 95 % CI: 0.34–0.71; p_{FDR} = 0.0083). The HLA-DRB1*03:01:01 allele was significantly more frequent in the study group compared to controls (OR = 3.03; 95 % CI: 2.02–4.55; p_{FDR} < 0.01) and was equally distributed among AIH and OS patients. Overall, we observed no significant sex-related differences in HLA allele frequencies. The described findings are presented in Table 2.

HLA haplotype frequencies were also analyzed in the study and control groups. Considering that

Table 2. Alleles of *HLA* genes, which occurrence differs in the study and control groups (p_{FDR} < 0.05)
Таблица 2. Аллели генов *HLA*, встречаемость которых различается в исследуемой и контрольной группах (p_{FDR} < 0,05)

Allele *Аллель*	Study group *Исследуемая группа* *n = 160*	Control group *Контрольная группа* *n = 320*	$p_{\chi 2}$	p_{FDR}	OR (95 % CI) *ОШ (95 % ДИ)*
A*01:01:01	52	53	0.0003	0.0128	2.15 (1.43; 3.23)
B*08:01:01	47	31	2.7910^{-7}	2.01×10^{-5}	3.38 (2.10; 5.44)
C*07:01:01	59	68	0.0011	0.0391	1.90 (1.30; 2.78)
DPB1*01:01:01	20	13	0.0014	0.0433	3.22 (1.58; 6.55)
DQB1*02:01:01	61	45	3.85×10^{-8}	6.05×10^{-6}	3.11 (2.06; 4.70)
DQB1*03:01:01	44	157	0.0002	0.0083	0.49 (0.34; 0.71)
DRB1*03:01:01	62	47	5.60×10^{-8}	6.05×10^{-6}	3.03 (2.02; 4.55)

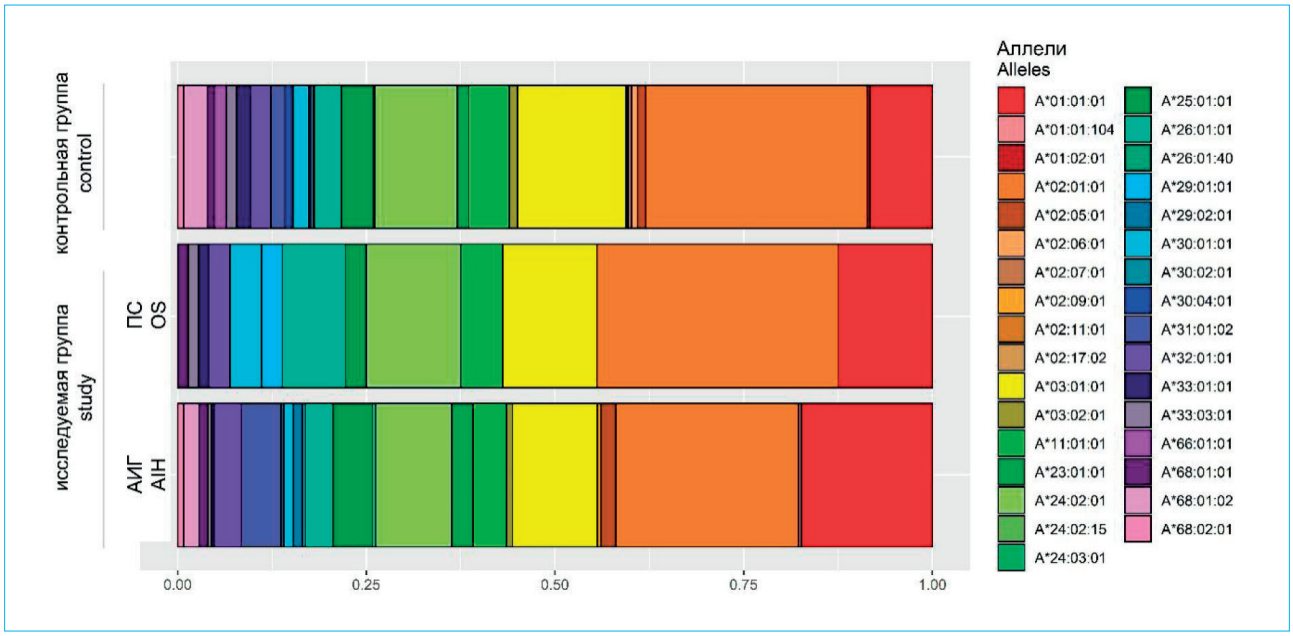

Figure 2. Distribution of *HLA-A* gene alleles in the study and control groups. The study group included patients diagnosed with autoimmune hepatitis (AIH; $n = 124$) and overlap syndrome (OS; $n = 36$)

Рисунок 2. Распределение аллелей гена *HLA-A* в исследуемой и контрольной группах. Исследуемая группа включала пациентов с диагностированным аутоиммунным гепатитом (АИГ; $n = 124$) и перекрестным синдромом (ПС; $n = 36$)

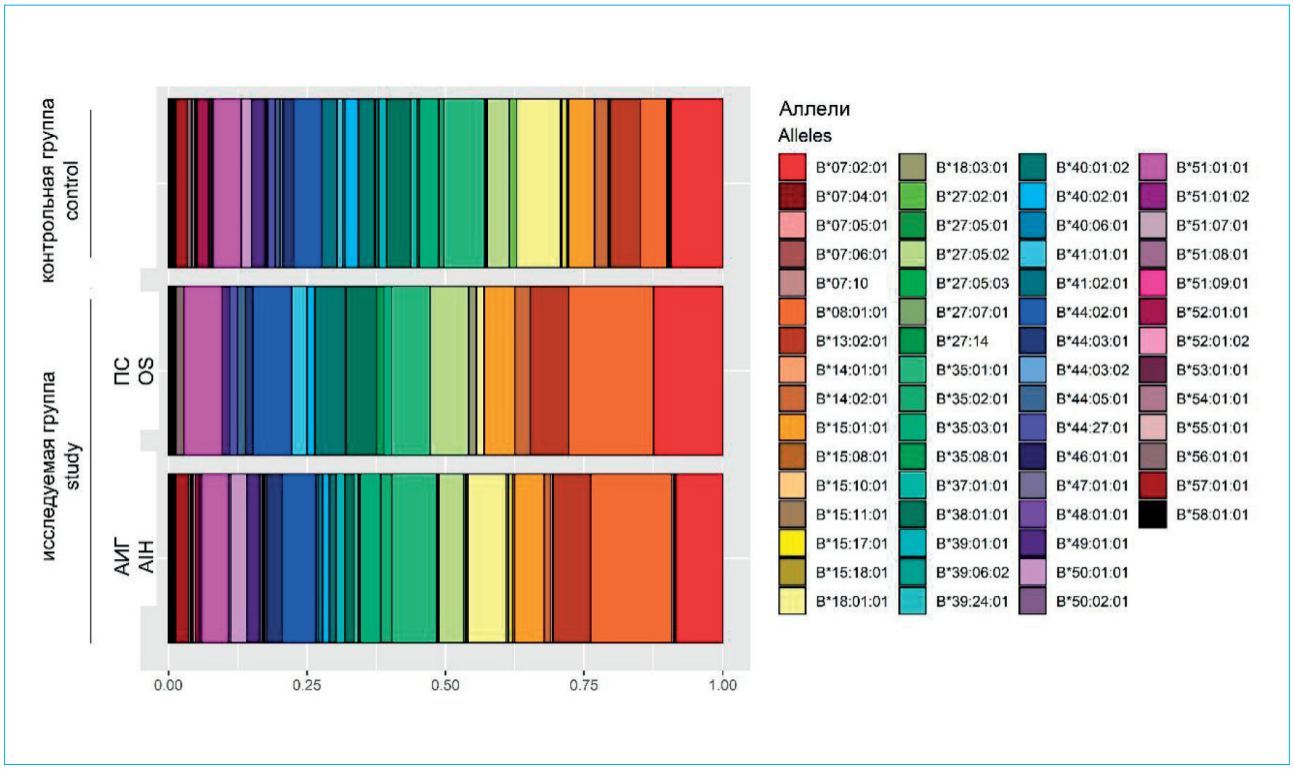

Figure 3. Distribution of *HLA-B* gene alleles in the study and control groups. The study group included patients diagnosed with autoimmune hepatitis (AIH; $n = 124$) and overlap syndrome (OS; $n = 36$)

Рисунок 3. Распределение аллелей гена *HLA-B* в исследуемой и контрольной группах. Исследуемая группа включала пациентов с диагностированным аутоиммунным гепатитом (АИГ; $n = 124$) и перекрестным синдромом (ПС; $n = 36$)

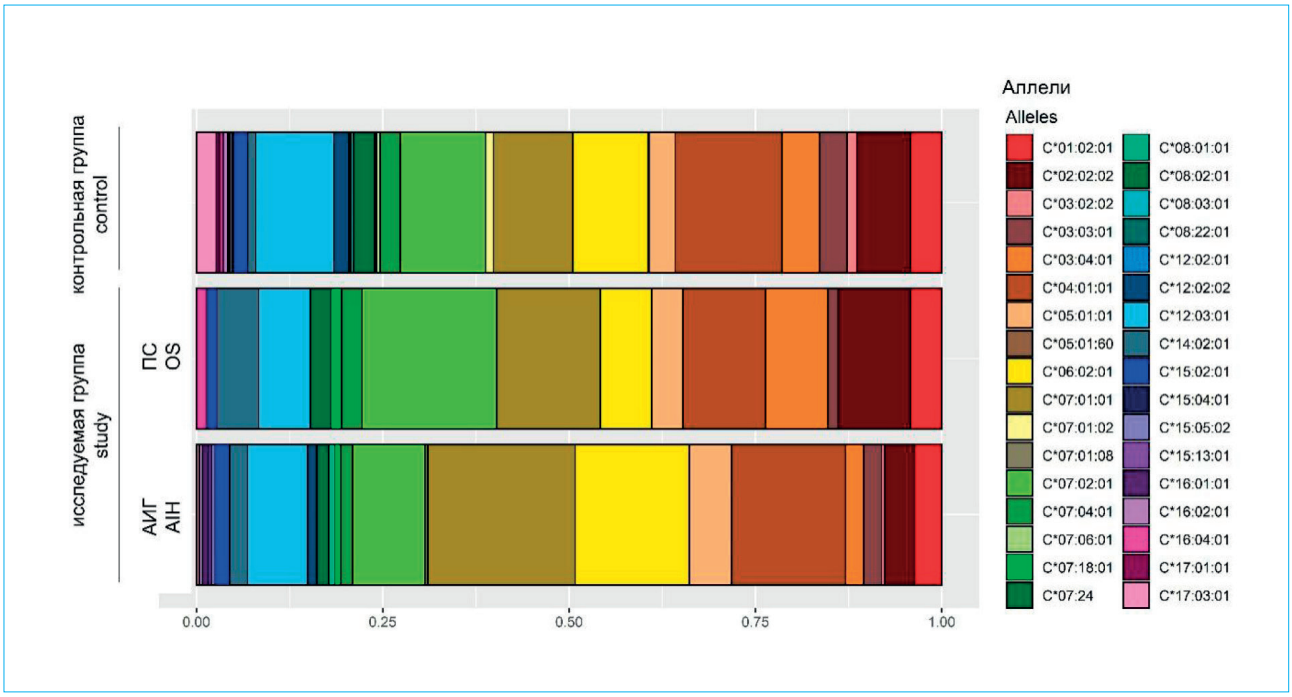

Figure 4. Distribution of *HLA-C* gene alleles in the study and control groups. The study group included patients diagnosed with autoimmune hepatitis (AIH; $n = 124$) and overlap syndrome (OS; $n = 36$)

Рисунок 4. Распределение аллелей гена *HLA-C* в исследуемой и контрольной группах. Исследуемая группа включала пациентов с диагностированным аутоиммунным гепатитом (АИГ; $n = 124$) и перекрестным синдромом (ПС; $n = 36$)

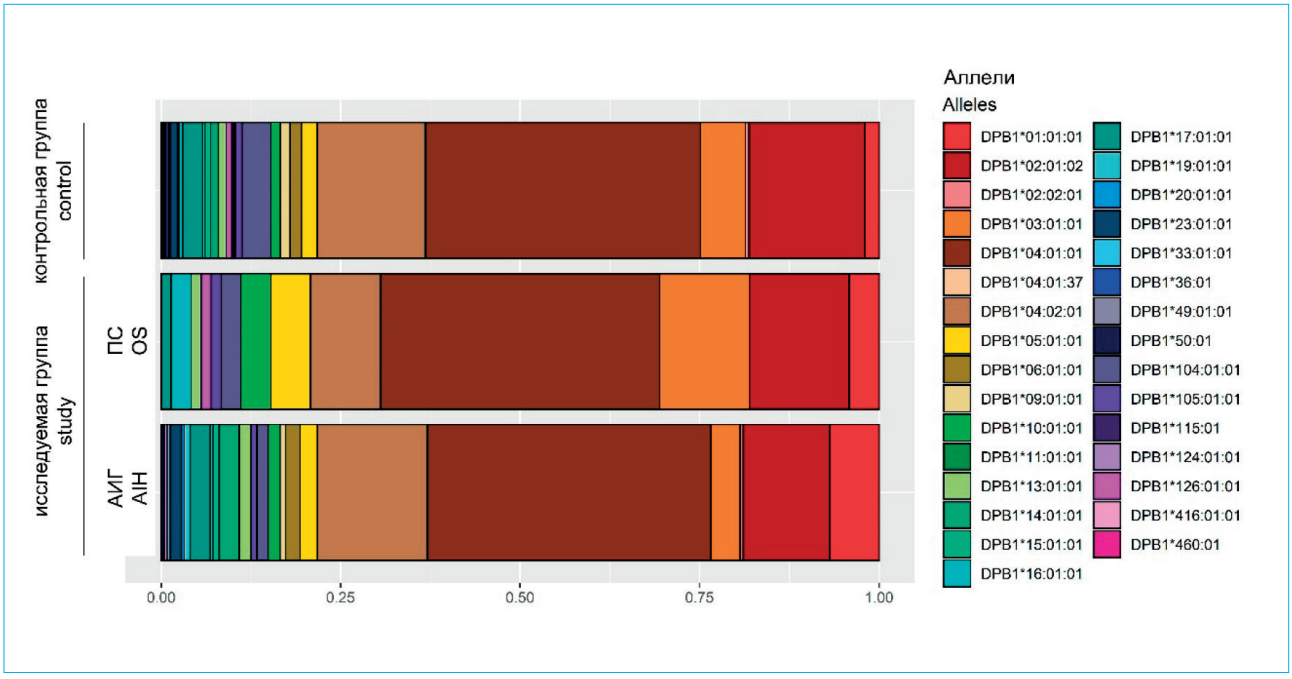

Figure 5. Distribution of *HLA-DPB1* gene alleles in the study and control groups. The study group included patients diagnosed with autoimmune hepatitis (AIH; $n = 124$) and overlap syndrome (OS; $n = 36$)

Рисунок 5. Распределение аллелей гена *HLA-DPB1* в исследуемой и контрольной группах. Исследуемая группа включала пациентов с диагностированным аутоиммунным гепатитом (АИГ; $n = 124$) и перекрестным синдромом (ПС; $n = 36$)

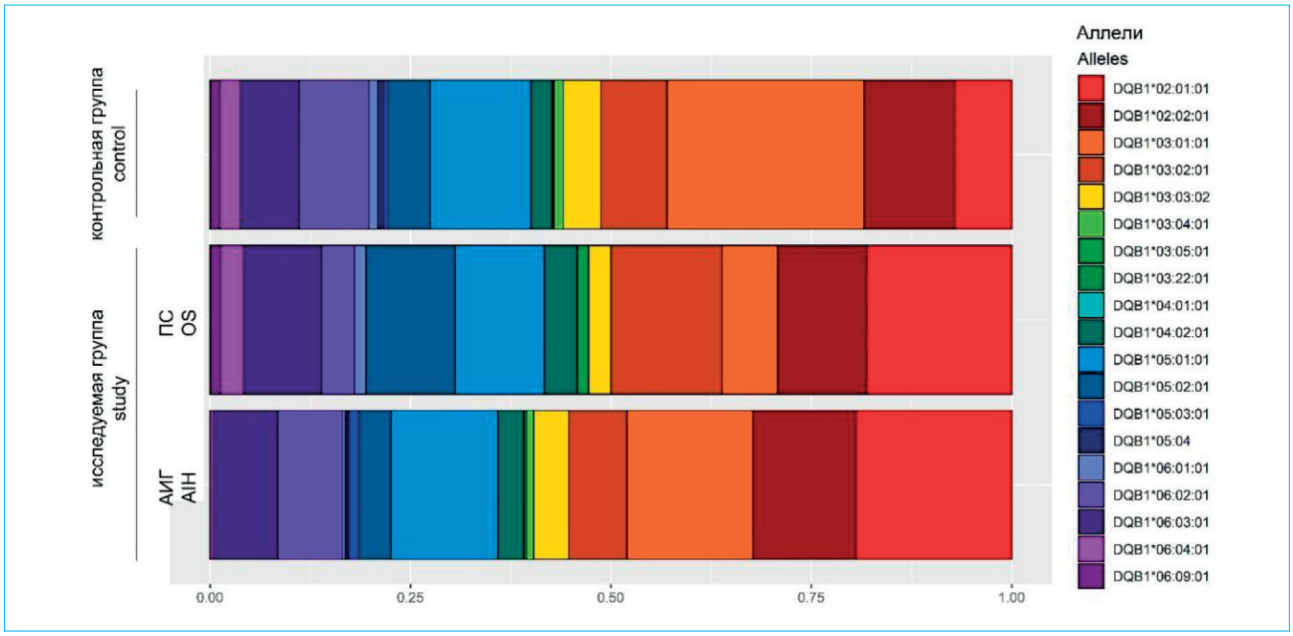

Figure 6. Distribution of *HLA-DQB1* gene alleles in the study and control groups. The study group included patients diagnosed with autoimmune hepatitis (AIH; $n = 124$) and overlap syndrome (OS; $n = 36$)

Рисунок 6. Распределение аллелей гена *HLA-DQB1* в исследуемой и контрольной группах. Исследуемая группа включала пациентов с диагностированным аутоиммунным гепатитом (АИГ; $n = 124$) и перекрестным синдромом (ПС; $n = 36$)

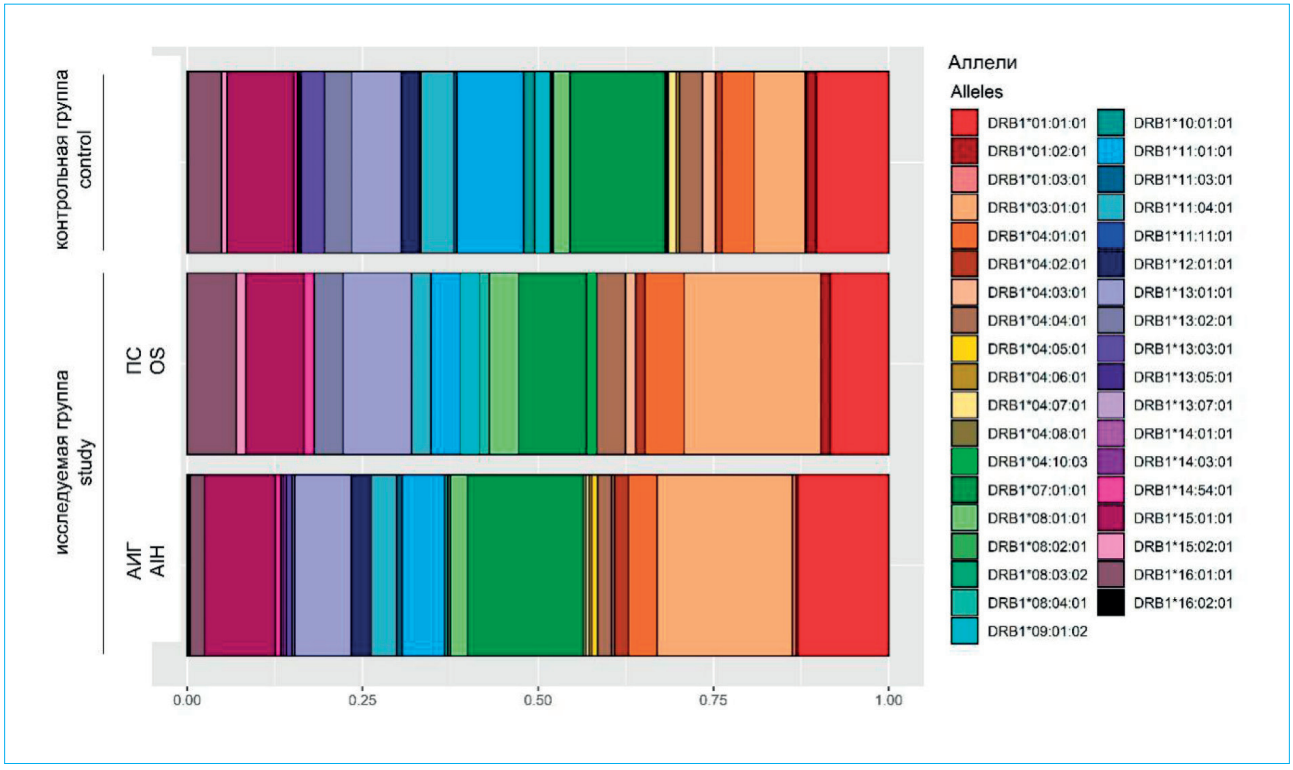

Figure 7. Distribution of *HLA-DRB1* gene alleles in the study and control groups. The study group included patients diagnosed with autoimmune hepatitis (AIH; $n = 124$) and overlap syndrome (OS; $n = 36$)

Рисунок 7. Распределение аллелей гена *HLA-DRB1* в исследуемой и контрольной группах. Исследуемая группа включала пациентов с диагностированным аутоиммунным гепатитом (АИГ; $n = 124$) и перекрестным синдромом (ПС; $n = 36$)

Table 3. Haplotypes of HLA genes, which occurrence differs in the study and control groups ($p_{FDR} < 0.05$)

Таблица 3. Гаплотипы генов HLA, встречаемость которых различается в исследуемой и контрольной группах ($p_{FDR} < 0,05$)

Haplotype ***Гаплотип***	**Study group** ***Исследуемая группа n = 160***	**Control group** ***Контрольная группа n = 320***	$p_{\chi 2}$	p_{FDR}	**OR (95% CI)** ***ОШ (95% ДИ)***
A*01:01:01-B*08:01:01-C*07:01:01-DQB1*02:01:01-DRB1*03:01:01	32	16	5.66×10^{-7}	0.0340	4.75 (2.52; 8.96)
A*01:01:01-B*08:01:01-C*07:01:01-DQB1*02:01:01	32	16	5.66×10^{-7}	0.0075	4.75 (2.52; 8.96)
A*01:01:01-B*08:01:01-C*07:01:01-DRB1*03:01:01	32	16	5.66×10^{-7}	0.0075	4.75 (2.52; 8.96)
A*01:01:01-B*08:01:01-DQB1*02:01:01-DRB1*03:01:01	33	17	5.21×10^{-7}	0.0075	4.63 (2.49; 8.62)
A*01:01:01-C*07:01:01-DQB1*02:01:01-DRB1*03:01:01	32	16	5.66×10^{-7}	0.0075	4.75 (2.52; 8.96)
B*08:01:01-C*07:01:01-DQB1*02:01:01-DRB1*03:01:01	39	21	6.09×10^{-8}	0.0040	4.59 (2.59; 8.12)
A*01:01:01-B*08:01:01-C*07:01:01	33	19	2.30×10^{-6}	0.0081	4.12 (2.26; 7.51)
A*01:01:01-B*08:01:01-DQB1*02:01:01	33	17	5.21×10^{-7}	0.0022	4.63 (2.49; 8.62)
A*01:01:01-B*08:01:01-DRB1*03:01:01	33	17	5.21×10^{-7}	0.0022	4.63 (2.49; 8.62)
A*01:01:01-C*07:01:01-DQB1*02:01:01	32	16	5.66×10^{-7}	0.0022	4.75 (2.52; 8.96)
A*01:01:01-C*07:01:01-DRB1*03:01:01	32	16	5.66×10^{-7}	0.0022	4.75 (2.52; 8.96)
A*01:01:01-DQB1*02:01:01-DRB1*03:01:01	34	21	4.02×10^{-6}	0.0127	3.84 (2.15; 6.88)
B*08:01:01-C*07:01:01-DQB1*02:01:01	39	21	6.09×10^{-8}	0.0005	4.59 (2.59; 8.12)
B*08:01:01-C*07:01:01-DRB1*03:01:01	39	21	6.09×10^{-8}	0.0005	4.59 (2.59; 8.12)
B*08:01:01-DQB1*02:01:01-DRB1*03:01:01	46	25	2.61×10^{-9}	8.23×10^{-5}	4.76 (2.79; 8.11)
C*07:01:01-DPB1*04:01:01-DQB1*02:01:01	27	15	1.84×10^{-5}	0.0484	4.13 (2.13; 8.01)
C*07:01:01-DPB1*04:01:01-DRB1*03:01:01	27	15	1.84×10^{-5}	0.0484	4.13 (2.13; 8.01)
C*07:01:01-DQB1*02:01:01-DRB1*03:01:01	42	23	2.00×10^{-8}	0.0003	4.60 (2.65; 7.98)
A*01:01:01-B*08:01:01	34	20	2.04×10^{-6}	0.0016	4.05 (2.24; 7.30)
A*01:01:01-C*07:01:01	36	27	3.21×10^{-5}	0.0175	3.15 (1.83; 5.41)
A*01:01:01-DQB1*02:01:01	34	21	4.02×10^{-6}	0.0024	3.84 (2.15; 6.88)
A*01:01:01-DRB1*03:01:01	34	21	4.02×10^{-6}	0.0024	3.84 (2.15; 6.88)
B*08:01:01-C*07:01:01	40	26	8.64×10^{-7}	0.0008	3.77 (2.20; 6.45)
B*08:01:01-DQB1*02:01:01	46	25	2.61×10^{-9}	7.10×10^{-6}	4.76 (2.79; 8.11)
B*08:01:01-DRB1*03:01:01	46	25	2.61×10^{-9}	7.10×10^{-6}	4.76 (2.79; 8.11)
C*07:01:01-DQB1*02:01:01	42	23	2.00×10^{-8}	2.72×10^{-5}	4.60 (2.65; 7.98)
C*07:01:01-DRB1*03:01:01	42	23	2.00×10^{-8}	2.72×10^{-5}	4.60 (2.65; 7.98)
DPB1*04:01:01-DQB1*02:01:01	36	28	5.46×10^{-5}	0.0248	3.03 (1.77; 5.18)
DPB1*04:01:01-DRB1*03:01:01	36	28	5.46×10^{-5}	0.0248	3.03 (1.77; 5.18)
DQB1*02:01:01-DRB1*03:01:01	58	44	2.66×10^{-8}	2.90×10^{-5}	3.57 (2.27; 5.61)

the alleles HLA-A*01:01:01, HLA-B*08:01:01, HLA-C*07:01:01, HLA-DQB1*02:01:01, and HLA-DRB1*03:01:01 were significantly more frequent in the study group, haplotypes including these alleles were also more frequently observed among participants with AIH and OS. Additionally, the haplotypes DPB1*04:01:01-DQB1*02:01:01 and DPB1*04:01:01-DRB1*03:01:01 were more frequently found in the study group. Table 3 presents the haplotypes whose frequencies differed significantly between the study group and the comparison group.

Logistic regression was used to evaluate *HLA* gene alleles as prognostic markers. To balance the odds, half of the comparison group was randomly removed, resulting in 160 participants from both the study and control groups being included in the analysis. A table was created indicating the presence or absence of alleles and haplotypes listed in Tables 2 and 3. The study participants were evenly divided into two samples with stratification by disease. The first group was used to train the logistic regression model, and the second group was used for testing. The logistic regression model yielded the following metrics: accuracy — 0.688, sensitivity — 0.487, specificity — 0.887. The resulting ROC curve is shown in Figure 8.

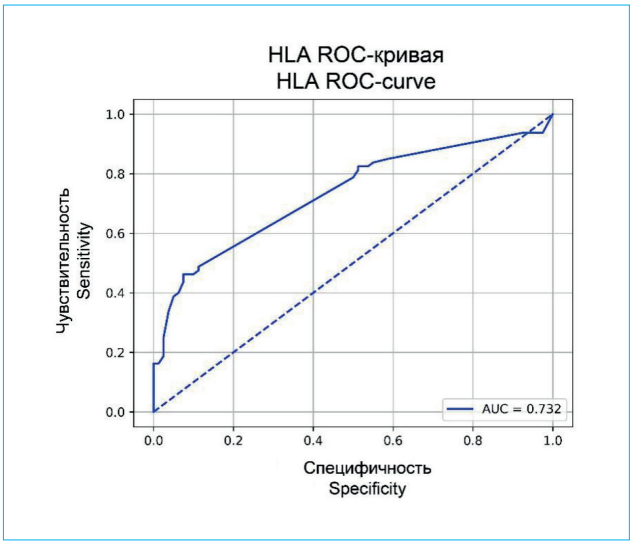

Figure 8. ROC-curve of logistic regression built on the alleles and haplotypes given in Tables 1 and 2; AUC — area under the curve

Рисунок 8. ROC-кривая логистической регрессии, построенной на аллелях и гаплотипах, приведенных в таблицах 1 и 2; AUC — площадь под кривой

Discussion

In this study, we obtained the allele distributions of the *HLA-A/B/C/DPB1/DQB1/DRB1* genes in a representative sample of patients with AIH/OS, as well as in conditionally healthy participants. We found a statistically significant association between the alleles A*01:01:01, B*08:01:01, and C*07:01:01 with AIH/OS. In most recent studies focused on HLA and AIH, the alleles of these genes were not investigated. Interestingly, these alleles were noted in some earlier studies. The association between HLA-A1 and HLA-B8 was first reported by I.R. Mackay and P.J. Morris (1972), and subsequently observed in several other works [26–29]. M.D. Strettell et al. (1997) found an increased frequency of HLA-C*07 in a sample of 87 AIH patients and 100 conditionally healthy participants from the English population [30]. We also observed that the HLA-DPB1*01:01:01 allele was significantly more frequent in the study group compared to the control group. To the best of our knowledge, this observation has not been reported in other studies. G. Opelz et al. (1977) found that the DPB1*04 allele was more characteristic of AIH patients compared to healthy controls in a Danish population (26 alleles in 38 AIH patients and 22 alleles in 91 controls) [28]. In our study, the frequency of DPB1*04:01:01 was not significantly different between the study and control groups. The HLA-DQB1*02:01:01 allele was more common in the study group than in the control group. This observation is consistent with findings in both Russian [22] and UK populations [31]. On the other hand, the DQB1*03:01:01 allele was statistically significantly more frequent in the control group, aligning with findings from the Mexican population by M.N. Vázquez-García et al. (1998) [32]. The alleles of the *HLA-DRB1* gene are the most commonly studied in AIH research. In this study, we found a statistically significant association between DRB1*03:01:01 and AIH. It should be noted that DRB1*03 is a well-established risk factor in many populations [29, 31, 33, 34]. According to the literature, the DRB1*04 allele is also frequently associated with AIH. For instance, an increased frequency of DRB1*04 has been reported in Russian [22], Mexican [32], and Indian populations [35]. However, in this study, the frequency of DRB1*04 alleles did not differ significantly between the study and control groups. Notably, the haplotypes DPB1*04:01:01-DQB1*02:01:01 and DPB1*04:01:01-DRB1*03:01:01 were more frequently observed in the study group.

To assess the potential of these alleles/haplotypes as predictors for AIH, we applied

a logistic regression model. The model showed a relatively low accuracy of 0.688, which may reflect the fact that the development of AIH and OS could be influenced by multiple factors beyond *HLA* genes. The sensitivity of the model was relatively low (0.487). In general, low sensitivity of genetic factors in complex autoimmune diseases is expected, as disease development clearly depends on a multitude of factors. For example, it has been shown that over 90 % of patients with ankylosing spondylitis carry the HLA-B*27 allele [36], but only 1–2 % of these allele carriers actually develop the disease [37]. Despite the low predictive accuracy, the logistic regression model in our study demonstrated relatively high specificity (0.887). Overall, despite the moderate predictive accuracy, the high specificity suggests that *HLA* alleles could be used to identify individuals at potential risk for AIH.

Conclusions

In this study, alleles and haplotypes of *HLA* genes potentially associated with the development of autoimmune hepatitis and overlap syndrome were identified in a representative sample of the Russian population. The investigation of the role of *HLA* system genes in the development of the disease among Russian AIH patients indicates significant differences in the prevalence of specific alleles between the study and control groups. Overall, our findings are consistent with data presented in several international studies. In particular, the HLA-DRB1*03:01:01 allele was found to be associated with the disease, as reflected in numerous publications. The logistic regression model based on the data did not exhibit high accuracy, which may be attributed to the complex etiology of the disease and the presence of multiple predictors. On the other hand, the high specificity of the model suggests that *HLA* gene alleles could be used to identify individuals who belong to a potential high-risk group.

References / Литература

1. *Hahn J.W., Yang H.R., Moon J.S., Chang J.Y., Lee K., Kim G.A., et al.* Global incidence and prevalence of autoimmune hepatitis, 1970–2022: A systematic review and meta-analysis. *EClinicalMedicine.* 2023;65:102280. DOI: 10.1016/j.eclinm.2023.102280
2. *Grønbæk L., Vilstrup H., Jepsen P.* Autoimmune hepatitis in Denmark: Incidence, prevalence, prognosis, and causes of death. A nationwide registry-based cohort study. *J Hepatol.* 2014;60(3):612–7. DOI: 10.1016/j.jhep.2013.10.020
3. *Bittermann T., Lewis J.D., Levy C., Goldberg D.S.* Sociodemographic and geographic differences in the US epidemiology of autoimmune hepatitis with and without cirrhosis. *Hepatology.* 2023;77(2):367–78. DOI: 10.1002/hep.32653
4. *Lim J., Kim H.J.* Epidemiology of autoimmune liver disease in Korea: Evidence from a nationwide real-world database. *Orphanet J Rare Dis.* 2024;19(1):178. DOI: 10.1186/s13023-024-03086-0
5. *Durazzo M., Belci P., Collo A., Prandi V., Pistone E., Martorana M., et al.* Gender specific medicine in liver diseases: A point of view. *World J Gastroenterol.* 2014;20(9):2127–35. DOI: 10.3748/wjg.v20.i9.2127
6. *Buzzetti E., Parikh P.M., Gerussi A., Tsochatzis E.* Gender differences in liver disease and the drug-dose gender gap. *Pharmacol Res.* 2017;120:97–108. DOI: 10.1016/j.phrs.2017.03.014
7. *Higuchi T., Oka S., Furukawa H., Tohma S., Yatsuhashi H., Migita K.* Genetic risk factors for autoimmune hepatitis: Implications for phenotypic heterogeneity and biomarkers for drug response. *Hum Genomics.* 2021;15(1):6. DOI: 10.1186/s40246-020-00301-4
8. *Sirbe C., Simu G., Szabo I., Grama A., Pop T.L.* Pathogenesis of autoimmune hepatitis-cellular and molecular mechanisms. *Int J Mol Sci.* 2021;22(24):13578. DOI: 10.3390/ijms222413578
9. *Alvarez F., Berg P.A., Bianchi F.B. Bianchi L., Burroughs A.K., Cancado E.L., et al.* International Autoimmune Hepatitis Group report: Review of criteria for diagnosis of autoimmune hepatitis. *J Hepatol.* 1999;31(5):929–38. DOI: 10.1016/s0168-8278(99)80297-9
10. *Manns M.P., Lohse A.W., Vergani D.* Autoimmune hepatitis – Update 2015. *J Hepatol.* 2015;62(1 Suppl):S100–1. DOI: 10.1016/j.jhep.2015.03.005
11. *Czaja A.J.* Behavior and significance of autoantibodies in type 1 autoimmune hepatitis. *J Hepatol.* 1999;30(3):394–401. DOI: 10.1016/s0168-8278(99)80096-8
12. *Muratori P., Lalanne C., Fabbri A., Cassani F., Lenzi M., Muratori L., et al.* Type 1 and type 2 autoimmune hepatitis in adults share the same clinical phenotype. *Aliment Pharmacol Ther.* 2015;41(12):1281–7. DOI: 10.1111/apt.13210
13. *Сандлер Ю.Г., Винницкая Е.В., Александрова Е.Н.* Клинические фенотипы аутоиммунного гепатита. *Эффективная фармакотерапия.* 2024;20(2):86–97. [*Sandler Y.G., Vinnitskaya E.V., Aleksandrova E.N.* Clinical phenotypes of autoimmune hepatitis. *Effective pharmacotherapy.* 2024;20(2):86–97. (In Russ.)]. DOI: 10.33978/2307-3586-2024-20-2-86-97
14. *Freedman B.L., Danford C.J., Patwardhan V., Bonder A.* Treatment of overlap syndromes in autoimmune liver disease: A systematic review and meta-analysis. *J Clin Med.* 2020;9(5):1449. DOI: 10.3390/jcm9051449
15. *Medhasi S., Chantratita N.* Human leukocyte antigen (HLA) system: Genetics and association with bacterial and viral infections. *J Immunol Res.* 2022;2022:9710376. DOI: 10.1155/2022/9710376
16. *Berryman M.A., Ilonen J., Triplett E.W., Ludvigsson J.* Important denominator between autoimmune comorbidities: A review of class II HLA, autoimmune disease, and the gut. *Front Immunol.* 2023;14:1270488. DOI: 10.3389/fimmu.2023.1270488
17. *Donaldson P.T.* Genetics in autoimmune hepatitis. *Semin Liver Dis.* 2002;22(4):353–64. DOI: 10.1055/s-2002-35705
18. *van Gerven N.M., de Boer Y.S., Zwiers A., Verwer B.J., Drenth J.P., van Hoek B., et al.; Dutch Autoimmune Hepatitis Study Group.* HLA-DRB1*03:01 and HLA-DRB1*04:01 modify the presentation and outcome in autoimmune hepatitis type-1. *Genes Immun.* 2015;16(4):247–52. DOI: 10.1038/gene.2014.82
19. *Furumoto Y., Asano T., Sugita T., Abe H., Chuganji Y., Fujiki K., et al.* Evaluation of the role of HLA-DR anti-

gens in Japanese type 1 autoimmune hepatitis. *BMC Gastroenterol.* 2015;15:144. DOI: 10.1186/s12876-015-0360-9
20. *Pando M., Larriba J., Fernandez G.C., Fainboim H., Ciocca M., Ramonet M., et al.* Pediatric and adult forms of type I autoimmune hepatitis in Argentina: Evidence for differential genetic predisposition. *Hepatology.* 1999;30(6):1374–80. DOI: 10.1002/hep.510300611
21. *Zhang H.P., Liu Y.M., Li Z., Ma Y.X., Li L.J., Zhao D.T., et al.* Clinical characteristics and HLA genotypes in Chinese patients with anti-SLA/LP-positive autoimmune hepatitis. *Ann Transl Med.* 2021;9(2):153. DOI: 10.21037/atm-20-8036
22. *Барановский А.Ю., Мительмлик У.А., Райхельсон К.Л., Марченко Н.В., Зубарева А.С., Семенов Н.В. и др.* HLA-антигены I и II класса при аутоиммунных заболеваниях печени в Северо-Западном регионе России. *Вестник Северо-Западного государственного медицинского университета им. И.И. Мечникова.* 2010;2(4):55–8. [*Baranovsky A.Yu., Mitelglik U.A., Raikhelson K.L., Marchenko N.V., Zubareva A.S., Semenov N.V., et al.* HLA-antigenes class I and II in autoimmune liver diseases in the North-Western region of Russia. *Herald of North-Western State Medical University named after I.I. Mechnikov.* 2010;2(4):55–8. (In Russ.)].
23. *Kishore A., Petrek M.* Next-generation sequencing based HLA typing: Deciphering immunogenetic aspects of sarcoidosis. *Front Genet.* 2018;9:503. DOI: 10.3389/fgene.2018.00503
24. *Hennes E.M., Zeniya M., Czaja A.J., Parés A., Dalekos G.N., Krawitt E.L., et al.* Simplified criteria for the diagnosis of autoimmune hepatitis. *Hepatology.* 2008;48(1):169–76. DOI: 10.1002/hep.22322
25. *Wang S., Wang M., Chen L., Pan G., Wang Y., Li S.C.* SpecHLA enables full-resolution HLA typing from sequencing data. *Cell Rep Methods.* 2023;3(9):100589. DOI: 10.1016/j.crmeth.2023.100589
26. *Mackay I.R., Morris P.J.* Association of autoimmune active chronic hepatitis with HL-A1,8. *Lancet.* 1972;2(7781):793–5. DOI: 10.1016/s0140-6736(72)92149-6
27. *Lindberg J., Lindholm A., Lundin P., Iwarson S.* Trigger factors and HL-A antigens in chronic active hepatitis. *Br Med J.* 1975;4(5988):77–9. DOI: 10.1136/bmj.4.5988.77
28. *Opelz G., Vogten A.J., Summerskill W.H., Schalm S.W., Terasaki P.I.* HLA determinants in chronic active liver disease: Possible relation of HLA-Dw3 to prognosis. *Tissue Antigens.* 1977;9(1):36–40. DOI: 10.1111/j.1399-0039.1977.tb01077.x
29. *Donaldson P.T., Doherty D.G., Hayllar K.M., McFarlane I.G., Johnson P.J., Williams R.* Susceptibility to autoimmune chronic active hepatitis: Human leukocyte antigens DR4 and A1-B8-DR3 are independent risk factors. *Hepatology.* 1991;13(4):701–6.
30. *Strettell M.D., Thomson L.J., Donaldson P.T., Bunce M., O'Neill C.M., Williams R.* HLA-C genes and susceptibility to type 1 autoimmune hepatitis. *Hepatology.* 1997;26(4):1023–6. DOI: 10.1002/hep.510260434
31. *Manabe K., Donaldson P.T., Underhill J.A., Doherty D.G., Mieli-Vergani G., McFarlane I.G., et al.* Human leukocyte antigen A1-B8-DR3-DQ2-DPB1*0401 extended haplotype in autoimmune hepatitis. *Hepatology.* 1993;18(6):1334–7.
32. *Vázquez-García M.N., Aláez C., Olivo A., Debaz H., Pérez-Luque E., Burguete A., et al.* MHC class II sequences of susceptibility and protection in Mexicans with autoimmune hepatitis. *J Hepatol.* 1998;28(6):985–90. DOI: 10.1016/s0168-8278(98)80347-4
33. *Oliveira L.C., Porta G., Marin M.L., Bittencourt P.L., Kalil J., Goldberg A.C.* Autoimmune hepatitis, HLA and extended haplotypes. *Autoimmun Rev.* 2011;10(4):189–93. DOI: 10.1016/j.autrev.2010.09.024
34. *Terziroli Beretta-Piccoli B., Mieli-Vergani G., Vergani D.* HLA, gut microbiome and hepatic autoimmunity. *Front Immunol.* 2022;13:980768. DOI: 10.3389/fimmu.2022.980768
35. *Kaur N., Minz R.W., Anand S., Saikia B., Aggarwal R., Das A., et al.* HLA DRB1 alleles discriminate the manifestation of autoimmune hepatitis as type 1 or type 2 in North Indian population. *J Clin Exp Hepatol.* 2014;4(1):14–8. DOI: 10.1016/j.jceh.2013.12.002
36. *Sheehan N.J.* The ramifications of HLA-B27. J R Soc Med. 2004;97(1):10–4. DOI: 10.1177/014107680409700102
37. *Reveille J.D.* The genetic basis of ankylosing spondylitis. *Curr Opin Rheumatol.* 2006;18(4):332–41. DOI: 10.1097/01.bor.0000231899.81677.04

Information about the authors

Mikhail D. Chanyshev* — Cand. Sci. (Biol.), Senior Researcher, Laboratory for Genomic Research, Central Research Institute of Epidemiology of the Federal Service for Surveillance on Consumer Rights Protection and Human Wellbeing.
Contact information: chanish@mail.ru;
111123, Moscow, Novogireevskaya str., 3A.
ORCID: https://orcid.org/0000-0002-6943-2915

Yulia G. Sandler — Cand. Sci. (Med.)., Senior Researcher, Hepatology Research Department, Loginov Moscow Clinical Scientific Center.
Contact information: sandlerjulia2012@gmail.com;
111123, Moscow, Novogireevskaya str., 1, build. 1.
ORCID: https://orcid.org/0000-0003-4291-812X

Natalia V. Vlasenko — Researcher, Laboratory of Viral Hepatitis, Central Research Institute of Epidemiology of the Federal Service for Surveillance on Consumer Rights Protection and Human Wellbeing.
Contact information: vlasenko@cmd.su;
111123, Moscow, Novogireevskaya str., 3A.
ORCID: https://orcid.org/0000-0002-2388-1483

* Corresponding author / Автор, ответственный за переписку

Сведения об авторах

Чанышев Михаил Дамирович* — кандидат биологических наук, старший научный сотрудник лаборатории геномных исследований, ФБУН «Центральный научно-исследовательский институт эпидемиологии» Федеральной службы по надзору в сфере защиты прав потребителей и благополучия человека.
Контактная информация: chanish@mail.ru;
111123, г. Москва, ул. Новогиреевская, 3а.
ORCID: https://orcid.org/0000-0002-6943-2915

Сандлер Юлия Григорьевна — кандидат медицинских наук, старший научный сотрудник Научно-исследовательского отдела гепатологии, ГБУЗ «Московский клинический научно-практический центр им. А.С. Логинова» Департамента здравоохранения города Москвы.
Контактная информация: sandlerjulia2012@gmail.com;
111123, г. Москва, ул. Новогиреевская, 1, корп. 1.
ORCID: https://orcid.org/0000-0003-4291-812X

Власенко Наталья Викторовна — научный сотрудник лаборатории вирусных гепатитов, ФБУН «Центральный научно-исследовательский институт эпидемиологии» Федеральной службы по надзору в сфере защиты прав потребителей и благополучия человека.
Контактная информация: vlasenko@cmd.su;
111123, г. Москва, ул. Новогиреевская, 3а.
ORCID: https://orcid.org/0000-0002-2388-1483

Natalia A. Bodunova — Cand. Sci. (Med.), Head of the Center for Personalized Medicine, Loginov Moscow Clinical Scientific Center.
Contact information: n.bodunova@mknc.ru;
111123, Moscow, Novogireevskaya str., 1, build. 1.
ORCID: https://orcid.org/0000-0002-3119-7673

Albina G. Glushchenko — Laboratory Assistant, Laboratory for Genomic Research, Central Research Institute of Epidemiology of the Federal Service for Surveillance on Consumer Rights Protection and Human Wellbeing.
Contact information: albinagluschenko@gmail.com;
111123, Moscow, Novogireevskaya str., 3A.
ORCID: https://orcid.org/0009-0002-8851-8703

Anzhelika S. Chegodar — Clinical Geneticist, Center for Personalized Medicine, Loginov Moscow Clinical Scientific Center.
Contact information: a.chegodar@mknc.ru;
111123, Moscow, Novogireevskaya str., 1, build. 1.
ORCID: https://orcid.org/0000-0001-7753-3698

Anastasiia V. Vykhodtseva — Technologist, Laboratory for Genomic Research, Central Research Institute of Epidemiology of the Federal Service for Surveillance on Consumer Rights Protection and Human Wellbeing.
Contact information: vyhodtseva@cmd.su;
111123, Moscow, Novogireevskaya str., 3A.
ORCID: https://orcid.org/0009-0005-1911-9620

Elena V. Vinnitskaya — Dr. Sci. (Med.), Head of the Hepatology Research Department, Loginov Moscow Clinical Scientific Center.
Contact information: evinn@mail.ru;
111123, Moscow, Novogireevskaya str., 1, build. 1.
ORCID: https://orcid.org/0000-0002-0344-8375

Kamil F. Khafizov — Cand. Sci. (Biol.), Head of Laboratory for Genomic Research, Central Research Institute of Epidemiology of the Federal Service for Surveillance on Consumer Rights Protection and Human Wellbeing.
Contact information: kkhafizov@gmail.com;
111123, Moscow, Novogireevskaya str., 3A.
ORCID: https://orcid.org/0000-0001-5524-0296

Vasiliy G. Akimkin — Dr. Sci. (Med.), Professor, Director, Central Research Institute of Epidemiology of the Federal Service for Surveillance on Consumer Rights Protection and Human Wellbeing.
Contact information: vgakimkin@yandex.ru;
111123, Moscow, Novogireevskaya str., 3A.
ORCID: https://orcid.org/0000-0003-4228-9044

Бодунова Наталья Александровна — кандидат медицинских наук, заведующий Центром персонализированной медицины, ГБУЗ «Московский клинический научно-практический центр им. А.С. Логинова» Департамента здравоохранения города Москвы.
Контактная информация: n.bodunova@mknc.ru;
111123, г. Москва, ул. Новогиреевская, 1, корп. 1.
ORCID: https://orcid.org/0000-0002-3119-7673

Глущенко Альбина Григорьевна — лаборант лаборатории геномных исследований, ФБУН «Центральный научно-исследовательский институт эпидемиологии» Федеральной службы по надзору в сфере защиты прав потребителей и благополучия человека.
Контактная информация: albinagluschenko@gmail.com;
111123, г. Москва, ул. Новогиреевская, 3а.
ORCID: https://orcid.org/0009-0002-8851-8703

Чегодарь Анжелика Сергеевна — врач-генетик Центра персонализированной медицины, ГБУЗ «Московский клинический научно-практический центр им. А.С. Логинова» Департамента здравоохранения города Москвы.
Контактная информация: a.chegodar@mknc.ru;
111123, г. Москва, ул. Новогиреевская, 1, корп. 1.
ORCID: https://orcid.org/0000-0001-7753-3698

Выходцева Анастасия Владимировна — технолог лаборатории геномных исследований, ФБУН «Центральный научно-исследовательский институт эпидемиологии» Федеральной службы по надзору в сфере защиты прав потребителей и благополучия человека.
Контактная информация: vyhodtseva@cmd.su;
111123, г. Москва, ул. Новогиреевская, 3а.
ORCID: https://orcid.org/0009-0005-1911-9620

Винницкая Елена Владимировна — доктор медицинских наук, заведующий отделом гепатологии, ГБУЗ «Московский клинический научно-практический центр им. А.С. Логинова» Департамента здравоохранения города Москвы.
Контактная информация: evinn@mail.ru;
111123, г. Москва, ул. Новогиреевская, 1, корп. 1.
ORCID: https://orcid.org/0000-0002-0344-8375

Хафизов Камиль Фаридович — кандидат биологических наук, руководитель лаборатории геномных исследований, ФБУН «Центральный научно-исследовательский институт эпидемиологии» Федеральной службы по надзору в сфере защиты прав потребителей и благополучия человека.
Контактная информация: kkhafizov@gmail.com;
111123, г. Москва, ул. Новогиреевская, 3а.
ORCID: https://orcid.org/0000-0001-5524-0296

Акимкин Василий Геннадьевич — доктор медицинских наук, профессор, директор, ФБУН «Центральный научно-исследовательский институт эпидемиологии» Федеральной службы по надзору в сфере защиты прав потребителей и благополучия человека.
Контактная информация: vgakimkin@yandex.ru;
111123, г. Москва, ул. Новогиреевская, 3а.
ORCID: https://orcid.org/0000-0003-4228-9044

Authors' contributions

Concept and design of the study: Chanyshev M.D., Sandler Yu.G.
Collection and processing of the material: Vlasenko N.V., Bodunova N.A., Chegodar A.S., Vykhodtseva A.V.
Statistical analysis: Glushchenko A.G.
Writing of the text: Chanyshev M.D., Sandler Yu.G.
Editing: Vinnitskaya E.V., Khafizov K.F., Akimkin V.G.
Proof checking and approval with authors: Chanyshev M.D.

Вклад авторов

Концепция и дизайн исследования: Чанышев М.Д., Сандлер Ю.Г.
Сбор и обработка материалов: Власенко Н.В., Бодунова Н.А., Чегодарь А.С., Выходцева А.В.
Статистическая обработка: Глущенко А.Г.
Написание текста: Чанышев М.Д., Сандлер Ю.Г.
Редактирование: Винницкая Е.В., Хафизов К.Ф., Акимкин В.Г.
Проверка верстки и ее согласование с авторским коллективом: Чанышев М.Д.

Submitted: 22.08.2024 Accepted: 24.10.2024 Published: 30.04.2025
Поступила: 22.08.2024 Принята: 24.10.2024 Опубликована: 30.04.2025