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Research article

FREQUENCY EVALUATION OF THE GENETIC VARIANT LCT RS4988235 (-13910 C>T), ASSOCIATED WITH LACTOSE INTOLERANCE, IN THE RUSSIAN FEDERATION

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Most published studies of the prevalence of genetic predisposition to lactose intolerance in Russia have limitations, which makes it difficult to provide a complete assessment for Russia as a whole. Moreover, no comparison with the neighboring countries was performed.

The aim of this work was to analyze the frequency of the LCT gene rs4988235 regulatory region variant associated with lactose intolerance in Russian regions and in some neighboring countries.

As a material, buccal epithelium of 40,111 investigated subjects was used. Genotyping was performed using a real-time polymerase chain reaction with hybridization-fluorescence signal detection.

The frequency of C allele associated with lactose intolerance was 67.73 ± 0.03 % on average. The prevalence of the CC genotype in Russia averaged 46.1 %; CT, 34.22 %; TT, 10.66 %, significantly different from European and Asian populations. The maximum frequency of the C allele was found in Yakutia (84.0 % ± 0.6 %); the minimum (54.4 ± 0.7 %), in the Vladimir region. A reliable moderate correlation was found between the prevalence of the T allele and the proportion of the East Slavic population in Russian regions. The frequency of the C allele in Belarus (67.8 ± 0.4 %) and Ukraine (68.7 ± 0.3 %) is comparable with the same for Russia; in Armenia (86.4 ± 1.3 %), Georgia (87.3 ± 1.0 %), Kazakhstan (82.1 ± 0.1 %), Kyrgyzstan (81.9 ± 0.6 %) and Uzbekistan (86.4 ± 0.7 %), significantly higher than in Russia.

Data concerning the frequency of rs4988235 in Russia regions were obtained from a large all-Russian population. Discovered similarities and differences are evidently related to the ethnic composition of Russia regions and neighboring countries.

Keywords: *genetics, lactose intolerance, lactase deficiency, personalized nutrition, carbohydrate, lactase, LCT gene, diet.*

Lactose intolerance means the inability to digest lactose, the milk sugar that constitutes a major component of milk and dairy products. This can lead to unpleasant symptoms such as diarrhea, flatulence and vomiting. It arises due to the deficiency of the lactase, an enzyme which hydrolyzes lactose into glucose and galactose, facilitating its absorption in the intestine. In newborns, lactase is expressed at high levels, but its activity generally decreases after weaning. Consequently, adults may have difficulty while digesting lactose and develop adverse symptoms when consuming milk (primary lactose intolerance) [1–3].

According to a large meta-analysis conducted in 2017, the global prevalence of lactose intolerance is estimated at approximately 68 %. However, it varies widely across countries: from as low as 4 % in Ireland and Denmark to 85 % in China, 98 % in Vietnam, and

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nearly 100 % in Yemen. In North, South and West Europe, the average prevalence of lactose malabsorption is around 28 %, whereas in the Middle East it is approximately 70 %. The prevalence of lactose malabsorption in Russia was estimated at 61 % in this meta-analysis [4].

The age-related decline in lactase production is genetically programmed. Lactase is encoded by the LCT gene and its well-studied variation, -13910 C>T (rs4988235), which is located in intron 13 of the MCM6 gene near a regulatory region, is frequent in Europe and Russia. The ancestral allele C is associated with decreased expression of the LCT gene and, consequently, a reduction in lactase levels with age resulting in lactose intolerance. In contrast, the TT genotype allows lactase activity and lactose digestion to persist into adulthood. The heterozygous genotype (CT) may also retain moderate lactase activity [1–3, 5, 6].

Until recently, published studies on the genetic predisposition to lactose intolerance in the Russian Federation (RF) were most often limited to specific local populations and/or ethnic groups, or were a small part of broader global investigations, with limited sample sizes [7–13]. This has made it difficult to comprehensively determine genetics of lactose intolerance across the entire Russian population. The only large-scale nationwide study in Russia was published in 2023 [14]. This work is noteworthy for its sample size and scope but does not include all regions and requires an expanded sample (at least for certain areas) to refine the results. Additionally, the ethnic diversity in Russia and the active migration of the population make it important to investigate genetic variants across different regions of the country. Furthermore, comparisons of genotype frequencies in Russia with those in neighboring countries have not been made. Such comparisons would be valuable in the context of differences in ethnic composition and active migration processes.

Therefore, **the aim of this study** is to analyze the frequency of the regulatory variant rs4988235 of the LCT gene associated with lactase deficiency across the RF as a whole and in its various regions, as well as in some neighboring countries.

Materials and methods. The study analyzed buccal epithelial samples from 40,111 individuals of both sexes from 67 regions of the Russian Federation. Regional samples with fewer than 30 participants were assumed non-representative and excluded from the analysis. Additionally, samples were collected from participants in the following countries: Armenia (33 individuals), Belarus (368), Georgia (55), Kazakhstan (3,011), Kyrgyzstan (144), Uzbekistan (125), and Ukraine (707).

Participants collected buccal epithelial material themselves using specialized collection kits (cotton swabs in sterile packaging). The dried sealed samples were then delivered to the laboratory via courier service. Upon submitting the biomaterial, participants signed an informed consent for processing and use of their personal data for scientific research purposes. DNA was extracted using adsorption on silicon dioxide crystals. Genotyping of the rs4988235 variant was performed using real-time PCR with hybridization-fluorescent signal detection. The primers, probes, and amplification conditions were developed by the National Center for Genetic Research and approved for medical use as part of the reagent kit ‘Metabolic Kit 60’ (registration approval No. P012-00110-77/00651190, dated May 15, 2023).

Statistical analysis was conducted as follows. The Hardy-Weinberg equilibrium (HWE) test for genotype frequencies was performed using the χ^2 test. Genotype and allele frequency comparisons between study groups, standard deviations, standard errors of allele frequencies, and distribution assessments were calculated using Excel. Comparisons of Russian frequencies with frequencies in neighboring ex-Soviet countries and with data from European and Asian populations (1000 Genomes) were performed using the χ^2 test. Differences between groups were considered statistically significant at $P < 0.05$.

To analyze the correlation between allele frequencies and the ethnic composition of different Russian regions, Pearson correlation coefficient was calculated using data from the 2020 All-Russian Census[1]. Only individuals who reported their ethnicity were included. To determine the percentage of "Eastern Slavs", the proportions of individuals identifying as "Russian", "Belarusian", and "Ukrainian" were summed.

Results and discussion. The overall country distribution of rs4988235 genotypes in the Russian Federation was as follows: CC, 46.1 %; CT, 43.2 %; and TT, 10.7 %; the allele frequencies were 67.7 % for C and 32.3 % for T respectively. The distribution of genotypes and alleles across individual regions is presented in Table 1, with a visual representation of the frequency of the polymorphic T allele associated with normal lactose tolerance, as shown in the Figure. The overall genotype distribution for Russia deviated from Hardy – Weinberg equilibrium. Regional analysis identified deviations from Hardy – Weinberg equilibrium in Kostroma Region, Kamchatka Krai, and Stavropol Krai, indicating that these populations were not in equilibrium.

The observed genotype frequencies in Russia significantly differed from those reported for the general European and Asian populations (1000 Genomes data), the frequency of the C allele in Russia was significantly higher than in western, northern and southern European populations but lower than in South Asian and East Asian populations, the latter of which show nearly 100 % prevalence of this allele ($p < 0.05$). Across Russian regions, the prevalence of the CC genotype, associated with lactase deficiency, ranged from 31.9 % in Vladimir Region to 71.8 % in Yakutia.

Table 1

Genotype and allele frequencies of LCT -13910 C>T (rs4988235) in the Russian Federation by regions, %

RF Regions	*N*	Genotype Frequency			Allele Frequency (Actual)		
		CC	CT	TT	C	T	Error
1	2	3	4	5	6	7	8
Sakha Republic (Yakutia)	131	71.80	24.40	3.80	84.00	16.00	0.60
Kabardino-Balkar Republic	49	63.30	28.60	8.20	77.60	22.50	0.90
Republic of Dagestan	197	59.90	35.00	5.10	77.40	22.60	0.50
Murmansk Region	66	59.10	33.30	7.60	75.80	24.20	0.80
Republic of North Ossetia-Alania	43	55.80	37.20	7.00	74.40	25.60	1.00
Ulyanovsk Region	91	52.80	41.70	5.50	73.60	26.40	0.70
Kursk Region	50	58.00	30.00	12.00	73.00	27.00	0.90
Sakhalin Region	584	53.60	38.20	8.20	72.70	27.30	0.30
Chuvash Republic	41	48.80	46.30	4.90	72.00	28.10	1.00
Smolensk Region	79	49.40	44.30	6.30	71.50	28.50	0.70
Yaroslavl Region	138	51.50	39.90	8.70	71.40	28.60	0.54
Rostov Region	942	51.00	40.80	8.30	71.30	28.70	0.20
Republic of Tatarstan	1425	51.60	39.40	9.00	71.30	28.70	0.20
Republic of Karelia	87	48.30	46.00	5.80	71.30	28.70	0.70
Republic of Buryatia	128	52.30	37.50	10.20	71.10	28.90	0.60
Republic of Bashkortostan	462	50.80	40.30	8.90	71.00	29.00	0.30
Kostroma Region	79	44.30	53.20	2.50	70.90	29.10	0.70
Bryansk Region	132	48.50	44.70	6.80	70.80	29.20	0.60
Stavropol Region	271	52.40	36.20	11.40	70.50	29.50	0.40
Primorsky Region	460	48.30	43.90	7.80	70.20	29.80	0.30
Orenburg Region	120	51.70	36.70	11.70	70.00	30.00	0.60

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[1] Natsional'nyi sostav naseleniya [National composition of the population]. *FADN Rossii*, May 30, 2023. Available at: https://fadn.gov.ru/otkritoe-agenstvo/vserossijskaya-perepis-naseleniya-2020/file-download/qj8-sbvyq8bcn5ryvreagigm8pno9rg9 (September 25, 2024) (in Russian).

End of the Table 1

1	2	3	4	5	6	7	8
Zabaikalsky Region	648	49.40	40.10	10.50	69.40	30.60	0.30
Astrakhan Region	44	43.20	52.30	4.60	69.30	30.70	1.00
Samara Region	841	48.20	42.10	9.80	69.20	30.80	0.20
Tver Region	248	47.60	42.70	9.70	69.00	31.10	0.40
Republic of Mordovia	130	46.90	43.90	9.20	68.90	31.20	0.60
Lipetsk Region	56	50.00	37.50	12.50	68.80	31.30	0.80
Irkutsk Region	792	47.00	43.30	9.70	68.60	31.40	0.20
Republic of Crimea	763	46.30	44.30	9.40	68.40	31.60	0.20
Volgograd Region	166	47.60	41.60	10.80	68.40	31.60	0.50
Tambov Region	90	44.40	47.80	7.80	68.30	31.70	0.70
Moscow Region	15,125	46.80	43.00	10.20	68.30	31.70	0.10
Krasnodar Region	1580	47.70	41.30	11.10	68.30	31.70	0.20
Khabarovsk Region	413	47.20	42.10	10.70	68.30	31.70	0.30
Kamchatka Region	96	41.70	53.10	5.21	68.20	31.80	0.60
Tula Region	97	42.30	51.60	6.20	68.00	32.00	0.60
Amur Region	75	48.00	40.00	12.00	68.00	32.00	0.70
Republic of Mari El	39	48.70	38.50	12.80	68.00	32.10	1.00
Nizhny Novgorod Region	357	47.30	41.20	11.50	67.90	32.10	0.30
Tyumen Region	346	47.70	40.20	12.10	67.80	32.20	0.30
Novosibirsk Region	2694	44.30	44.50	11.30	66.50	33.50	0.10
Kaluga Region	82	45.10	42.70	12.20	66.50	33.50	0.70
Altai Region	211	42.20	47.90	10.00	66.10	33.90	0.40
Khanty-Mansi Autonomous Okrug	444	42.30	47.30	10.40	66.00	34.00	0.30
Omsk Region	119	42.00	47.90	10.10	66.00	34.00	0.60
Penza Region	93	44.00	43.00	12.90	65.60	34.40	0.70
Leningrad Region	3041	43.10	44.70	12.10	65.50	34.50	0.10
Voronezh Region	278	44.20	42.50	13.30	65.50	34.50	0.40
Chelyabinsk Region	848	43.80	43.40	12.90	65.50	34.60	0.20
Kemerovo Region	319	43.00	44.50	12.50	65.20	34.80	0.40
Republic of Khakassia	60	46.70	36.70	16.70	65.00	35.00	0.80
Saratov Region	167	41.30	47.30	11.40	65.00	35.00	0.50
Yamalo-Nenets Autonomous Okrug	221	42.10	45.30	12.70	64.70	35.30	0.40
Perm Krai	254	40.90	46.90	12.20	64.40	35.60	0.40
Sverdlovsk Region	1501	40.60	47.10	12.30	64.20	35.80	0.20
Tomsk Region	189	41.30	45.00	13.80	63.80	36.20	0.50
Ivanovo Region	102	41.20	45.10	13.70	63.70	36.30	0.60
Kaliningrad Region	226	40.30	46.90	12.80	63.70	36.30	0.40
Komi Republic	44	36.40	54.60	9.10	63.60	36.40	1.00
Udmurt Republic	83	34.90	55.40	9.60	62.70	37.40	0.70
Krasnoyarsk Krai	380	39.70	45.50	14.70	62.50	37.50	0.30
Belgorod Region	186	34.40	52.70	12.90	60.80	39.40	0.50
Kirov Region	301	36.20	47.80	16.00	60.10	39.90	0.40
Ryazan Region	179	35.80	48.00	16.20	59.80	40.20	0.50
Vologda Region	399	35.10	48.90	16.00	59.50	40.50	0.30
Arkhangelsk Region	118	34.80	44.90	20.30	57.20	42.80	0.60
Vladimir Region	91	31.80	45.10	23.10	54.40	45.60	0.70
Total	40,111	46.12	43.22	10.66	67.73	32.27	0.03

Note: N – Number of examined individuals.

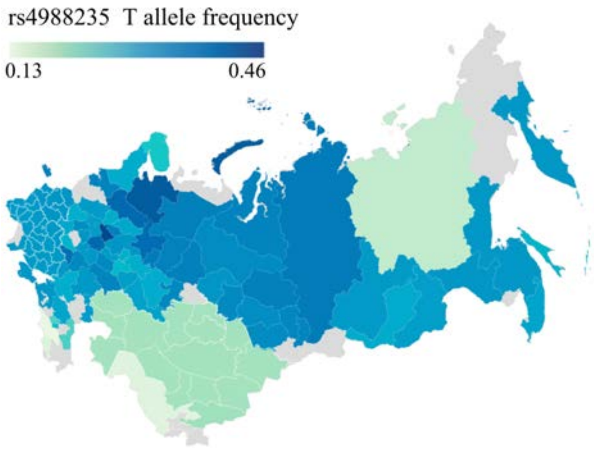

Figure. Visual representation of the prevalence of T allele across regions of the Russian Federation and neighboring ex-Soviet countries (darker regions correspond to higher prevalence of the allele (see scale), while gray regions represent areas with a small sample size (data unavailable))

The distribution of different rs4988235 genotypes in the studied neighboring ex-Soviet countries is presented in Table 2. Among these studied populations, those from Kazakhstan and Kyrgyzstan deviated from Hardy – Weinberg equilibrium, while populations from other countries were found to be in equilibrium. In Belarus and Ukraine, the frequency of the C allele was comparable to the overall Russian frequency but differed significantly from those observed in other analyzed countries (Armenia, Georgia, Kazakhstan, Uzbekistan, Kyrgyzstan) ($p < 0.05$). The frequency of the C allele in Armenia, Georgia, Kazakhstan, Uzbekistan, and Kyrgyzstan was significantly higher than the average in Russia ($p < 0.05$).

Prevalence across Russian regions. The highest prevalence of the homozygous genotype TT, associated with good lactose tolerance in adulthood, was found in Vladimir region (23 %) and Arkhangelsk region (20.3 %). Similarly, a relatively high prevalence of this genotype (~16 %) was observed in Ryazan, Vologda, and Kirov regions where the lactose intolerance-associated CC genotype was the least common. The lowest prevalence of the T allele (< 6 %) was observed in Yakutia where the C allele, linked to lactose intolerance, showed a high prevalence (> 74 %) as well as in the Caucasus regions (Dagestan, Kabardino-Balkaria, and North Ossetia).

To analyze the relationship between the frequency of the T allele and the proportion of East Slavic populations (Russians, Belarusians, Ukrainians) in various Russian regions, a correlation coefficient was calculated, which was $r = 0.5007$ for the T allele. This result indicates a moderate positive linear relationship between the frequency of the T allele and the proportion of East Slavic populations, which was statistically significant ($p < 0.05$).

The ethnic composition of Yakutia includes a relatively small proportion of Russians (32.6 %), less than 1 % of Belarusians and Ukrainians, and the Yakut population is predominant (55.3 %, based on the 2020 census published by the Federal Agency for

Table 2

Distribution of the genetic variant rs4988235 associated with lactose tolerance / intolerance in some ex-Soviet countries

Country	*N*	Genotype Frequency (%)			Allele Frequency (%)		
		CC	CT	TT	C	T	Standard Error (%)
Armenia	33	75.80	21.20	3.00	86.40	13.60	1.30
Belarus	368	46.70	42.40	10.90	67.90	32.10	0.40
Georgia	55	76.40	21.80	1.80	87.30	12.70	1.00
Kazakhstan	3011	68.20	27.80	4.10	82.10	17.90	0.10
Kyrgyzstan	144	70.10	23.60	6.30	81.90	18.10	0.60
Uzbekistan	125	74.40	24.00	1.60	86.40	13.60	0.70
Ukraine	707	48.70	40.00	11.30	68.70	31.30	0.30
Russia (RF)	40,111	46.12	43.22	10.66	67.73	32.27	0.03

Note: *N* – number of examined individuals.

Nationalities in 2023[2] [15]). Previous studies reported T allele frequency of approximately 5–6 % among the Yakuts [12, 13][3], which does not statistically differ from the 3.8 % observed in our study (noting that our research was geographically rather than ethnically focused). Thus, our findings are in agreement with earlier studies on the Yakut population.

In Dagestan, Kabardino-Balkaria, and North Ossetia, the Russian population constitutes a small proportion (19.8 % in Kabardino-Balkaria, 3.2 % in Dagestan, and 18.9 % in North Ossetia) with minimal numbers of Ukrainians and Belarusians (< 0.2 % in each region). These regions also showed a high percentage of individuals with the CC genotype. Previous studies have reported a relatively low T allele frequency (13 %) in Dagestanians [11][3], lower than the 25.6 % observed in our study. However, that study had a smaller sample size than ours.

Relatively high T allele and TT genotype frequencies were observed in Udmurtia and the Komi Republic. In Udmurtia, Russians account for 67.7 % of the population (with 0.4 % Belarusians and Ukrainians), followed by Udmurts (24.1 %) and Tatars (5.5 %). The T allele frequency in the Udmurt population was previously reported to be around 33 % [11][3], comparable to our findings (37.5 %). In the Komi Republic, Russians constitute 69.7 % (with additional 2.4 % of Belarusians and Ukrainians), and Komi people make up 22.2 %. A previous study on the Komi population reported that 14–14.5 % had the TT genotype, while 41–42 % (depending on the subpopulation) had the CC genotype associated with lactose intolerance [7]. The discrepancies between our results and the previous study may be attributed to our smaller sample size and the geographically rather than ethnically targeted sampling.

Thus, the prevalence of the rs4988235 genotypes varies across different regions of the Russian Federation, with differences observed between regions having diverse ethnic compositions. According to the correlation analysis, there is a moderate correlation between the prevalence of lactose persistence genotypes and the proportion of East Slavic population in these areas.

Until recently, no large-scale comprehensive studies have been conducted with their focus on genetic determinants of lactose intolerance in various regions of the Russian Federation. In 2023, a study was published [14] that included the analysis of genotypes from 24,439 individuals across different regions of Russia. This study, similar to ours, found a high degree of lactose intolerance genotypes in North Ossetia, Chechnya, Dagestan, and Kabardino-Balkaria. However, compared to these data, our study showed a significantly higher prevalence of the C allele in Yakutia, which is consistent with earlier studies. On the other hand, the minimum prevalence of this allele was found in the Vladimir region in our study, whereas in publication [14] it was found in the Zabaikalskii Krai where, according to our data, the distribution of the C and T alleles significantly differs from the previously identified one. For some other regions, our findings also differ from those obtained in the mentioned study. For example, the frequency of the CC genotype in the Ivanovo region was 26.2 % in the study [14] vs. 41.2 % in our data; in Murmansk region, 33.8 % in [14] vs. 59.1 % in our data; and in the Ulyanovsk region, 42.5 % in [14] vs. 52.8 % in our data. It should be noted that the nationwide sample in our study is significantly (more than 1.5 times) larger.

The prevalence of genotypes in neighboring countries compared to the Russian Federation. The prevalence of rs4988235 genotypes in neighboring ex-Soviet countries (Belarus, Ukraine, Armenia, Georgia, Kazakhstan,

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[2] Natsional'nyi sostav naseleniya [National composition of the population]. *FADN Rossii*, May 30, 2023. Available at: https://fadn.gov.ru/otkritoe-agenstvo/vserossijskaya-perepis-naseleniya-2020/file-download/qj8-sbvyq8bcn5ryvreagigm8pno9rg9 (September 25, 2024) (in Russian).

[3] Global Lactase Persistence Association Database GLAD. *UCL: University College London*. Available at: https://www.ucl.ac.uk/biosciences/gee/molecular-and-cultural-evolution-lab/global-lactase-persistence-association-database-glad (September 25, 2024).

Uzbekistan, and Kyrgyzstan) (Table 2) is generally in agreement with findings from adjacent Russian regions and the national composition of these countries. The genotype frequencies in Belarus and Ukraine are comparable to those in Russia. Meanwhile, significantly lower T allele frequencies ($p < 0.05$), associated with good lactose tolerance, were observed in Georgia, Uzbekistan, and Armenia compared to Russia, Belarus, and Ukraine.

Belarus borders Smolensk and Bryansk regions, while Ukraine borders Bryansk, Kursk, and Belgorod Oblasts. Allele frequencies in these Russian regions are comparable with those of the bordering countries. Previous studies reported T allele frequency of 23 % among Belarusians, although the sample size was smaller than in our study [13][4].

The Russian-Kazakh border spans Astrakhan, Volgograd, Saratov, Orenburg, Chelyabinsk, Kurgan, Tyumen, Omsk, and Novosibirsk regions, as well as Altai Krai and the Altai Republic, with minimal overlap in Samara region. In most of these regions, the frequency of the C allele was significantly lower than in Kazakhstan ($p < 0.05$), except in Kurgan Oblast and the Altai Republic, where sample sizes were insufficient for representativeness.

The Russian-Georgian border includes Dagestan, Ingushetia, Kabardino-Balkaria, Karachay-Cherkessia, North Ossetia-Alania, Chechnya, and Krasnodar Krai. The frequency of the C allele in Krasnodar Krai was significantly lower than in Georgia ($p < 0.05$). Differences between Georgia and samples from North Ossetia, Dagestan, and Kabardino-Balkaria were not statistically significant though there was a trend toward lower C allele frequency in the Russian regions. Data on genotypes in Adygea, Karachay-Cherkessia, Chechnya and Ingushetia are absent due to limited sample sizes.

Armenia, Kyrgyzstan, and Uzbekistan do not share a direct border with the Russian Federation. However, Armenia borders Georgia while Kyrgyzstan and Uzbekistan border Kazakhstan. The frequencies of the C and T alleles do not differ between these countries. Allele and genotype frequencies similar to those found in these countries were previously reported in the South Asian region according to the 1000 Genomes and GNOMAD databases. It is worth noting that earlier studies reported frequency of the polymorphic T allele among Uzbeks as 4 % [13], among Taiko-Uzbeks as 10 %, and among Uzbek Kazakhs as 16 % [15]. In our study, we found frequency of 13.6 % in Uzbekistan. One recent study in Armenia identified extremely low frequency (2.7 %) of the T allele [16], which is notably lower than our findings (13.6 %) and the results of an earlier study (18 %) [13][5]. To be fair, we should note the relatively small sample size (33 individuals) from Armenia in our study.

The ethnic composition of Armenia, Georgia, Kazakhstan, Uzbekistan, and Kyrgyzstan significantly differs from the ethnic composition of both the Russian Federation as a whole and, to a lesser extent, its border regions. At the same time, Belarus and Ukraine not only have a significant Russian population, but also Ukrainians and Belarusians are genetically much closer to the Russian ethnic group than to the Caucasian and Central Asian ethnicities. Therefore, the observed differences, or their absence, as well as the heterogeneity of distribution across regions of the Russian Federation, are likely related to the ethnic composition of both the Russian Federation and neighboring ex-Soviet countries.

Diagnostic and dietary implications of rs4988235. The rs4988235 polymorphism is a well-established diagnostic marker for lactose intolerance susceptibility. Genetic testing is a safer and more convenient alternative to intestinal biopsy or endoscopy as it can be performed using buccal epithelial or blood samples and

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[4] Global Lactase Persistence Association Database GLAD. *UCL: University College London*. Available at: https://www.ucl.ac.uk/biosciences/gee/molecular-and-cultural-evolution-lab/global-lactase-persistence-association-database-glad (September 25, 2024).

[5] Ibid.

avoids exposing patients to invasive procedures or potentially intolerable substances like lactose during hydrogen breath tests. Genotyping has shown good correlation with breath testing results [17, 18]. A comparison between genotyping and lactose tolerance tests (lactose loading followed by blood glucose assessment) revealed a 94 % concordance rate [19].

It is noteworthy that, despite the nearly 100 % correlation between LCT genotypes and lactose intolerance phenotypes in European populations, rs4988235 does not predict lactose persistence universally across populations [20]. Recent studies suggest that this variant arose approximately 3000 years ago and spread rapidly across Europe [21, 22]. At present, the ‘favorable’ T allele is prevalent in Europe (~ 50 % overall, reaching 60–70 % or more in northern regions) according to the 1000 Genomes. That is, the rs4988235 polymorphism is typical exactly for the European population. This genetic adaptation has penetrated some regions in the South-West Asia; however, other alleles associated with lactose tolerance are found in Africa (e.g., rs41380347) [23]. In the Middle East (the Arabia in particular), the rs41380347 (-13915 T>G) polymorphism, which is different from the European one, is prevalent [24].

Additionally, gut microbiota composition and its ability to process lactose as well as the gut ability to remove products of this metabolism may influence occurrence and intensity of lactose intolerance. In some cases, prebiotics can improve lactose tolerance since microorganisms are able to process it [25, 26]. On the other hand, unpleasant symptoms caused by milk consumption can result from not only genetic lactose intolerance but also immune reactions to milk proteins (primarily casein) [27] or some gut disorders. Therefore, differential diagnosis of lactose intolerance and genetic testing for rs4988235 are essential tools in clinical practice.

Conclusion. Based on the analysis of genotypes from more than 40,000 individuals, we determined that the average prevalence of the T allele associated with lactose tolerance was 32.3 % across Russia ranging from a minimum of 16 % in Yakutia to a maximum of 45.6 % in the Vladimir region. The frequencies of alleles and genotypes vary across regions depending on their ethnic composition. A statistically significant moderate correlation was identified between the prevalence of the T allele and the proportion of East Slavic population in a given Russian region. The distribution of genotypes and alleles in Russia significantly differs from that observed in Europe as well as in South and East Asia. We also compared allele frequencies in Russia's border regions with those of neighboring countries and found notable differences with countries in the Caucasus and Central Asia, but not with Belarus and Ukraine.

Earlier studies, although they provide certain insights into the evolution and adaptation of populations / ethnic groups to specific living conditions and their co-evolution with types of subsistence cultures, lacked sufficient data on the distribution of genotypes across the entire territory of the Russian Federation. The data from the only previously published large-scale study on the genetics of lactose intolerance in Russia [14] are partially in agreement with our findings but show discrepancies for certain regions. It is worth noting that the sample size in our study is more than 1.5 times larger than that of [14], and we also analyzed the genotypes of residents from neighboring countries.

Unfortunately, our survey did not include information on the presence or absence of clinical manifestations of lactose intolerance among participants or their ethnicity. Therefore, the evaluation of the population data was based solely on census data for the respective regions. However, our findings are generally in agreement with the ethnic composition from census data and with previously reported allele / genotype frequencies for certain ethnic groups. These data provide valuable insights into the prevalence of genetic predisposition to lactose intolerance/lactose tolerance across different regions of Russia and neighboring ex-Soviet countries.

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