dian 64.375 dB) also has a significantly (p=0.02268) less hearing loss (moderate phenotype) compared to the phenotypically more "severe" reference genotype c.[35delG];[35delG] (median 115.0 dB) (Table 2). However, it should be noted that earlier on a larger sample of patients with genotype c.[-23+1G>A];[-23+1G>A], with a median of 85.41 dB (which corresponds to IV degree of hearing loss), it was shown wide individual variability of hearing thresholds, ranging from mild hearing loss to deafness [1].

Conclusion. Thus, the analysis of the state of hearing in individuals with mutations in the *GJB2* (Cx26) gene in Buryatia revealed the following:

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ASSOCIATION OF POLYMORPHISMS OF THE GENES *HTR2A* AND *5-HTT* WITH SMOKING IN YAKUTS

Tobacco smoking is the most common form of addiction worldwide. The aim of our study was to determine whether the rs6311 polymorphisms of the *HTR2A* gene and the 5HTTLPR and rs25531 polymorphisms of the *5-HTT* gene are associated with smoking in the Yakut population. The study involved 223 people, including 115 smokers and 108 non-smokers. The results of the analysis of the relationship between the rs6311 polymorphism of the *HTR2A* gene and smoking showed that in the group of smokers, allele A was somewhat more common than in the group of non-smokers (OR - 1.138, 95% CI = [0.742-1.138]). Analysis of the distribution of alleles and genotypes of the 5-HTTLPR polymorphism of the *5-HTT* gene showed the predominance of the short S allele (74.8–89.4%) and the SS genotype (61.7–81.5%) in both samples. Smokers had a significantly ($p<0.05$) higher frequency of the risk allele L (OR -2.830, 95% CI= [1.674 -4.783]) compared to non-smokers. When analyzing the 5-HTTLPR and rs25531 polymorphisms grouped into groups, it was found that the frequency of the L' allele was four times higher in the sample of smokers ($p<0.001$) than in the sample of non-smokers (OR -4.844, 95% CI = [2.503-9.372]). An analysis of the distribution of combinations of genotypes of both studied genes showed the predominance of people with a combination of GG genotypes of the *HTR2A* gene and S'S' of the *5-HTT* gene, which showed a protective effect on smoking (OR -0.550, 95% CI = [0.319-0.948]). A significant association with smoking was shown by a combination of heterozygous genotypes AG of the *HTR2A* gene and L'S' of the 5-HTT gene (OR -13.637, 95% CI= [1.752-106.144]). This study established a significant association of *5-HTT* gene polymorphisms with smoking in the Yakut population. In connection with the equivalent serotonin expression of the S and LG alleles, 5HTTLPR and rs25531 polymorphisms, it is more informative to carry out their generalized analysis.

Keywords: nicotine addiction, smoking, 5-HTT, HTR2A, rs6311, 5HTTLPR, rs25531, Yakut population

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Introduction. Nicotine addiction is the most common and severe disease, included in the ICD-10 F17 group of diseases - "Mental and behavioral disorders associated with the use of psychoactive substances" [1]. Dependence arises on the basis of the entry of nicotine into the reaction with alpha-4-beta-2-acetylcholine receptors in the brain, which leads to the formation of a steady craving for tobacco, withdrawal syndrome that develops when smoking is stopped, and a number of side effects.

Nicotine dependence is closely related to psychological and social factors [2, 5, 6]. Individual differences in proneness to addictive behaviors, including nicotine addiction, are partly mediated by genetic factors. Current estimates of the heritability of all major addictive disorders range from 40% to 80% [3]. The share of genetic factors of nicotine addiction accounts for 50 to 75% [9, 12].

One of the effects of nicotine is to alter serotonin levels, hence genes encoding receptors or transporters involved in serotonergic pathways are potential candidates in the mechanism of nicotine addiction [18].

The *HTR2A* gene encodes the serotonin receptor, which is the key to the monoaminergic regulation of the body, which determines the biological functions and behavior of a person. The polymorphic variant rs6311 (-1438 A>G) is potentially associated with impaired efficiency of post-transcriptional processes and is considered a risk factor for neuropsychiatric and cognitive pathologies [20]. The presence of the A allele increases the transcriptional activity of the gene; several studies have shown that this allele is associated with smoking [13, 14, 15, 16].

The 5-HTTLPR polymorphic region (rs4795541) is a functional insertion/deletion polymorphism of 44 base pairs in the promoter region of the serotonin transporter gene, *5-HTT* [7]. This polymorphism was identified by two allelic variants, long (L with 16 repeats) and short (S with 14 repeats) forms, which affect the transcriptional efficiency of the *5-HTT* gene. The rs25531 polymorphism is within this polymorphism and results in two higher-expressing L-LA allele variants and lower-expressing LG variants—indicating that 5-HTTLPR may be functionally triallelic rather than biallelic [19]. Despite a large number of association studies of this polymorphism with nicotine dependence, data on which 5-HTTLPR allelic variant contributes to smoking are ambiguous [12].

The aim of our study was to determine whether the rs6311 polymorphisms of the *HTR2A* gene and the 5HTTLPR and rs25531 polymorphisms of the *5-HTT* gene are associated with smoking in the Yakut population.

Material and research methods. The experimental part of the study was carried out in the Laboratory of Hereditary Pathology of the Department of Molecular Genetics of the Yakut Scientific Center for Complex Medical Problems (YSC CMP). The material of the study was DNA samples from the collection of biomaterial (DNA) of the populations of the Republic of Sakha (Yakutia) YSC CMP, using the UNU "Genome of Yakutia" (reg. No. USU_507512). The study included participants who filled out a questionnaire approved by the Local Committee on Biomedical Ethics at the YSC CMP and voluntarily signed an informed consent to conduct a genetic study.

A total of 223 DNA samples of volunteers without chronic diseases (56 women and 167 men) of Yakut nationality were studied, the average age of which was 46 ± 0.08. For molecular genetic analysis, genomic DNA samples were isolated from whole blood using a Newteryx commercial DNA isolation kit (Yakutsk, Russia).

The study of polymorphisms was carried out by polymerase chain reaction (PCR) followed by restriction fragment length analysis (RFLP). The conditions for amplification and restriction are presented in table 1.

Statistical analysis of the results of the study was carried out using the program: "Office Microsoft Excel 2010", "Statistica 8.0". The frequencies of rs6311, 5-HTTLPR and rs25531 were determined by direct counting.

When analyzing the contingency of the frequency of an unfavorable allele with smoking, a four-field contingency table and a Yates-adjusted χ-square test were used. The following formula was used to calculate the odds ratio:

$$OR = \frac{A*D}{B*C}$$

where OR is the odds ratio; A, B, C, D are the number of observations in the cells of the contingency table. To assess the significance of the odds ratio, the boundaries of the 95% confidence interval (95% CI) were calculated. Results were considered significant at $p<0.05$.

Results and discussions:

An analysis of the distribution of allele and genotype frequencies of the polymorphic variant of the HTR2A gene (rs6311) in the group of smokers and non-smokers did not reveal significant differences; the G allele and the homozygous GG genotype prevailed in both groups (Table 2).

The results of the analysis of the relationship between the rs6311 polymorphism of the HTR2A gene and smoking showed that in the group of smokers allele A was somewhat more common than in the group of non-smokers (OR - 1.138; 95% CI = [0.742-1.138]), however, the significance of the differences was not significant (p=0.628) and the confidence interval showed a wide range.

Analysis of the distribution of alleles and genotypes of the 5-HTTLPR polymorphism of the 5-HTT gene showed the predominance of the short S allele

Table 1

Conditions for PCR-RFLP analysis

Polymorphism	Primer structure	Amplicon length	Annealing conditions	Restriction enzyme	Interpretation
rs6311	F:AACCAACTTATTTCCTACCAC R:AAGCTGCAAGGTAGCAACAGC	469 bp	57°C	*Msp* I	Genotype AA – 469 bp; Genotype GG – 243+226 bp; Genotype AG - 469, 243+226 bp
5-HTTLPR	F:GAGGGACTGAGCTGGACAAC-CCAC R:GGCGTTGCCGCTCTGAATGC	486 bp, 529 bp	62°C	-	Allele S - 486 bp, Allele L - 529 bp
rs25531				*Msp* I	Genotype LA -125+62+343 bp; Genotype LG - 125+62+ 174+167 bp Genotype SA - 125+62+ 299 bp

Примечание. п.н. – пар нуклеотидов.

Table 2

Calculation of the odds ratio of the rs6311 polymorphism of the HTR2A gene with smoking

Genotype and Allele	Smokers n (%)	non-smokers n (%)	X^2	OR (95 % CI)	P value
Genotype AA	4 (3.5)	4 (3.7)	0.650	1.138 (0.742-1.746)	0.723
Genotype AG	53 (46.1)	44 (40.7)			
Genotype GG	58 (50.4)	60 (55.6)			
Allele A	26.5 ± 0.029	24.1 ± 0.029	0.235		0.628
Allele G	73.5 ± 0.029	75.9 ± 0.029			

* n - is the number; Chi-square test with Yates correction; OR is the odds ratio; CI - confidence interval

Table 3

Calculation of the odds ratio of biallelic 5-HTTLPR polymorphism with smoking

Genotype and Allele	Smokers n (%)	non-smokers n (%)	X^2	OR (95 % CI)	P value
Genotype LL	14 (12.2)	3 (2.8)	12.323	2.830 (1.674-4.783)	0.002
Genotype SL	30 (26.1)	17 (15.7)			
Genotype SS	71 (61.7)	88 (81.5)			
Allele L	25.2 ± 2.863	10.6± 2.099	14.943		0.000
Allele S	74.8 ± 2.863	89.4± 2.099			

Table 4

Calculation of the odds ratio of grouped 5-HTTLPR and rs25531 polymorphisms with smoking

Genotype and Allele	Smokers n (%)	non-smokers n (%)	X^2	OR	P value
Genotype L'L'	11 (9.6)	1 (0.9)	20.204	4.844 (2.503-9.372)	0.000
Genotype L'S'	29 (25.2)	10 (9.3)			
Genotype S'S'	75 (65.2)	97 (89.8)			
Allele L'	22.2 ± 2.739	5.6 ± 1.559	24.009		0.000
Allele S'	77.8 ± 2.739	94.4 ± 1.559			

Table 5

Distribution of the combination of genotypes of the HTR2A gene and the 5-HTT gene with the calculation of the odds ratio to smoking

HTR2A	*5-HTT*	Smokers n (%)	non-smokers n (%)	X^2	OR	P value
AA	L'L'	2 (1.7)	0 (0.0)	0.444	-	0.506
AA	L'S'	1 (0.9)	0 (0.0)	0.001	-	0.975
AA	S'S'	1 (0.9)	4 (3.7)	0.953	0.228 (0.025-2.074)	0.33
AG	L'L'	3 (2.6)	0 (0.0)	1.228	-	0.268
AG	L'S'	13 (11.3)	1 (0.9)	8.508	**13.637 (1.752-106.144)**	0.004
AG	S'S'	37 (32.2)	43 (39.8)	1.101	0.717 (0.414-1.242)	0.295
GG	L'L'	6 (5.2)	1 (0.9)	2.11	5.890 (0.697-49.750)	0.147
GG	L'S'	15 (13.0)	9 (8.3)	0.843	1.650 (0.690-3.946)	0.359
GG	S'S'	37 (32.2)	50 (46.3)	4.094	**0.550 (0.319-0.948)**	0.044

(74.8–89.4%) and the SS genotype (61.7–81.5%) in both samples (Table 3).

Smokers had a significantly ($p<0.05$) higher frequency of the risk allele L (OR -2.830; 95% CI= [1.674 -4.783]) compared to non-smokers.

Due to the equivalent serotonin expression of the S and LG alleles, the 5HTTLPR and rs25531 polymorphisms, and a more accurate analysis of the association with smoking, the LGLG, LGS, and SS genotypes were combined into the S'S' genotype group. The LALA genotype into the L'L' genotype, and the LALG and LAS genotypes into the L'S' group (Table 4).

When analyzing the 5-HTTLPR and rs25531 polymorphisms grouped into groups, it was found that the L' allele frequency ($p<0.001$) was four times higher in the sample of smokers than in the sample of non-smokers (OR -4.844; 95% CI = [2.503-9.372]).

To study the relationship of both genes (HTR2A and 5-HTT) with smoking, in samples of smokers and non-smokers, various combinations of genotypes were analyzed (Table 5).

An analysis of the distribution of genotype combinations showed the predominance of people with a combination of GG genotypes of the HTR2A gene and S'S' 5-HTT gene, which showed a protective effect on smoking (OR - 0.550; 95% CI = [0.319-0.948]). A significant association with smoking was shown by a combination of heterozygous genotypes AG of the HTR2A gene and L'S' of the 5-HTT gene (OR -13.637; 95% CI= [1.752-106.144]).

Due to the different frequency of occurrence of the studied polymorphisms in different ethnic samples, we cannot statistically reliably state that the relationship between these polymorphisms and smoking that we found is suitable for all people. This pilot experiment allows us to draw only small conclusions on the study of the above genes in the Yakut population. Thus, our results are consistent with the studies of Lerman C et al. (2000) and Ishikawa H et al. (1999), who also found a protective effect of the S allele on smoking [16, 17]. In studies by Siemińska A. et al. (2008) among the Polish population, they did not find a link between 5-HTTLPR polymorphism and smoking [18]. Many researchers have studied this polymorphism with addictive behavior, and in the works of Stefan Bleich et al. (2007) they found an association of the L – allele with obsessive-compulsive craving for alcohol [19]. In a study by Gerra G et al (2005), the frequency of the short S genotype was higher in smokers than in non-smokers [20].

Conclusion. This study established a significant association of 5-HTT gene polymorphisms with smoking in the Yakut population. In connection with the equivalent serotonin expression of the S and LG alleles, 5HTTLPR and rs25531 polymorphisms, it is more informative to carry out their generalized analysis. For the rs6311 polymorphism of the HTR2A gene, no statistically significant association with smoking was found, probably due to the fact that the frequency of the A allele has a relatively rare occurrence, which must be taken into account and, possibly, later validation of the population is required. Despite the discovery of an association between 5-HTT gene polymorphisms and smoking, additional studies are required in similar populations but with larger sample sizes to further explore interactions with other candidate genes and addictive behaviors.

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