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Association of *DRD2/ANKK1 Taq1A* polymorphism with depression in an open 45–64 year-old male population (international epidemiological HAPIEE and WHO MONICA programs)

Objective: *to study the association of DRD2/ANKK1 Taq1A polymorphism with depression in an open 45–64-year-old male population from Novosibirsk.*

Patients and methods. *A representative sample of an open 45–64-year-old male population (n=781) was surveyed within Screening IV of the international HAPIEE program and the WHO MONICA-psychosocial program in 2003–2005. All the study participants filled out the WHO MONICA-psychosocial Program Depression Scale. The DRD2/ANKK1 Taq1A C32806T (rs 1800497) polymorphism was genotyped using the published methods within the budgeting topic.*

The Pearson's chi-square (χ^2) test was applied to test the statistical significance of differences between the groups. Significance in all types of analysis was taken at $p \leqslant 0.05$.

Results and discussion. *The prevalence of depression in the open 45–64-year-old male population was 36.3%: 13.5% of the examinees had severe depression (SD) and 22.8% had moderate depression (MD). A comparative intergroup analysis showed that the odds ratio (OR) for the incidence of SD was 3.86 times higher in the T/C genotype carriers than in the C/C genotype ones, who, on the contrary, had no depression; the OR for the incidence of SD was also 3.28 times higher in the T/C genotype carriers, while MD was more common in the homozygous C/C genotype carriers. The OR for the incidence of SD was 2.63 times higher in the DRD2 T allele carriers than in the C allele carriers who did not suffer from depression in most cases.*

Conclusion*. A significant association was established between the carriage of Taq1A (T allele) and depression in 45–64-year-old males.*

Keywords: *depression; population; males; DRD2/ANKK1 Taq1A polymorphism.*

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For reference: *Gafarov VV, Gromova EA, Panov DO et al. Association of DRD2/ANKK1 Taq1A polymorphism with depression in an open 45–64 year-old male population (international epidemiological HAPIEE and WHO MONICA programs). Nevrologiya, neiropsikhiatriya, psikhosomatika = Neurology, Neuropsychiatry, Psychosomatics. 2019;11(2):37–41.*

DOI*: 10.14412/2074-2711-2019-2-37-41*

According to the estimates of various authors, the contribution of heredity to the development of depression ranges from 35% to 40%, and, therefore, an active search for specific loci is underway [1]. A number of studies have already analyzed dopamine receptor genes and their association with bipolar disorder, depression, or depressive symptoms [2]. Since the beginning of the 1990s, the polymorphisms of the DRD2 gene have been actively studied, with great attention being paid to the Taq1A polymorphism (C32806T), the substitution C> T; as Taq1A, or the A1 (T) allele, has long been associated with low dopamine density and lower than average glucose metabolism in the human brain [4–6]. Studies using positron emission tomography have demonstrated that this A1 allele is associated with a low density of dopamine receptors [7]. However, recent studies have shown that Taq1A polymorphism is located next to the DRD2 gene, within the PKK2 protein kinase gene (ANKK1), therefore, the current locus designation is DRD2 / ANKK1 Taq1A. It is believed that this polymorphism is functional and causes the substitution of amino acids (Glu713Lys) in the structure of the enzyme kinase, which can affect the specificity of its substrate binding and alter dopaminergic neuromediation [8].

In a study by J.A. Stapleton et al. [9], it was found that individuals with the Taq1A variant allele (T-allele) and a history of depression are likely to experience particular difficulties when trying to quit smoking and may need additional treatment for depression other than standard nicotine replacement doses. This discovery may explain previous conflicting results for Taq1A and smoking cessation in the studies that have not considered depression, as well as understand the main link between depression and smoking. At the same time, M. Elovainio et al. [10] suggest that Taq1A polymorphism moderately affects stressful life events and depressive symptoms.

The purpose of this study is to investigate the association of the polymorphism of the DRD2 / ANKK1 Taq1A C32806T gene (rs 1800497) with depression in an open male population 45–64 years old in Novosibirsk.

Patients and methods. As a part of the IV screening of the international program HAPIEE (Health, Alcohol and Psychosocial factors In Eastern Europe) [11] and the WHO MONICA-psychosocial program [12] in 2003–2005 a represen-

tative sample of men 45–64 years old living in Oktyabrsky district of Novosibirsk was examined (n = 781, mean age 56.48 ± 0.2 years).

All study participants independently completed the Depression Questionnaire, which was proposed and tested in the WHO MONICA-psychosocial program. We distinguished three levels of depression: high (HD), moderate (MD) and low (LD) [12].

Within the framework of the budget topic, 156 men were selected from the study sample using the method of random numbers, and genotyping of the DRD2 / ANKK1 Taq1A C32806T gene (rs 1800497) was performed in the laboratory of molecular genetic research according to the techniques described in literature [13]. Statistical analysis was performed using the SPSS software package, version 11.5 [14]. The frequency distribution of genotypes for the studied polymorphic loci was checked for compliance with the Hardy – Weinberg equilibrium. To check the statistical significance of the differences between the groups we used Pearson χ^2 test [15]. Statistical significance in all types of analysis was taken at $p \leqslant 0.05$.

Table 1. Frequency of genotypes and alleles of the rs1800497 polymorphism of the DRD2 / ANKK1 gene in male population of 45–64 years old

Indicator	Frequency, n (%)
Genotype:	
T/T	2 (1.3)
T/C	40 (25.6)
C/C	114 (73.1)
Allele:	
T	44 (14.1)
C	268 (85.9)
Compliance with Hardy-Weinberg equilibrium: $\chi 2 = 0.5$; C-allele frequency = 0.86; T-allele frequency = 0.14	

Table 2. The frequency distribution of the genotypes of the DRD2 / ANKK1 gene in an open male population 45–64 years old with different levels of depression, n (%)

Indicator	LD	MD	HD
Genotype:			
T/T	1 (1.1)	1 (2.7)	0
T/C	17 (19.3)	8 (21.6)	15 (48.4)
C/C	70 (79.5)	28 (75.7)	16 (51.6)
	χ^2=11.347; df=4; p=0.023		
Allele:			
T	19 (10.8)	10 (13.5)	15(24.2)
C	157 (89.2)	64 (86.5)	47 (75.8)
	χ^2=6.822; df=2; p=0.033		

High level of depression (HD), moderate (MD) and low (LD)

Table 3. Comparative analysis of the OR for the onset of depression in men 45–64 years old with different polymorphisms of the DRD2 / ANKK1 gene

Indicator				
	HD		**LD**	
	n	%	n	%
Carriers of genotype *T/C*	15	48.4	17	19.5
Carriers of genotype *C/C*	16	51.6	70	80.5
	χ^2=9.623; df=1; p=0.002			
Fisher Bilateral Test	0.004			
OR	3.86			
95% CI	1.599–9.321			
	HD		**MD**	
	n	%	n	%
Carriers of genotype *T/C*	15	48.4	8	22.2
Carriers of genotype *C/C*	16	51.6	28	77.8
	χ^2=5.058; df=1; p=0.025			
Fisher Bilateral Test	0.038			
OR	3.281			
95% CI	1.142–9.462			
	HD		**LD**	
	n	%	n	%
Carriers of genotype *T*	15	24.2	19	10.8
Carriers of genotype *C*	47	75.8	157	89.2
	χ^2=6.721; df=1; p=0.01			
Fisher Bilateral Test	0.019			
OR	2.637			
95 % CI	1.244–5.590			

Results. The prevalence of depression in the open population of men aged 45–64 was 36.3% (HD –13.5%, and MD – 22.8%). The most frequently detected rs1800497 polymorphism was the homozygous C / C genotype (73.1%), the least common was T / T genotype (1.3%), C-allele was found in a greater number of cases (85.9%) than T-allele (14.1%; Table. 1).

In the individuals with the heterozygous T / C genotype, HD was more common (48.4%) than MD (21.6%); 79.5% of the individuals with the homozygous C / C genotype did not have depression (2 = 11.347; df = 4; p = 0.023). The T-allele of the DRD2 gene was more common in men with HD (24.2%), the C-allele was found in the individuals without depression (89.2%; χ^2 = 6.822; df = 2; p = 0.033; Table 2).

A comparative intergroup analysis showed that the odds ratio (OR) for the onset of HD was higher in T / C genotype carriers (48.4%) than in C / C genotype carriers, who most often did not have depression (80.5%; OR 3.86; 95% confidence interval [CI] 1.599–9.321; χ^2 = 9.623; df = 1; p = 0.002); also in the carriers of T / C genotype OR for HD was higher (48.4%) than for MD, unlike the carriers of the homozygous C / C genotype (77.8%; OR = 3.281; 95% CI 1.142–9.462; p <0.038; χ^2 = 5.058; df = 1; p = 0.025). In the carriers of the T-allele of the DRD2 gene, OR for HD was higher (24.2%) than among the carriers of the C-allele who did not suffer from depression (89.2%; 2.637; 95% CI 1.244–5.590; χ^2 = 6.721; df = 1; p = 0.01; Table 3).

Discussion. The dopaminergic system is a kind of indicator of psychopathology or, on the contrary, mental well-being, and is an integral part of motivation, training and reward processing. Of the dopamine receptor (DR) genes, the D2 dopamine receptor (DRD2) gene is one of the most fully studied; abnormalities in the DRD2 gene lead to a reward deficien-

cy syndrome [8]. Reward deficiency syndrome is characterized by the absence of the usual sensations of satisfaction as a result of a disturbance in "the brain reward cascade" due to a decrease in the number of dopamine receptors, leading to insufficient binding and a decrease in the level of extracellular dopamine which affects the mood and craving of people to search for novelty [16]. In addition to drug addiction, pathological gambling and other types of behavior aimed at receiving remuneration, DRD2 is also associated with depression [17], which prompted us to search for this connection, especially since in the 45–64-year-old male population that was studied the level of depression was extremely high. The most widely studied single nucleotide polymorphism (SNP) is the polymorphism of the DRD2 / ANKK1 Taq1A C32806T gene (rs 1800497) [3]. Some studies have shown that individuals with the Taq1A minor allele (T-allele) have a decreased binding of DRD2 in the striatum compared with subjects without the A1 allele [4]. It is assumed that it indirectly participates in the expression of DRD2 or interacts with another SNP of the DRD2 gene [5]. As in the case of other DRD2 mutations, carriers of the A1 allele have a lower density of the receptors compared with individuals who do not have such an allele [7], which explains the existing functional differences in carriers of the A1 allele and related psychopathology, such as depression in men [18] and an increased risk of mood disorders [19, 20].

In the population we studied, homozygous carriers of the A1 (T) allele were not widely represented, however, the presence of the A1 (T) allele in the heterozygous men was more often accompanied by depression compared with the carriers of two C-alleles. Our comparative analysis has shown that OR for developing HD in heterozygous individuals (T / C) was almost 4 times higher than that of homozygous C / C carriers, who most often had no depression; also in the carriers of the T / C genotype, the incidence of HD was more than 3 times higher, in contrast to the carriers of the homozygous C / C genotype, who more often had MD. Also, the carriers of the T-allele of the DRD2 gene had a 2.6 times greater OR for developing of HD than the carriers of the C-allele, in whom depression was not detected in most cases.

Conclusion

1. The prevalence of depression in the open population of men 45–64 years old was 36.3% (HD – 13.5% and MD – 22.8%).

2. In the individuals with the heterozygous T / C genotype, HD was more common (48.4%) than MD (21.6%); there was no depression in 79.5% of individuals with the homozygous C / C genotype. Allele T was more common in men with HD (24.2%), allele C – in non-depressed individuals (89.2%).

3. OR for development of major depression was 3.86 times higher in T / C genotype carriers than in C / C genotype carriers, who most often did not experience depression; also, OR for HD was 3.2 times higher in the carriers of the T / C genotype, compared with the carriers of the C / C genotype, who more often had MD.

4. In the carriers of the T-allele, OR for HD was 2.6 times higher than in the carriers of the C– allele.

The work was carried out within the framework of the budget topic GZ № 0324-2018-0001, Reg. № AAAA-A17-117112850280-2.

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Article received 25.02.2019