Association of the circadian rhythm gene ARNTL/BMAL1 with personal anxiety among people aged 25–64 (WHO international program "MONICA-psychosocial (MOPSY)")

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Objective: *to study associations between personal anxiety (PA) and single nucleotide polymorphism rs2278749 of the ARNTL gene among individuals aged 25–64 years living in Novosibirsk.*
Material and methods. *Under the WHO program "MONICA-psychosocial (MOPSY)", a random representative sample of the population aged 25–64 years in Novosibirsk was studied (725 men, mean age – 43.4±0.4 years, response – 71.3%; 710 women, mean age – 44.8±0.4 years, response – 72%). The general examination was carried out according to standard methods included in the protocol of the WHO program.*
To assess PA, a form of Spielberger self-assessment scales was proposed. Every second respondent underwent genotyping of the studied polymorphisms of the ARNTL gene.
Results. *The C/C genotype of the ARNTL gene was found in the general population in 60.7% of individuals (in 61.2% of men and 60.5% of women); the C/T genotype was found in 34.1% of individuals (in 35.1% of men and 33.5% of women) and the T/T genotype in the general population was found in 5.2% of individuals (in 3.7% of men and 6% women). The probability of PA development among carriers of the CT+TT genotypes of the ARNTL gene was 2 times higher ($p<0.05$) in the general population and 2.4 times ($p<0.05$) among women; among T allele carriers, it was 1.8 times higher ($p<0.05$) in the population and 2.1 times ($p<0.05$) among women. Carriers of the C/T genotype of the ARNTL gene were 30.3% more likely to believe that they almost always take everything too personally ($p=0.024$). Carriers of the C/T genotype (21%) almost always, and carriers of the T/T genotype (27.8%) often would like to be as happy as others ($p=0.031$). The answer "I often feel satisfaction" prevailed (38.2%) among the carriers of the C/C genotype, and the answer "Almost never feel satisfaction" among the carriers of the C/T genotype (5.9%) of the ARNTL gene ($p=0.044$) .*
Conclusion. *It was found that the C/C genotype of the ARNTL gene was the most common in the population; the probability of PA occurrence among carriers of CT+TT genotypes, carriers of the T allele is 2 times higher than in carriers of other genotypes of the ARNTL gene.*

Keywords: *personal anxiety; gene ARNTL/BMAL1; population.*
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Introduction

Circadian rhythms are approximately 24-hour fluctuations in behavioral or physiological processes that allow the body to anticipate routine environmental changes and prepare for the appropriate alignment in order to adapt to these changes. Circadian rhythms are generated by the internal clock, the main pacemaker of which is located in the suprachiasmatic nuclei of the anterior hypothalamus. This internal clock is synchronized with the external 24-hour clock, following time-giving cues, primarily the daily light-to-dark transitions in the habitat. The master circadian clock coordinates peripheral oscillators that keep a number of physiological functions in sync, such as hormone release, body temperature, cardiovascular function, and physical activity. Recently, there has been increasing interest in the impact of these rhythm disturbances on health [1]. At the molecular level, circadian rhythms are generated by a network of proteins. The CLOCK protein [2] binds to the ARNTL (BMAL1) protein [3]. The NPAS2 protein [4] can replace the CLOCK and ARNTL2 (BMAL2) proteins instead of ARNTL [5]. Paired CLOCK/NPAS2-ARNTL/ARNTL2 heterodimers then activate the transcription of their target genes [6].

In the scientific literature, genetic variations in the genes of the circadian clock are usually examined in connection with sleep disorders [7]. However, desynchronization of circadian rhythms can also lead to other serious disorders, such as neuropsychiatric diseases, including mood disorders, neurodegenerative diseases, metabolic disorders, dysfunction of the cardiovascular system, cancer, and dysregulation of the immune system [8].

With regard to the above diseases, certain variants of the *ARNTL* gene are considered in connection with mood disorders [9], however, in some cases, the above associations are contradictory [10–11], and therefore, the established links between circadian clock gene polymorphisms and predisposition to a disease remain incomplete. Therefore, we hypothesized that genetic vari-

ability in the key regulators of circadian rhythms, the *ARNTL* genes, may contribute to the risk of developing anxiety.

Based on the foregoing, **the aim** of our study was to investigate the association between the single nucleotide polymorphism rs2278749 of the ARNTL gene and personal anxiety in the open population aged 25–64 years in Novosibirsk.

Materials and methods

Within the framework of the budget topic Reg. No. 122031700094-5, a representative sample of the population of 25–64 years old in Novosibirsk was studied (men n=725, mean age 43.4±0.4 years, response – 71.3%; women n=710, mean age 44.8±0.4 years, response – 72%). General examination was carried out according to the standard methods included in the WHO program "MONICA-psychosocial (MOPSY)" [12].

The participants of the screening, in addition to the standard epidemiological examination, underwent psychological testing, which determined the level of personal anxiety (PA). To assess PA, a form of Spielberger self-assessment scales modified by Yu.L. Khanin and consisting of 20 statements was proposed. [13]. Respondents completed the psychosocial questionnaire on their own. For each statement, 4 gradations were provided reflecting the degree of anxiety intensity: 1 – "almost never", 2 – "sometimes", 3 – "often", 4 – "almost never". When analyzing the results of self-assessment, it was taken into account that the overall final indicator could be within the range from 20 to 80 points. At the same time, the higher the final indicator, the higher the level of PA. When interpreting the indicators, the following approximate estimates of anxiety were used: up to 30 points – low PA (LPA), 31–44 points – moderate PA (MPA), 45 and more – high PT (HPA). The questionnaire underwent strict standardization and quality control testing in specialized European centers [14]. For every second respondent, genotyping of the studied gene polymorphisms was carried out in the laboratory of molecular genetic research of the Research Institute of Therapy and Preventive Medicine – a branch of the Institute of Cytology and Genetics of the Siberian Branch of the Russian Academy of Sciences, Novosibirsk (head of the laboratory, Doctor of Medical Sciences Maksimov V.N.).

Statistical analysis was carried out using the SPSS software package version 11.5 [15]. The distribution of genotype frequencies for the studied polymorphic loci was checked for compliance with the Hardy–Weinberg equilibrium. To test the statistical significance of differences between the groups, Pearson's χ^2 chi-square test was used [16]. To assess the relative risk of developing the disease by the method of logistic regression, genetic (genotypes and alleles) parameters were used as covariates (factors), PA was the dependent variable [17]. Reliability in all types of analysis was accepted at a significance level of $p \leqslant 0.05$ [15–17].

Table 1. *Frequency of occurrence of alleles, genotypes of the single nucleotide polymorphism rs2278749 of the ARNTL gene in the population aged 25–64 years in Novosibirsk, n (%)*

Frequency, n (%)	Allele		Genotype			Compliance with the equilibrium of Hardy–Weinberg
	C	T	C/C	C/T	T/T	
General Population	543 (77.8)	155 (22.2)	212 (60.7)	119 (34.1)	18 (5.2)	χ^2=0.2622 C allele frequency = 0.7888; T allele frequency = 0.2112
Men	211 (78.7)	57 (21.3)	82 (61.2)	47 (35.1)	5 (3.7)	χ^2=0.1927 C allele frequency = 0.795; T allele frequency = 0.205
Women	332 (77.2)	98 (22.8)	130 (60.5)	72 (33.5)	13 (6.0)	χ^2=0.9394 C allele frequency = 0.7851; T allele frequency = 0.2149

Results

Table 1 shows the frequencies of alleles, genotypes of the single nucleotide polymorphism rs2278749 of the *ARNTL* gene in the open population aged 25–64 years. The most common genotype in all groups was the C/C genotype of the *ARNTL* gene: in the general population it was found in 60.7% of individuals, among men in 61.2%, and among women in 60.5%. The heterozygous C/T genotype was found in 34.1% of individuals (35.1% of men and 33.5% of women). The T/T genotype was the least common in the general population – 5.2% of individuals (3.7% of men and 6% of women) (Table 1)

Table 2. *The frequency of occurrence of genotypes and alleles of the single nucleotide polymorphism rs2278749 of the ARNTL gene in the population aged 25–64 years in Novosibirsk in comparison with the level of anxiety, n (%)*

Indicator	General population			Male			Female	
	LPA	MPA	HPA	LPA	MPA	HPA	MPA	HPA
Genotype:								
C/C	4 (100.0)	57 (59.4)	151 (60.6)	4 (100.0)	36 (60.0)	42 (60.0)	21 (58.3)	109 (60.9)
C/T	0	33 (34.4)	86 (34.5)	0	20 (33.3)	27 (38.6)	13 (36.1)	59 (33.0)
T/T	0	6 (6.2)	12 (4.8)	0	4 (6.7)	1 (1.4)	2 (5.6)	11 (6.1)
Total	4 (100)	96 (100)	249 (100)	4 (100)	60 (100)	70 (100)	36 (100.0)	179 (100.0)
	χ^2=4.29; df=4; p>0.05			χ^2=6.673; df=4; p>0.05			χ^2=0.137; df=2; p>0.05	
Allele:								
C	8 (100.0)	147 (76.6)	388 (77.9)	8 (100.0)	92 (76.7)	111 (79.3)	55 (76.4)	277 (77.4)
T	0	45 (23.4)	110 (22.1)	0	28 (23.3)	29 (20.7)	17 (23.6)	81 (22.6)
Total	8 (100.0)	192 (100.0)	498 (100.0)	8 (100)	120 (100.0)	140 (100.0)	72 (100.0)	358 (100.0)
	χ^2=4.188; df=2; p>0.05			χ^2=4.151; df=2; p<0.05			χ^2=0.001; df=2; p>0.05	

Table 3. *Probability of PA occurrence among carriers of the single nucleotide polymorphism rs2278749 of the ARNTL gene (logistic regression analysis)*

rs2278749 ARNTL	Коэффициент регрессии B	Стандартная ошибка	Статистика Вальда	Степень свободы	Значимость (p)	Exp (B)	Confidence interval for Exp (B)
CT+TT							
in general population	0.721	0.329	4.801	1	0.028	2.056	1.079–3.918
in female population	0.880	0.406	4.697	1	0.030	2.412	1.088–5.346
Allele T							
general population	0.629	0.288	4.766	1	0.029	1.876	1.066–3.298
in female population	0.761	0.356	4.555	1	0.033	2.140	1.064–4.302

When distributing the frequencies of genotypes and alleles of the single nucleotide polymorphism rs2278749 of the *ARNTL* gene in the open population aged 25–64 years compared with the level of personal anxiety, both in the general population and among men and women, we did not find statistically significant differences (Table 2).

The probability of developing personal anxiety among carriers of the CT+TT genotypes of the *ARNTL* gene was 2 times higher (95% CI 1.079–3.918; $p<0.05$) in the general population and 2.4 times higher (95% CI 1.088–5.346; $p<0.05$) among women. The results of the construction of the logistic regression model showed that the probability of personal anxiety among the carriers of the allele T of the *ARNTL* gene was 1.8 times higher (95% CI 1.066–3,298; $p<0.05$) in the general population, and 2.1 times higher (95 % CI 1.064–4.302; $p<0.05$) among women (Table 3).

Several questions of the Spielberger Personal Anxiety Scale were analyzed among carriers of different genotypes of the single nucleotide polymorphism rs2278749 of the *ARNTL* gene. Carriers of the C/T genotype of the *ARNTL* gene were 30.3% more likely to believe that they almost always take everything too personally ($\chi^2=14.582$, df=6, p=0.024). Carriers of the C/T genotype (21%) almost always, and carriers of the T/T genotype (27.8%) often would like to be as happy as others ($\chi^2=13.922$, df=6, p=0.031). The answer "I often feel satisfaction" prevailed (38.2%) among carriers of the C/C genotype, and "I almost never feel satisfaction" among carriers of the C/T genotype (5.9%) of the ARNTL gene ($\chi^2=12.955$, df=6, p=0.044) (Table 4).

Discussion

Approximately 60–70% of people with anxiety have serious sleep problems:

They complain of bad sleep, reporting difficulties in its initiation and maintenance. Polysomnographic studies have shown that in comparison with healthy people, sleep of people with anxiety is characterized by a longer latency, an increase in wakefulness and a decrease in sleep efficiency [18]. Since the "sleep-wakefulness" cycle is inextricably regulated by the circadian clock, serious sleep problems in people with anxiety suggest the potential role of circadian dysfunction. Circadian rhythms regulate the expression of neuron genes and animal behavior [19]. Approximately 24-hour rhythms are endogenously controlled by transcription-translation loops of the genetic feedback [20]. In mammals, transcription factors CLOCK and BMAL1 form heterodimers and activate the transcription of *Period (Per)* and *CryptoChrome (Cry)* genes. In turn, Per and Cry proteins bind to Clock-Bmal1 heterodimers, are translocated into the cell nucleus, and repress the transcription of their own genes [21]. With mood disorders, daily profiles of circadian biomarkers, including cortisol and melatonin, are often abnormal [22]. All these data confirm the fact that the dysfunction of the circadian rhythm system can contribute to the pathogenesis of anxiety [23].

Table 4. *The frequency of occurrence of genotypes of the single nucleotide polymorphism rs2278749 of the ARNTL gene in the population aged 25–64 years in Novosibirsk in comparison with individual questions of the Spielberger Anxiety Scale, n (%)*

Statement, genotype	Possible answer: almost never	sometimes	often	almost always	total
I take everything too personally					
C/C	24 (11.3)	57 (26.9)	83 (39.2)	48 (22.6)	212 (100)
C/T	2 (1.7)	39 (32.8)	42 (35.3)	36 (30.3)	119 (100)
T/T	1 (5.6)	6 (33.3)	7 (38.9)	4 (22.2)	18 (100)
Total	27 (7.7)	102 (29.2)	132 (37.8)	88 (25.2)	349 (100)
	$\chi^2=14.582$; df=6; p=0.024				
I would like to be as happy as others					
C/C	27 (12.7)	103 (48.6)	56 (26.4)	26 (12.3)	212 (100)
C/T	10 (8.4)	63 (52.9)	21 (17.6)	25 (21.0)	119 (100)
T/T	3 (16.7)	10 (55.6)	5 (27.8)	0 (0)	18 (100)
Total	40 (11.5)	176 (50.4)	82 (23.5)	51(14.6)	349 (100)
	$\chi^2=13.922$; df=6; p=0.031				
I feel satisfied					
C/C	2 (0.9)	120(56.6)	81(38.2)	9(4.2)	212(100)
C/T	7 (5.9)	60(50.4)	42(35.3)	10(8.4)	119(100)
T/T	0 (0)	12(66.7)	6(33.3)	0(0)	18 (100)
Total	9 (2.6)	192 (55.0)	129 (37.0)	19 (5.4)	349 (100)
	$\chi^2=12.955$; df=6; p=0.044				

The *ARNTL* gene (*BMAL1* or *MOP3*) operates in the center of genetic feedback loops that control circadian expression of genes in cells [24]. Its deletion leads to a complete loss of circadian rhythms in mice [25]. Human clock genes directly regulated by *BMAL1* have been identified as risk genes for mood disorders; for example, in logistic regression analysis, winter depression was associated with three circadian clock genes *PER2*, *ARNTL*, and *NPAS2* [26].

In our study, we found that the likelihood of personal anxiety among carriers of the CT+TT genotypes of the *ARNTL* gene was 2 times higher in the general population, and 2.4 times higher among women. The relative chance of developing personal anxiety was 1.8 times higher among carriers of the T allele of the *ARNTL* gene in the general population, and 2.1 times higher in the female population.

Carriers of the C/T genotype of the *ARNTL* gene were 30.3% more likely to believe that they almost always take everything too personally, would like to be as happy as others, and almost never experienced life satisfaction. And carriers of the T/T genotype often would like to be as happy as others.

This once again confirms our earlier study conducted in an open population of men. Carriers of the C/T genotype were more likely to experience serious conflicts in the family, more often experienced disappointment; more often had disturbing dreams and woke up tired and exhausted; in addition, they were more likely to have a high level of vital exhaustion, and they were more likely to get upset. Carriers of the T/T genotype were more likely to take trouble to heart and be more punctual [27].

Conclusions

1. The most common genotype in all groups was the C/C genotype of the *ARNTL* gene: in the general population it was found in 60.7% of individuals (in 61.2% of men and in 60.5% of women). Heterozygous C/T genotype occurred in 34.1% of people (35.1% of men and 33.5% of women). The T/T genotype in the general population was found in 5.2% of people (3.7% of men and 6% of women).
2. The probability of personal anxiety among carriers of CT+TT genotypes of *ARNTL* gene was 2 times higher (95% CI 1.079–3.918; $p<0.05$) in the general population, and 2.4 times higher (95% CI 1.088–5.346; $p<0.05$) among women. The relative chance of personal anxiety among the carriers of T allele of the *ARNTL* gene was 1.8 times higher (95% CI 1.066–3,298; $p<0.05$) in the general population, and 2.1 times higher (95% CI 1.064–4.302; $p<0.05$) in the population of women.
3. The carriers of the C/T genotype of *ARNTL* 30.3% more often believed that they almost always take everything too close to heart ($\chi^2=14.582$, df=6, $p=0.024$). Carriers of the C/T genotype (21%) almost always, and the carriers of the T/T genotype (27.8%) often would like to be as happy as others ($\chi^2=13.922$, df=6, $p=0.031$). The answer "I often feel satisfaction" prevailed (38.2%) among the carriers of the C/C genotype, and the answer "I almost never feel satisfaction" – among the carriers of the genotype C/T (5.9%) of the *ARNTL* gene ($\chi^2=12.955$, df=6, $p=0.044$).

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