UDC 612.386, 575.174.015.3
DOI: 10.21668/health.risk/2025.3.15.eng

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Research article

FREQUENCY EVALUATION OF THE GENETIC VARIANT MARKING HLA-DQ2.5 ASSOCIATED WITH RISC OF CELIAC DISEASE IN THE RUSSIAN FEDERATION

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Published data on prevalence of genetic predisposition to celiac disease in the Russian Federation (RF) are scarce and limited to local populations; moreover, they are mainly based on studies conducted in patients already affected by the disease. This makes it difficult to comprehensively assess prevalence of risk-associated variants in the general Russian population. Moreover, there is very little available information on prevalence of these variants in post-Soviet countries.

We analyzed frequencies of rs2187668 in an intron of an HLA-DQ2.5 gene (A allele is a marker of the HLA-DQ2.5 haplotype) across the Russian Federation (RF) and several post-Soviet countries.

DNA was obtained from buccal epithelial samples of 33,773 individuals. Genotyping was performed using real-time polymerase chain reaction (PCR) with hybridization-fluorescence signal detection.

The average prevalence of the HLA-DQ2.5 variant was 8.49 % within the RF, ranging from 5.13 % in the Astrakhan Region to 18.06 % in the Kostroma Region. The observed frequencies in the RF are comparable to those reported in European populations (1000 Genomes). The frequency of the rs2187668 A allele (HLA-DQ2.5) was higher than in East Asia and comparable to that in South Asia (1000 Genomes). Regions of the RF identified as having an elevated risk of celiac disease include those where the frequency of the risk-associated allele exceeds 13 % (Kostroma, Lipetsk, Yaroslavl, and Smolensk Regions; Republic of North Ossetia; Republic of Mari El). Among the studied post-Soviet countries, the highest frequency of HLA-DQ2.5 was found in Kazakhstan (11.38 %, significantly higher than in the RF), and the lowest in Belarus (8.33 %). The variant frequencies in Belarus and Ukraine were comparable to those in the RF.

This large-scale study is the first to provide data on distribution of HLA-DQ2.5 genotype and allele frequencies across the RF and its regions. It also presents the first published data on the frequencies of HLA-DQ2.5 genotypes and alleles in Belarus, Ukraine, and Kyrgyzstan.

Keywords: *genetics, coeliac disease, gluten intolerance, main histocompatibility complex, HLA, HLA-DQ2.5, personalized nutrition, gluten, gastroenterology, intestinal diseases.*

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Coeliac disease or celiac disease (CD) is a chronic autoimmune disease, mainly affecting the small intestine, and is caused by consumption of gluten. This disease (K90.0 in ICD-10) is a chronic multi-organ immune-mediated enteropathy affecting small intestine with typical pathomorphological changes in intestinal villi in genetically predisposed individuals. The pathology develops as a response to consumption of gluten [1]. Celiac disease prevalence mostly ranges between 0.7 and 2.9 % in the general population [2–4]. However, apart from apparent cases, approximately 8 % of people with celiac disease have its symptomless form and up to 20 % show an immunologic response to gliadin [5]. One should also distinguish between actual celiac disease, wheat allergy and non-celiac gluten hypersensitivity / intolerance [1].

To our knowledge, there have been no large-scale epidemiological studies on celiac disease prevalence in the Russian Federation (RF). In 2018, S.V. Bykova with colleagues published a review where they mentioned that data on prevalence of the diagnosed celiac disease varied extremely in identified risk groups, between 1:85 in Ryazan and 1.2:1000 in Tomsk. As calculated, overall prevalence of the diagnosed celiac disease can vary between 1:100 and 1:250 in Russia [3]. A review by L.V. Savvateeva and others also describes results obtained by some sporadic studies. According to them, celiac disease prevalence varies between 0.02 % (Arkhangelsk region, Chelyabinsk, and Saint Petersburg) and 0.3 % (Sverdlovsk region). However, all studies covered by both reviews had been published prior to 2010; therefore, we can expect them to have become rather outdated over the last 15 years [6]. We have not been able to find any later publications with more up-to-date information.

Gluten intolerance develops largely due to genetic predisposition. Some genetic determinants of gluten intolerance, which create an elevated risk of its development, are well-known and variants of these genes are commonly analyzed in clinical practice. In particular, the best-known variants of the main histocompatibility locus include *HLA-DQ2* (*HLA-DQ2.2* and *HLA-DQ2.5*), *HLA-DQ8*, *HLA-DQ7.5* and some rarer ones [7]. The heterodimer *HLA-DQ2* consists of two subunits α and β, which are coded by *HLA-DQA1*05* and *HLA-DQB1*02* accordingly [8]. Two types of *HLA-DQ2* heterodimers are *HLA-DQ2.5* (formed by *DQA1*0501* and *B1*0201* alleles) and *HLA-DQ2.2* (formed by *DQA1*0201* and *B1*0202* alleles). Patients with *HLA-DQ2.5* heterodimers have an especially high risk of celiac disease against *HLA-DQ2.5* carriers whereas people with *HLA-DQ2.2* heterodimers have a lower risk [9, 10]. HLA-DQ2.5 homozygous individuals have an at least fivefold higher risk of disease development compared to HLA-DQ2.5/x heterozygous individuals [11].

Genetic diagnostics is included in the clinical guidelines valid in the RF and, according to them, allows excluding celiac disease (in case alleles associated with celiac disease risk are absent)[1]. However, these recommendations also emphasize that genotyping alone might not be enough to diagnose the disease since *HLA-DQ2/DQ8* variants are found in approximately 30–40 % of the healthy population[1]. Global Practical Guidelines issued by

[1] Russian Non-Governmental Organization Russian Pediatrician Union; Society of Children's Gastroenterologists, Hepatologists, and Nutritionists; Occupational Non-Governmental Organization (Association) of Children's Doctors Initiative by Pediatricians and Neonatologists in Clinical Practice Development; National Association of Organizations and Citizens Supporting Patients with Celiac Disease and Gluten Intolerance Life without Gluten. Tseliakiya. Klinicheskie rekomendatsii [Celiac disease. Clinical Guidelines], 2021, 58 p. Available at: https://www.pediatr-russia.ru/information/klin-rek/proekty-klinicheskikh-rekomendatsiy/%D0%A6%D0%B5%D0%BB%D0%B8%D0%B0%D0%BA%D0%B8%D1%8F%20%D0%9A%D0%A0_%D0%BD%D0%B0%20%D1%81%D0%B0%D0%B9%D1%82_22.07.2021.pdf (July 30, 2025) (in Russian); Tseliakiya u detei. Klinicheskie rekomendatsii [Celiac disease in children. Clinical Guidelines]. Moscow, Ministry of Health of the Russian Federation, 2016, 43 p. Available at: https://www.pediatr-russia.ru/information/klin-rek/deystvuyushchie-klinicheskie-rekomendatsii/%D0%A6%D0%B5%D0%BB%D0%B8%D0%B0%D0%BA%D0%B8%D1%8F%20%D0%B4%D0%B5%D1%82%D0%B8%20%D0%A1%D0%9F%D0%A0.v1%20%D1%81%20%D0%BF%D1%80%D0%B0%D0%B2%D0%BA%D0%B0%D0%BC%D0%B8.pdf (July 30, 2025) (in Russian).

the World Gastroenterology Organization label the foregoing factors as the most significant genetic ones in celiac disease development[2]. The *HLA-DQ2* heterodimer is present in the vast majority of CD patients including approximately 95 % of CD patients of Northern-European descent; the rest have *HLA-DQ8* [12]. Therefore, presence of risk alleles *HLA* is considered a mandatory but not sufficient factor for celiac disease development (*DQ2* and *DQ8* are absent in < 1 % of CD patients) [7].

In the Russian Federation (RF), studies with their focus on prevalence of genetic predisposition (*HLA-DQ2/DQ8*) to gluten intolerance are scarce; as a rule, they have been conducted on limited local populations and this makes a comprehensive assessment at the national level very difficult. To the best of our knowledge, data on the RF as a whole and on many regions are either absent or have not been published so far. In addition, very few data are available on frequency of genetic factors associated with the celiac disease risk in post-Soviet countries; epidemiological studies are also scarce in them. Finally, the most significant fact is that overwhelming majority of available studies has been accomplished involving patients with already diagnosed celiac disease thereby failing to provide a true picture of genotype frequency in the general population. Among latest studies, we can mention a work by L.A. Opryatin and others with its focus on celiac disease prevalence in children with dermatological symptoms. However, this study again involved children with already diagnosed pathologies. Interestingly, the authors found the complete concurrence of IgA, IgG antibodies and risk alleles *HLA-DQ2/DQ8* presence [13].

The aim of this study was to analyze frequencies of rs2187668 in an intron of an *HLA-DQ2.5* gene, which was the most significantly associated with the celiac disease risk, across the Russian Federation (RF), in different RF regions and in several neighboring post-Soviet countries.

Materials and methods. We analyzed buccal epithelium taken from 33,773 people of both sexes for each variant in 67 regions of the Russian Federation; we did not estimate any gluten intolerance signs. Regional samples that were made of less than 30 participants were considered non-representative and therefore were excluded from the analysis. We also performed genotyping of residents from some post-Soviet countries: 336 from Belarus, 625 from Ukraine, 2646 from Kazakhstan, 112 from Kyrgyzstan, and 122 from Uzbekistan.

Buccal epithelium was collected by the participants themselves using special sampling kits (sterile tampon probes); after that, dried sealed materials were delivered to a laboratory by courier. Prior to biomaterial sampling, the participants gave their informed written consent to personal data collection and analysis within this research.

DNA was extracted by adsorption on silicon dioxide crystals (based on[3] [14]). Genotyping of rs2187668 was accomplished by PCR with hybridization-fluorescent real-time detection. The polymorphism was selected as a marker of the *HLA-DQ2.5* haplotype based on a study by A.J. Monsuur et al. [15]. Primers, probes and amplification conditions were developed by National Center for Genetic Research LLC and allowed for use for medical purposes as a part of the Metabolic Kit 60 (registration certificate No. P012-00110-77/00651190 от 15.05.2023).

Statistical data analysis was accomplished as follows: frequencies of genotypes were tested for conformity with the Hardy – Weinberg equilibrium using the χ^2 method. Frequencies of genotypes and alleles in the analyzed groups were compared, standard sample deviation and standard error of allele frequency were calculated, and the normal distribution graph was built in Excel. Frequencies

[2] World Gastroenterology Organization Global Guidelines. Celiac disease. *World Gastroenterology Organization (WGO)*, 2016, 38 p. Available at: https://www.worldgastroenterology.org/UserFiles/file/guidelines/celiac-disease-english-2016.pdf (July 30, 2025).

[3] Boom R., Sol C.J., Salimans M.M., Jansen C.L., Wertheim-van Dillen P.M., van der Noordaa J. Rapid and simple method for purification of nucleic acids. *J. Clin. Microbiol.*, 1990, vol. 28, no. 3, pp. 495–503. DOI: 10.1128/jcm.28.3.495-503.1990

obtained for Russian regions were compared with those in neighboring post-Soviet countries as well as European and Asian populations (1000 Genomes) using the χ^2 test. Intergroup differences were considered significant at $p < 0.05$.

Results and discussion. ***HLA-DQ2.5 frequency in Russian regions.*** Frequencies of the analyzed variants per RF regions are provided in Table 1. The frequency of the A allele (*HLA-DQ2.5*) was 8.49 % on average in the RF varying between 5.13 % (the lowest level in the Astrakhan region) to 18.06 % (the highest level in the Kostroma region); that is, the different between the highest and lowest levels was 3.52 times. Frequencies of alleles and genotypes identified in Russia as a whole were comparable to those established in European populations (1000 Genomes). The allele A (HLA-DQ2.5) turned out to be more frequent in Russia against the Eastern Asia and its frequency was comparable to that found in the Southern Asia (1000 Genomes). However, we should remember that the 1000 Genomes project typically has rather small samples relative to ours and the allele itself is relatively not frequent in populations.

The frequency of the homozygous genotype, which corresponded to an especially high risk of celiac disease, was the highest in the Kursk region (4.88 %); it was also very frequent in the Kostroma region (with the highest allele A frequency) (4.17 % homozygotes), Yaroslavl region (4.27 %), and Smolensk region (3.95 %).

Table 1

Frequencies of alleles and genotypes of rs2187668 (*HLA-DQ2.5*) in the Russian Federation per regions

Region	*N*	AA	GA	GG	A	G	Standard error for alleles
Altai Krai	183	0.55 %	14.21 %	85.25 %	7.65 %	92.35 %	0.18 %
Amur region	60	1.67 %	16.67 %	81.67 %	10.00 %	90.00 %	0.31 %
Arkhangelsk region	108	1.85 %	15.74 %	82.41 %	9.72 %	90.28 %	0.23 %
Astrakhan region	39	0.00 %	10.26 %	89.74 %	5.13 %	94.87 %	0.38 %
Belgorod region	174	2.30 %	10.92 %	86.78 %	7.76 %	92.24 %	0.18 %
Bryansk region	102	3.92 %	17.65 %	78.43 %	12.75 %	87.25 %	0.23 %
Vladimir region	76	0.00 %	14.47 %	85.53 %	7.24 %	92.76 %	0.27 %
Volgograd region	141	0.00 %	12.06 %	87.94 %	6.03 %	93.97 %	0.20 %
Vologda region	370	1.08 %	17.30 %	81.62 %	9.73 %	90.27 %	0.12 %
Voronezh region	240	1.67 %	16.25 %	82.08 %	9.79 %	90.21 %	0.15 %
Zabaykalskii Krai	645	1.09 %	17.98 %	80.93 %	10.08 %	89.92 %	0.09 %
Ivanovo region	98	0.00 %	15.31 %	84.69 %	7.65 %	92.35 %	0.24 %
Irkutsk region	664	1.20 %	13.86 %	84.94 %	8.13 %	91.87 %	0.09 %
Kabardino-Balkarskaya Republic	44	2.27 %	9.09 %	88.64 %	6.82 %	93.18 %	0.36 %
Kaliningrad region	198	1.01 %	16.16 %	82.83 %	9.09 %	90.91 %	0.17 %
Kaluga region	73	1.37 %	12.33 %	86.30 %	7.53 %	92.47 %	0.28 %
Kamchatka Krai	83	1.20 %	14.46 %	84.34 %	8.43 %	91.57 %	0.26 %
Kemerovo region	294	1.02 %	16.33 %	82.65 %	9.18 %	90.82 %	0.14 %
Kirov region	191	1.05 %	17.80 %	81.15 %	9.95 %	90.05 %	0.17 %
Kostroma region	72	4.17 %	27.78 %	68.06 %	18.06 %	81.94 %	0.28 %
Krasnodar Krai	1304	1.61 %	14.03 %	84.36 %	8.63 %	91.37 %	0.07 %
Krasnoyarsk Krai	343	2.33 %	10.79 %	86.88 %	7.73 %	92.27 %	0.13 %
Kursk region	41	4.88 %	9.76 %	85.37 %	9.76 %	90.24 %	0.37 %
Leningrad region	2648	1.21 %	16.20 %	82.59 %	9.31 %	90.69 %	0.05 %
Lipetsk region	54	1.85 %	25.93 %	72.22 %	14.81 %	85.19 %	0.32 %
Moscow region	12429	1.34 %	13.88 %	84.79 %	8.28 %	91.72 %	0.02 %
Murmansk region	56	1.79 %	12.50 %	85.71 %	8.04 %	91.96 %	0.32 %
Nizhnii Novgorod region	324	1.23 %	10.80 %	87.96 %	6.64 %	93.36 %	0.13 %

End of the Table 1

Region	*N*	AA	GA	GG	A	G	Standard error for alleles
Novosibirsk region	2280	1.05 %	14.39 %	84.56 %	8.25 %	91.75 %	0.05 %
Omsk region	112	2.68 %	11.61 %	85.71 %	8.48 %	91.52 %	0.22 %
Orenburg region	111	1.80 %	19.82 %	78.38 %	11.71 %	88.29 %	0.22 %
Penza region	68	0.00 %	13.24 %	86.76 %	6.62 %	93.38 %	0.29 %
Perm Krai	234	1.28 %	12.39 %	86.32 %	7.48 %	92.52 %	0.15 %
Primorskii Krai	345	1.16 %	10.43 %	88.41 %	6.38 %	93.62 %	0.13 %
Bashkortostan Republic	417	0.72 %	14.39 %	84.89 %	7.91 %	92.09 %	0.12 %
Buryatiya Republic	82	0.00 %	12.20 %	87.80 %	6.10 %	93.90 %	0.26 %
Daghestan Republic	146	3.42 %	13.70 %	82.88 %	10.27 %	89.73 %	0.20 %
Kareliya Republic	74	1.35 %	10.81 %	87.84 %	6.76 %	93.24 %	0.28 %
Komi Republic	33	0.00 %	21.21 %	78.79 %	10.61 %	89.39 %	0.41 %
Crimea Republic	721	0.97 %	13.04 %	85.99 %	7.49 %	92.51 %	0.09 %
Marii El Republic	39	2.56 %	23.08 %	74.36 %	14.10 %	85.90 %	0.38 %
Mordoviya Republic	128	3.13 %	10.94 %	85.94 %	8.59 %	91.41 %	0.21 %
Severnaya Osetiya Republic	35	0.00 %	28.57 %	71.43 %	14.29 %	85.71 %	0.40 %
Tatarstan Republic	1079	0.74 %	14.83 %	84.43 %	8.16 %	91.84 %	0.07 %
Hakassiya Republic	58	1.72 %	17.24 %	81.03 %	10.34 %	89.66 %	0.31 %
Rostov region	660	1.21 %	14.55 %	84.24 %	8.48 %	91.52 %	0.09 %
Ryazan region	155	0.65 %	13.55 %	85.81 %	7.42 %	92.58 %	0.19 %
Samara region	747	1.34 %	11.91 %	86.75 %	7.30 %	92.70 %	0.09 %
Saratov region	148	2.03 %	15.54 %	82.43 %	9.80 %	90.20 %	0.19 %
Sakhalin region	563	1.24 %	11.19 %	87.57 %	6.84 %	93.16 %	0.10 %
Sverdlovsk region	1231	1.62 %	14.87 %	83.51 %	9.06 %	90.94 %	0.07 %
Smolensk region	76	3.95 %	18.42 %	77.63 %	13.16 %	86.84 %	0.27 %
Stavropol Krai	252	1.19 %	14.29 %	84.52 %	8.33 %	91.67 %	0.15 %
Tambov region	84	0.00 %	15.48 %	84.52 %	7.74 %	92.26 %	0.26 %
Tver region	194	2.58 %	11.86 %	85.57 %	8.51 %	91.49 %	0.17 %
Tomsk region	179	1.12 %	17.88 %	81.01 %	10.06 %	89.94 %	0.18 %
Tula region	87	1.15 %	9.20 %	89.66 %	5.75 %	94.25 %	0.25 %
Tyumen region	310	0.65 %	14.84 %	84.52 %	8.06 %	91.94 %	0.13 %
Udmurtskaya Republic	74	1.35 %	14.86 %	83.78 %	8.78 %	91.22 %	0.28 %
Ulyanovsk region	75	1.33 %	9.33 %	89.33 %	6.00 %	94.00 %	0.27 %
Khabarovsk Krai	338	0.89 %	16.27 %	82.84 %	9.02 %	90.98 %	0.13 %
Khanty-Mansi Autonomous Area	404	1.24 %	16.34 %	82.43 %	9.41 %	90.59 %	0.12 %
Chelyabinsk region	701	1.57 %	14.55 %	83.88 %	8.84 %	91.16 %	0.09 %
Chuvashskaya Republic	39	2.56 %	10.26 %	87.18 %	7.69 %	92.31 %	0.38 %
Sakha (Yakutiya) Republic	118	3.39 %	18.64 %	77.97 %	12.71 %	87.29 %	0.22 %
Yamal-Nenets Autonomous Area	205	0.00 %	15.61 %	84.39 %	7.80 %	92.20 %	0.17 %
Yaroslavl region	117	4.27 %	18.80 %	76.92 %	13.68 %	86.32 %	0.22 %
RF, total	33773	1.32 %	14.35 %	84.33 %	8.49 %	91.51 %	0.01 %

Note: *N* means the number of examined participants; variant A corresponds to *HLA-DQ2.5* haplotype.

Our data did not include information about the participants' diets or intestinal symptoms; therefore, it does not seem possible to make any conclusions about a relationship between gluten intolerance signs, levels of its consumption and presence of *HLA-DQ2.5* variants. However, if we compare our findings, for example, with data provided by the Federal State Statistics Service, we can certainly see some issues to discuss. Thus, for example, the Kursk region with the highest *HLA-DQ2.5* homozygote frequency is charac-

terized with very high consumption of bread and bakery products (142 kg/person a year, in 2023, the third place among RF regions per this indicator)[4]. On the other hand, the Astrakhan region, where the *HLA-DQ2.5* frequency turned out to be the lowest among RF regions, does not fall too far behind the Kursk region per bread and bakery products consumption (135 142 kg/person a year)[4]. Therefore, if we compare consumption of gluten-containing products with frequency of genetic risk factors of celiac disease, we can spot out regions where special attention should be paid to screening, symptoms and prevention of the disease.

Previous studies found lower frequency of *HLA-DQ2* and / or *HLA-DQ8* alleles unfavorable with respect to celiac disease in Russia against Europe [16, 17]. However, we should remember that only patients with already diagnosed celiac disease participated in both these studies, therefore any comparison with our findings is unjustified. Previous studies do not contain comprehensive data on frequencies of HLA-DQ2 genotypes among the population in Russia as a whole.

Therefore, our data are the first to show the actual frequency of *HLA-DQ2.5* associated with genetic predisposition to celiac disease among the population in 67 RF regions.

HLA-DQ2.5 frequency in post-Soviet countries. Allele and genotype frequencies established for the population of some post-Soviet countries are provided in Table 2.

The frequency of the allele A (*HLA-DQ2.5* variant), which increases the celiac disease risk substantially, varied in different post-Soviet countries, Russia included, between 8.33 % in Belarus and 11.38 % in Kazakhstan; the frequency of this variant was the lowest in the RF, Ukraine, and Belarus among the analyzed post-Soviet countries. Nevertheless, the difference between the RF and Kazakhstan, where the frequency was the highest, turned out to be authentic (the frequency of the allele A was higher in Kazakhstan relative to Russia). The same trend was established for Kyrgyzstan but the difference, however, was not authentic.

The border between Russia and Kazakhstan goes through the Astrakhan, Volgograd, Saratov, Orenburg, Chelyabinsk, Kurgan, Tyumen, Omsk, and Novosibirsk regions, Altai Krai, Altai Republic and (to the smallest extent) through the Samara region. Frequencies of alleles and genotypes turned out to be authentically lower in the Novosibirsk, Samara, Chelyabinsk, and Tyumen regions as compared with Kazakhstan; the difference between Kazakhstan and other near-border regions turned out to be insignificant. The Kurgan region and Altai Krai samples were made of less than 30 people and therefore were considered non-representative.

Table 2

Frequency of rs2187668 (*HLA DQ-2.5* marker) in some post-Soviet countries

Country	N	AA	GA	GG	A	G	Standard error
Belarus	336	1.19 %	14.29 %	84.52 %	8.33 %	91.67 %	0.13 %
Kazakhstan*	2646	2.19 %	18.37 %	79.44 %	11.38 %	88.62 %	0.05 %
Kyrgyzstan	112	1.79 %	17.86 %	80.36 %	10.71 %	89.29 %	0.23 %
Uzbekistan	122	0.82 %	18.03 %	81.15 %	9.84 %	90.16 %	0.22 %
Ukraine	625	1.12 %	14.88 %	84.00 %	8.56 %	91.44 %	0.10 %
Russia	33,773	1.32 %	14.35 %	84.33 %	8.49 %	91.51 %	0.01 %

Note: *N* means the number of examined people; variant A corresponds to *HLA-DQ2.5* haplotype; * means the difference with Russia is authentic ($p \leq 0.05$).

[4] Otchet o potreblenii osnovnykh produktov pitaniya naseleniem – khlebnye produkty za 5 let (2024 g.) [Report on Consumption of Main Food Products by the Population – bread and bakery products over 5 years (2024)]. *Rosstat: the official web-site of the Federal State Statistics Service*. Available at: https://rosstat.gov.ru/compendium/document/13278 (June 04, 2025) (in Russian).

Therefore, our findings obtained by analyzing the *HLA-DQ2.5* frequency in post-Soviet countries were basically comparable excluding a significant difference between Belarus and Kazakhstan. In particular, the frequencies of the genetic variant *HLA-DQ2.5* marker in Belarus and Ukraine were comparable to those established in Russia, which is easily explained by genetic proximity and active population migration between these three countries.

In 2023, an epidemiological study established prevalence of celiac disease in Belarus, which was equal to 15.2 cases per 100,000 of children. However, this study did not involve genotyping [18]. We have not been able to find any published epidemiological data on celiac disease prevalence in Ukraine. We have not found any previously published data on *HLA-DQ2* frequencies in Belarus or Ukraine either.

A previous study established relatively low, as compared with Russia, frequency of *HLA-DQ2* and / or *HLA-DQ8* alleles, but again among children with already diagnosed celiac disease [19]. Our study found higher *HLA-DQ2.5* frequency in Kazakhstan against Russia. It hardly seems justified to compare this study with ours since M.N. Sharipova with colleagues examined patients with already diagnosed disease whereas our study was conducted on a population, which included people regardless of any diagnosed disease.

The *HLA-DQ2.5* frequency turned out to be authentically lower in four regions bordering Kazakhstan (the Novosibirsk, Samara, Tyumen and Chelyabinsk regions) than in Kazakhstan. No significant differences were established for other RF regions bordering this country, including the Astrakhan region, where the *HLA-DQ2.5* frequency turned out to be among the lowest ones in the RF. However, it should be noted that the number of participants from the Astrakhan region was rather low (39 people); this was probably the reason for the difference not reaching statistical significance.

Some epidemiological data are available for the Tashkent district in Uzbekistan, where celiac disease prevalence amounts to 1:366 people [20]. An early study on genetic factors in Type 1 diabetes established the following frequencies of *DQA1*0501* and *DQB1*0201:* accordingly 43.42 % (diabetes patients) vs 20.09 % (healthy people) and 53.95 % (diabetes patients) vs 18.69 % (healthy people) among Uzbeks, as well as accordingly 36.07 % (diabetes patients) vs 29.57 % (healthy people) and 35 % (diabetes patients) vs 23.12 % (healthy people) among Russians[5]. However, similar studies have not obviously been conducted with regards to celiac disease.

Clinical significance of HLA locuses as regards celiac disease development. Although *HLA-DQ2* and *HLA-DQ8* markers are considered significant as regards celiac disease, their presence is not sufficient for the disease development. *HLA-DQ2/HLA-DQ8* variants are quite frequent in the global population (25–35 %), and celiac disease develops only in 3 % of such people, who have genetic markers associated with celiac disease risk [21]. In other words, genotyping of *HLA-DQ2/HLA-DQ8* has relatively low diagnostic value (although the procedure is useful for establishing a substantial risk factor). However, clinical guidelines point out that negative results obtained by *HLA* genotyping have high diagnostic and prognostic significance for celiac disease exclusion, since absence of typical *HLA-DQ2/HLA-DQ8* haplotypes makes celiac disease development highly unlikely. Therefore, *HLA-DQ2/HLA-DQ8* identification is useful for differential diagnostics [22] and is included in clinical guidelines. However, we should bear in mind that much rarer *HLA* vari-

[5] Alekseev L.P., Dedov I.I., Zilov A.V., Boldyreva M.N., Demidova I.Yu., Trofimov D.Yu., Khaitov R.M. Mezhpopulyatsionnyi podkhod v ustanovlenii assotsiirovannoi s HLA geneticheskoi predraspolozhennosti k insulinzavisimomu sakharnomu diabetu [Inter-population approach to establishing HLA-associated genetic predisposition to insulin-dependent diabetes]. *Diabetes mellitus*, 1998, vol. 1, no. 1, pp. 19–21. DOI: 10.14341/2072-0351-6210 (in Russian).

ants exist and they are able to influence the celiac disease risk. Taking them into account may raise diagnostic value (at least, as regards exclusion of the disease) [8]; however, the existing clinical guidelines include only *HLA-DQ2* and *HLA-DQ8*. In addition, recent studies pay considerable attention to micro-RNA as diagnostic markers [23, 24]. At present, the common opinion is that there is no 100 % precise method for celiac disease diagnostics; however, new clinical markers are being searched and tested to achieve more precise diagnostics and to minimize the necessity to perform biopsy [25].

HLA-DQ2.5 is the most significant risk factor of celiac disease. Use of rs2187668 to predict this haplotype showed 100 % sensitivity and 99.99 % specificity [15]. This makes it possible to successfully use this polymorphism for *HLA-DQ2.5* identification.

Despite a substantial contribution made by genetic determinants, celiac disease development is considered to be alimentary dependent; that is, it depends on gluten presence in a diet as well as, probably, its quality [21, 26, 27]. A meta-analysis showed a pronounced correlation between wheat consumption and celiac disease incidence in continent-level assessments; however, this correlation turned out to be inauthentic at the country level. In addition, this study did not find any correlation between wheat consumption and prevalence of the disease [28]. Another meta-analysis established a linear dependence between an administered gluten dose and a risk of celiac disease development / relapse [29]. A timely visit to a doctor and qualitative diagnostics play a significant role in establishing prevalence of the disease. We should bear in mind that celiac disease remains undiagnosed in many people [30]. Nevertheless, genetic testing remains an important instrument for differential diagnostics of celiac disease and other diseases with similar symptoms.

Relatively high *HLA-DQ2.5* prevalence in some regions can be considered an epidemiological risk factor for them. Thus, regions with an elevated celiac disease risk include the Kostroma region, the Lipetsk region, Severnaya Osetiya Republic, Marii El Republic, the Yaroslavl region, and the Smolensk region where the frequency of the allele associated with celiac disease risks was higher than 13 %. The Kostroma region deserves special attention since the frequency of the genetic variant associated with celiac disease risk is more than twofold higher there against the national average. This risk is less pronounced but still high in Yakutiya, the Bryansk region and the Orenburg region (the frequency of the risk-associated allele is higher than 11 %) as well as in Kazakhstan. It is advisable to have screening in these regions with its aim to identify and prevent celiac disease (especially its symptomless form) as well as to raise awareness about gluten intolerance, its forms, causes and symptoms among population. Among other things, screening activities can include genetic testing, which makes it possible to identify people with an elevated celiac disease risk, to timely modify their diets and prevent the disease or, at least, decrease likelihood of its development substantially. On the other hand, the Vologda region, the Tula region, and the Astrakhan region can be considered areas with a low celiac disease risk (still, this cannot justify neglect of screening and prevention). However, we should bear in mind that relatively small samples were examined in some regions (above 30 but below 100 people). In future, we are going to expand our study samples to make more precise assessments of allele and genotype frequencies in these regions as well as in those excluded from this work due to regional samples being too small, which prevented us from establishing *HLA-DQ2.5* frequencies and assess risk levels in them.

Conclusion. This large-scale study performed on an extensive sample (more than 33 thousand people for each variant) is the first to provide data on distribution of *HLA-DQ2.5* genotype and allele frequencies across the RF and its regions. We have detected which regions could be considered areas with elevated epidemiological risks as regards celiac disease (the Kostroma region, the Lipetsk region, Sev-

ernaya Osetiya Republic, Marii El Republic, the Yaroslavl region, and the Smolensk region). The study also presents the first published data on the frequencies of *HLA-DQ2.5* genotypes and alleles in Belarus, Ukraine, and Kyrgyzstan. Unfortunately, our questionnaire did not cover presence or absence of diagnosed celiac disease or symptoms that could indicate its onset in the participants. However, our data can be useful for estimating overall prevalence of this risk factor in Russia and neighboring countries and for further comparison with clinical data.

Funding. The research was not granted any sponsor support.

Competing interests. The authors declare no competing interests.

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Received: 30.07.2025
Approved: 08.09.2025
Accepted for publication: 26.09.2025