3. There are statistically significant intragroup differences for most parameters of the LPO-AOP between their gradations: “normal level” and the level “above normal” and/or “below normal”.

4. The level of plasma and erythrocyte concentration of the LPO-AOP system indicators is associated to a greater extent with the presence or absence of TH than with the gender of adolescents.

5. Evaluation of the significance of altered levels of LPO-AOP system indicators as metabolic markers of the presence and/or risk of developing TH in adolescents is relevant and requires further study.

The authors declare no conflict of interest.

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COMPARATIVE ANALYSIS OF THE 5-HTTLPR POLYMORPHISM OF THE *SLC6A4* GENE IN RUSSIAN AND YAKUT POPULATIONS

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The 5-HTTLPR polymorphism of the *SLC6A4* gene plays a key role in the regulation of serotonergic transmission and may influence susceptibility to anxiety and depressive disorders. This study presents a comparative analysis of the distribution of genotypes and alleles of this polymorphism in representatives of the Russian (n = 250) and Yakut (n = 260) ethnic groups. A significantly higher prevalence of the S allele (77.7%) and the homozygous SS genotype (63.8%) was observed in the Yakut population compared to the Russian group (44.8% and 20.8%, respectively; p < 0.001). The Russian sample was characterized by a higher frequency of the L allele and the SL genotype. The identified differences reflect the high frequency of the S allele characteristic of the Indigenous peoples of Siberia and underscore the ethnic specificity of genetic factors involved in psycho-emotional regulation.

Keywords: 5-HTTLPR polymorphism, *SLC6A4* gene, genetic diversity, ethnic populations, serotonergic system.

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Introduction. Depressive and anxiety disorders constitute a significant burden of disease in global populations, affecting not only individuals but also their families and society as a whole, making them one of the key socio-economic challenges of the 21st century [11, 14]. In the context of this problem, modern genomics has laid the foundation for the transition from syndromic diagnoses to biologically based approaches in psychiatry, opening the way for personalized treatment strategies [12]. It is predicted that in the next decade, research into the genetic basis of behavioral patterns will take a central place in psychiatry: in-depth analysis of the relationships between genomic variations and neurobiological mechanisms will transform approaches to the study of mental health and optimize therapeutic strategies for anxiety and depressive disorders [5].

Modern genomic studies actively contribute to the identification of genetic factors associated with the pathophysiology of anxiety and depressive disorders. As an example, we can consider the 5-HTTLPR polymorphism of the *SLC6A4* gene encoding the serotonin transporter. Despite the polygenic nature of mental disorders, the study of this gene demonstrates how individual genetic variations can affect neurobiological mechanisms associated with the regulation of emotions and stress resistance [3, 5]. Serotonin plays a key role in the regulation of mood, emotions and cognitive functions. The serotonin transporter (SERT), encoded by the *SLC6A4* gene, regulates the reuptake of the neurotransmitter into the synaptic cleft, affecting the duration and intensity of serotonergic transmission [7]. The 5-HTTLPR polymorphism, associated with variation in the length of the gene promoter region, modulates SERT activity: the short allele (S) is associated with reduced expression of the transporter, which may increase vulnerability to stress and increase the risk of depressive and anxiety disorders [13].

Meta-analyses demonstrate ethnic variability in the distribution of 5-HTTLPR alleles. It is known that the L allele is more common in Caucasian populations, while the S allele predominates in East Asian groups [15]. These differences may explain ethnic-specific patterns of response to antidepressants, such as selective serotonin reuptake inhibitors (SSRIs) [9]. However, data on indigenous peoples of Siberia, including the Yakuts, remain limited, making it difficult to develop personalized approaches in the region. The study of genetic characteristics of populations is an important aspect in the field of medicine and biology, since it allows us to identify ethnic specificity of predisposition to various diseases [6].

The present study focuses on the comparison of Russian (Caucasoid) and Yakut (indigenous peoples of Siberia) populations. Yakuts, with a unique gene pool formed in conditions of extreme climate and isolation, are of particular interest for the study of genetic adaptation and its relationship with mental health [4]. The work fills the gap in data on Siberian ethnic groups and expands the understanding of the role of 5-HTTLPR in the context of global genetic diversity. It is assumed that the Yakut population will demonstrate allele frequencies similar to East Asian groups, in contrast to Russians, which reflects their phylogenetic proximity to Asian ancestors. This may have practical significance for predicting the effectiveness of pharmacotherapy and developing ethnospecific guidelines in psychiatry.

The aim of this study was to investigate the differences in the distribution of genotypes (SS, SL, LL) and alleles (S, L) of the 5-HTTLPR polymorphism of the *SLC6A4* gene between the ethnic groups of Russians and Yakuts.

Materials and methods of the study. The work was carried out with the written informed consent of all participants. The survey program covered socio-demographic parameters (including health status, bad habits, marital status and hereditary diseases) together with anthropometric measurements. Participants independently filled out questionnaires individually during scientific expeditions to the regions of the Republic of Sakha (Yakutia). FSBSI «Yakut Scientific Center for Complex Medical Problems» (YSC CMP) using the Yakutia Genome Scientific Research Institute (registration number USU_507512). Genomic studies and bioinformatics analysis were performed by the staff of the Laboratory of Hereditary Pathology of the YSC CMP. The study sample included 510 people (250 representatives of the Russian and 260 Yakut ethnic groups) with confirmed ethnicity in three generations. The analysis included data from patients who gave consent for genetic studies in the period 2018–2024.

For molecular genetic analysis, DNA was extracted from whole blood using a commercial Newteryx DNA extraction kit (Russia, Yakutsk) according to the manufacturer's instructions. DNA concentration in each sample was determined on an Implen Nano Photometer spectrophotometer (Germany). Analysis of the 5-HTTLPR (44-BP INS / DEL) polymorphism of the *SLC6A4* gene was performed by polymerase chain reaction (PCR). Amplification of the gene region containing the polymorphic variant was carried out using primers manufactured by Lumiprob RUS LLC, Moscow. Reaction mixture: forward and reverse primer, 1 µl each; buffer - 2.5 µl; betaine - 5 µl; dNTPs - 4 µl; Taq polymerase - 0.25 µl; deionized water - 10.25 µl and DNA - 1 µl. The conditions for carrying out the amplification are presented in Table 1.

Interpretation of genotyping results was performed based on different band templates for the genotypes SS – 376 bp; SL – 420 bp, 376 bp; LL – 420 bp (Figure).

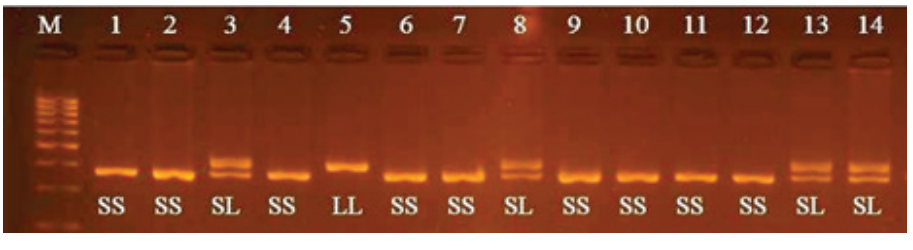
Statistical analysis of the obtained research results was performed using the program «Office Microsoft Excel 2010». Correspondence of genotype distribution to expected values of Hardy-Weinberg equilibrium and comparison of frequencies of allelic variants/genotypes were performed using the criterion X (chi-square) by the Pearson method for contingency tables 2x2, calculation of odds ratio (OR), 95% confidence interval (95% CI). Differences were considered statistically significant at $p<0.05$.

Results and discussion. Analysis of the distribution of alleles and genotypes of the 5-HTTLPR polymorphism of the *SLC6A4* gene showed significant differences in the distribution of genotypes and alleles between the groups (Table 2). In the sample of Russians, a significant difference ($p < 0.05$) in the frequen-

Table 1

Conditions for conducting PCR analysis

Gene	Primer sequence	Length of amplicon (b.p.)	Annealing temperature
SLC6A4	F: 5'-GGACCGCAAGGTGGGCGGGA-3' R: 5'-ATGCCAGCACCTAACCCCTAATGT-3'	SS – 376 b.p.; SL - 420 b.p., 376 b.p.; LL – 420 b.p.	62°C



Electropherogram of the amplification product of the SLC6A4 gene region in 4% agarose gel: lanes No. 1, 2, 4, 6, 7, 9, 10, 11, 12 – SS genotype; 3, 8, 13 and 14 – SL genotype; 5 – LL genotype; M – Step100 marker

Table 2

Distribution of the frequency of alleles and genotypes of the 5-HTTLPR polymorphism of the *SLC6A4* gene

Genotypes and alleles	Russians (n = 250)				p	Yakuts (n = 260)				p
	Women (n = 146)		Men (n = 104)			Women (n = 69)		Men (n = 191)		
	n	%	n	%		n	%	n	%	
SS	25	17.1	27	26.0	0.124	39	56.5	127	66.5	0.184
SL	69	47.3	51	49.0	0.882	18	26.1	54	28.3	0.849
LL	52	35.6	26	25.0	0.100	12	17.4	10	5.2	0.005
S	119	40.8	105	50.5	0.039	96	69.6	308	80.6	0.011
L	173	59.2	103	49.5		42	30.4	74	19.4	
X^2	0.066		0.038		-	10.17		1.722		-
p*	0.797		0.845		-	0.001		0.190		-

Note. p is the significance with the Yates correction, X2 is the Chi square according to Hardy Weinberg, p* is the significance according to Hardy Weinberg.

cy of alleles was revealed. In both samples, women had a higher frequency of the homozygous genotype LL than men (36% versus 25% and 17% versus 5%). But it is possible that the significant differences ($p < 0.05$) in the frequencies of genotypes and alleles between men and women in the Yakuts are associated with a smaller number (three times) of women studied.

When comparing the distribution of alleles and genotypes of women with women and men with men, significant differences ($p < 0.05$) were found between the samples. The Yakuts more often have the SS genotype (56–66% versus 17–26%) and the S allele (70–80% versus 41–50.5%), while among Russians, both women and men are dominated by carriers of the heterozygous SL genotype (47–49% versus 26–28%).

The analysis of the distribution of alleles and genotypes, as well as the calculation of the odds ratio between the samples of Russians and Yakuts, is presented in Table 3. These differences indicate a significant population diversity in the distribution of this polymorphism. The SS genotype is more common among Yakuts (64% vs. 21%, OR=6.72; $p <0.001$) and the S allele (78% vs. 45%; OR=4.29), while the SL genotype (48% vs. 28%, OR=0.41; $p <0.001$) and the allele prevail among Russians. L (55% vs. 22%; OR=0.23; $p <0.001$). The data obtained highlight the ethnic heterogeneity in the structure of the 5-HTTLPR polymorphism, which may influence differences in the neuropsychiatric profiles of populations.

According to the data in Table 2, the distribution of genotypes in Russians (as a whole, as well as separately in men and women) does not deviate from the Hardy–Weinberg equilibrium ($p^* > 0.05$). At the same time, Yakuts, especially in the subgroup of women, show a significant deviation, which is also confirmed in Table 3. At the same time, the Yakut balance is shifted towards homozygosity for the short S allele (SS genotype). Especially in women, this bias may be due to a smaller sample size, which increases sensitivity to statistical fluctuations.

Environmental and historical factors have played a key role in shaping population differences. Scientific research shows that the centuries-old habitation of populations in specific environmental conditions has determined not only their appearance and cultural characteristics, but also their morphofunctional characteristics, including metabolic adaptations.

Table 3

Frequency distribution of alleles and genotypes of the 5-HTTLPR polymorphism of the *SLC6A4* gene with odds ratio (OR)

Genotypes and alleles	Russians		Yakuts		OR (CI 95%)	p
	n	%	n	%		
SS	52	20.8	166	63.8	6.724 (4.523-9.997)	<0.001
SL	120	48	72	27.7	0.415 (0.287-0.599)	<0.001
LL	78	31.2	22	8.5	0.204 (0.122-0.340)	<0.001
S	224	44.8	404	77.7	4.291 (3.271-5.630)	<0.001
L	276	55.2	116	22.3	0.233 (0.178-0.306)	<0.001
X^2	0.218		10.514		-	-
*p**	0.641		0.001		-	-

Note. OR (95% CI) is the odds ratio with a 95% confidence interval, p is the Yates–adjusted significance, Chi is the Hardy Weinberg square, and p* is the Hardy Weinberg significance.

Table 4

Frequency of the S allele among Russian populations in various regions of Russia

Population (region)	Sample size (n)	The frequency of the S allele	A source
Russians (Vologda)	47	0,36	[7]
Russians (Moscow and Krasnodar)	127	0,38	[1]
Russians (Saint Petersburg)	908	0,38	[3]
Russians (Moscow and the Moscow region)	120	0,39	[2]
Russians (Arkhangelsk)	33	0,41	[10]
The Russians (Novosibirsk)	121	0,43	[13]
Russians (Yakutia)	250	0,45	This work

A.S. Gureev et al. (2014) found that the frequency of the S allele in African populations is lower than in other regions of the world [3]. An interesting fact is that the frequency of the S allele increases as populations move to the east of Asia, both in the northern and southern regions, reaching maximum values among the Japanese and Yakuts. These data emphasize the role of long-term adaptation to environmental conditions, including climate, nutrition, and photoperiodism, in the formation of population-specific traits. Thus, the predominance of the S-allele in Yakuts may be associated with evolutionary adaptation to extreme climatic conditions [13]. Decreased expression of the serotonin transporter (SERT) in S-allele carriers theoretically increases the level of serotonin in the synaptic cleft, which may contribute to resistance to chronic stress typical of the conditions of the Far North [4, 13].

Given the wide area of Russian settlement, from the European part to the northeast of Eurasia, significant regional genetic variability can be expected. In this regard, a comparative analysis of the frequency of the S-allele in the sample of Russians studied by us was carried out with data published in the literature from other regions of Russia (Table 4).

As can be seen from Table 4, the frequency of the S allele increases from west to east: from 0.36 in Vologda to 0.45 in Yakutia, which may be due to adaptation to different climatic and environmental conditions.

The revealed differences in the distribution of genotypes of the 5-HTTLPR *SLC6A4* gene between Russians and Yakuts are consistent with the population distribution features previously described in the literature. The Yakuts revealed the dominance of the SS genotype (63.8%) and the S-allele (77.7%), which corresponds to the high-frequency profiles observed in East Asian populations such as the Japanese (up to 80-85%) [3, 15]. At the same time, the data obtained reflect the unique features of the genetic structure of the indigenous population of Siberia, formed under the influence of factors of isolation, adaptation to extreme climate and demographic history of the region. The lowest S-allele frequencies (<25%) were found in African and African-American populations [3], which highlights the pronounced ethnic variability of this polymorphism. [3, 10]. These findings highlight the role of geography and ethnicity in shaping genetic patterns. The results obtained in this study are consistent with previously obtained data from A.N. Savostyanov et al. (2021), which also demonstrated a high frequency of the S-allele in the indigenous peoples of Siberia [13].

The revealed differences emphasize the need for an ethnospecific approach in psychiatry. Recent studies on the relationship of the 5-HTTLPR polymorphism with the effectiveness of therapy emphasize the ethnic conditionality of pharmacogenetic reactions. So, in a study by Y.J. Jang. and co-authors. (2021) found that carriage of the SS genotype, common among Asian populations, is associated with reduced efficacy of selective serotonin reuptake inhibitors (SSRIs), while the L-allele is considered prognostically significant in Caucasians [8]. These conclusions are consistent with the results of D. Jarčušková et al. (2024), which showed that in patients of the Slovak population, carriers of the short allele (S) demonstrated a statistically significantly lower therapeutic response to SSRI treatment in major depressive disorder (OR = 0.42; 95% CI: 0.20–0.85; p = 0.015) [9].

Conclusion. These data are of key importance for understanding the ethnospecific risks of developing pathologies associated with the serotonergic system, such as depressive and anxiety disorders. The results of the study can be used to optimize the diagnosis and treatment of mental disorders in multiethnic regions such as the Republic of Sakha (Yakutia). Taking into account the genetic characteristics of populations helps to reduce the risk of ineffective therapy and side effects, which corresponds to the principles of personalized medicine. Further work in this area will expand the understanding of the interaction of genetic and environmental factors in shaping human health.

The authors declare that there is no conflict of interest.

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