Association of polymorphic marker Val158Met of *COMT* gene with depression in an open population 25–44 years old (WHO international program MONICA, epidemiological study)

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Objective: *to investigate the association of the polymorphic marker Val158Met in the catechol-O-methyl transferase (COMT) gene with depression in an open population aged 25–44 years.*

Patients and methods. *A representative sample of the population living in Oktjabr'skij district of Novosibirsk aged 25–44 years (427 men, median age – 34±0.4 years, response rate – 71%; 548 women, median age 35±0.4 years, response rate – 72%) was screened in 2013–2016 (budget framework № 0324-2018-0001, Reg. № AAAA-A17-117112850280-2). In addition to the standard epidemiological examination, screening participants underwent psychological testing, which determined the level of depression. Study participants who underwent COMT Val158Met (rs4680) polymorphism genotyping were randomly assigned to a cohort of 224 men and 217 women. Pearson's χ^2 test was used to test the statistical significance of differences between these groups; $p \leqslant 0.05$ was considered statistically significant in all types of analysis.*

Results and discussion. *In an open population aged 25–44 years, the prevalence of severe depression (SD) was 13.2%, moderate depression – 24.4%. SD was more prevalent in COMT G/G genotype carriers (61.8%), compared to A/A genotype carriers (38.2%; $\chi^2=6.097$; df=2, p=0.047); the G allele carriers also had a higher prevalence of SD (55.3%), compared to A allele carries (44.7%; $\chi^2=5.408$; df=1; p=0.02). SD was less prevalent among male COMT A/A genotype carriers (15.8%), compared to G/A genotype carriers (84.2%; $\chi^2=4.603$; df=1; p=0.032). SD was more prevalent in female G/G genotype carriers (65.5%), compared to A/A genotype carriers (34.5%; $\chi^2=4.769$; df=1; p=0.029). The G allele was more common among women with SD (58.2%) than the A allele (41.8%; $\chi^2=6.658$; df=2; p=0.01). In a logistic regression model, COMT Val/Val genotype in the studied population [Relative risk (RR) 1.594], as well as G (Val) allele in the studied population (RR=1.378) and women (RR=1.557), significantly increased the risk of depression.*

Conclusion. *The data allows us to assume that COMT G/G polymorphism may be linked to a high depression level.*

Keywords: *catechol-O-methyl transferase; COMT; Val158Met; polymorphism markers; depression; population; men; women.*

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Introduction

Depression is one of the most common diseases in the world; nowadays about 300 million people on the Earth suffer from depression [1]. Depression has a huge impact on psychological, biological and social condition of a person [2]. Depression is a multi-factor disease associated with the influence of both genetic and social factors [3]. On average, according to different authors, heredity contributes to the development of depression as much as 35% to 40% [4].

Dysfunction of monoamines (serotonin, dopamine and norepinephrine) – neurotransmitters in the human brain – is believed to play a crucial part in the development of depression [5]. Dopamine is the most important nervous system regulator and behavior, reward [6], making decision [7], motivation, emotions [8], as well as psychomotor skills regulation [9] depend on it.

One of the genes participating in dopaminergic pathway and regulating concentration of extracellular dopamine together with other genes is the *COMT* gene (catechol-O-methyltransferase) located on chromosome 22q11.1-q11.2 [10]. Protein encoded by this gene is responsible for inactivation of catecholamines such as dopamine, adrenaline and noradrenaline by catalyzing the transfer of a methyl group from S-adenosyl methionine to a hydroxyl group in catechin nucleus [11]. The *COMT* gene has two promoters regulating transcription of separate mRNA [12] causing synthesis of two COMT proteins: soluble cytoplasmic (S-COMT) and membrane-bound protein (MB-COMT) [13]. MB-COMT is expressed primarily in the human brain, while S-COMT is expressed in peripheral tissues [12]. This allows us to suggest that MB-COMT is the one that regulates concentration of dopamine which then influence the relevant brain functions. It should be noted that missense mutation in exon 4 of 158 gene codon in *MB-COMT* causes substitution of valine amino acid for methionine (Val158Met, or 472A>G, or rs4680) which is associated with *COMT* activity [12]. Val/Val homozygotes have been proved to be more stable than Met/Met homozygotes; and COMT activity with Val/Val

homozygotes is about 40% higher than with Met/Met homozygotes having slower «destruction» of dopamine in anterior cortex, while Val/Met heterozygotes have intermediate enzyme activity [14].

Based on the background mentioned above we aimed to study an association between *COMT* gene polymorphism and the incidence of depression in open population aged of 25–44 years living in Novosibirsk.

Materials and methods

Under the screening (budget framework _ 0324-2018-0001, Reg. №AAAA-A17-117112850280-2A) a representative sample of Novosibirsk population aged of 25–44 years (men n=427, average age 34±0.4 years, response – 71%; women n=548, average age 35±0.4 years, response – 72%) was examined in 2013–2016.

The screening participants underwent psychological testing in addition to the standard epidemiological survey which determined the level of depression as high level of depression (HD), moderate level of depression (MD) and low level of depression (LD). The scale of depression (MONICA-MOPSY) was proposed and tested earlier in the WHO epidemiological study «MONICA-psychosocial» in 1994. The questionnaire underwent strict standardization and quality control testing in specialized European centers. Respondents completed a psychosocial questionnaire themselves [15].

A cohort of 224 men and 217 women was randomly formed from the study participants who were genotyped Val158Met (rs4680) polymorphism of the *COMT* gene in the laboratory of molecular genetic studies. Genotyping of the Val158Met (rs4680) polymorphism of the *COMT* gene was performed according to the following procedure. Direct primer 5-GGGCCTACTGTGGCTACTCAGCTGT-3, reverse primer 5-GGCATGCACACCTTGTCCTTCG-3. Polymerase chain reaction (PCR) conditions: 95 °C for 1 min; 30 cycles (95 °C – 30 s, 66 °C – 30 s, 72 °C – 30 s). The reaction mixture with a volume of 25 ml contained: 1.5 ml of total DNA; 75 mM Tris-HCl, pH=9.0; 20 mM $(NH_4)_2SO_4$; 0.01% Tween-20; 2 mM each primer; 2.5 mM $MgCl_2$; 0.2 mM each of dNTP; 1 unit. Act. *Taq* DNA polymerase. Restriction endonuclease AspLEI (SibEnzyme, Russia) was added to the PCR products. The result was evaluated after electrophoresis in 4% polyacrylamide gel and staining with 0.1% ethidium bromide. Product size 148 p.n. corresponded to allele A, 126 and 22 p.n. – allele G.

Statistical analysis was performed using the SPSS software package, version 11.5 [16]. The distribution of genotype frequencies for the studied polymorphic loci was checked for compliance with the Hardy–Weinberg equilibrium. To check the statistical significance of differences between groups, we used: Pearson's chi-square test (χ^2). The odds ratio (OR) when comparing groups was assessed as the probability of a carrier of a particular allele / genotype in one of the comparison groups with a 95% confidence interval (95% CI) [17]. To assess the relative risk (RR) of disease development by logistic regression, genetic parameters (genotypes and alleles) were used as covariates (factors), depression was a dependent variable [18]. Significance in all types of analysis was accepted at the level of $p \leqslant 0.05$ [16].

Results

In the open population of 25–44 years the prevalence of a high level of depression was 13.2%, moderate level of depression was 24.4%. 9% of men had a high level of depression, 20.9% of men had a moderate level; 16.3% of women had a high level, 26.6% of women had a moderate level (χ^2=18.71 df=2 p<0.0001). In an open population of 25–44 years of age, as well as among males and females, the frequencies of genotypes and alleles of rs4680 polymorphism of the *COMT* gene are in the Hardy–Weinberg equilibrium. In all groups the G/A genotype was most common (Tab. 1).

In the distribution of the *COMT* genotype frequencies in an open population of the population aged 25–44 years, no statistically significant differences were obtained in comparison with the level of depression (Tab. 2). When comparing the alleles of the *COMT* gene, it was found that the G allele prevailed among persons with HD in the general population (55.3%; χ^2=6.395; df=2, p=0.041); statistically significant differences were not found among men and women (see Table 2).

A high level of depression were found more often (61.8%) in an open population of men and women of 25–44 years among persons with G/G genotype of the *COMT* gene in comparison with carriers of the A/A genotype (38.2%) (χ^2=6.097 df=2, p=0.047). Carriers of the A/A genotype (23.6% and 17.1%) experienced a high level of depression less than carriers of the G/A genotype (76.4%) and carriers of all genotypes (82,9%) (4.912 df=1; p=0.027 and 6,084 df=1; p=0.014, respectively), see Table 3. Carriers of the G allele (55.3%) had a high level of depression more often than carriers of the A allele (44.7%) (5,408 df=1; p=0.02) (Table 3).

Depression was less common (15.8%) in the population of men aged 25–44 years among carriers of the A/A genotype of the *COMT* gene than among carriers of the G/A genotype (84.2%) 4,603 (df=1; p=0.032) (Table 4).

Table 1. *Prevalence of alleles, genotypes of the polymorphic locus rs4680 of the COMT gene in Novosibirsk population aged 25–44 years, n (%)*

Indicator	Allele		Genotype			Correspondence to the Hardy–Weinberg equilibrium
	A	G	A/A	G/A	G/G	
In general population	457 (51,8)	425 (48,2)	121 (27,4)	215 (48,8)	105 (23,8)	χ^2=16,11 A allele frequency=0,61 ;G allele frequency =0,39
Males	246 (54,9)	202 (45,1)	68 (30,4)	110 (49,1)	46 (20,5)	χ^2=4,56 A allele frequency=0,63 ; G allele frequency = 0,37
Females	211 (48,6)	223 (51,4)	53 (24,4)	105 (48,4)	59 (27,2)	χ^2 =9,06 A allele frequency=0,61 ;G allele frequency = 0,39

Table 2. *Prevalence of genotypes and alleles of the polymorphic locus rs4680 of the COMT gene in Novosibirsk population aged 25–44 years in association with depression severity*

Indicator	Frequency, n (%)								
	in general population			males			females		
	LD	MD	HD	LD	MD	HD	LD	MD	HD
Genotype:									
A/A	74 (31,8)	34 (25,8)	13 (17,1)	49 (32,7)	16 (30,2)	3 (14,3)	25 (30,1)	18 (22,8)	10 (18,2)
G/A	111 (47,6)	62 (47)	42 (55,3)	69 (46)	25 (47,2)	16 (76,2)	42 (50,6)	37 (46,8)	26 (47,3)
G/G	48 (20,6)	36 (27,3)	21 (27,6)	32 (21,3)	12 (22,6)	2 (9,5)	16 (19,3)	24 (30,4)	19 (34,5)
	χ^2=7,624; df=4; p>0,05			χ^2=6,924; df=4; p>0,05			χ^2=5,506; df=4; p>0,05		
Allele:									
A	259 (55,6)	130 (49,2)	68 (44,7)	167 (55,7)	57 (53,8)	22 (52,4)	92 (55,4)	73 (46,2)	46 (41,8)
G	207 (44,4)	134 (50,8)	84 (55,3)	133 (44,3)	49 (46,2)	20 (47,6)	74 (44,6)	85 (53,8)	64 (58,2)
	χ^2=6,395; df=2; p=0,041			χ^2=0,233; df=2; p>0,05			χ^2=5,481; df=2; p>0,05		

In an open population of young women aged of 25–44 years carriers of the G/G genotype had high levels of depression (65.5%) more often than carriers of the A/A genotype (34.5) (χ^2=4,769 df=1; p=0.029). G allele (58.2%) was more common among women with high levels of depression than A allele (41.8%) (6,658 df=2; p=0.01) (Table 5).

The results of constructing a logistic regression model showed that the Val/Val genotype of the *COMT* gene in the population (OR=1.594; 95% CI 1.041–2.442; p<0.032), as well as the G allele (Val) as in the population (OR=1.378; 95% CI 1.057–1.796; p<0.018) and among women (OR=1.557; 95% CI 1.054–2.298; p<0.026) increases the risk of depression (Table 6).

Discussion

In our population among young people working age of 25–44 years the prevalence of high levels of depression was very high – 13.2%. According to the WHO report (2018) depression can become a serious health disorder, especially if it is prolonged and takes a moderate or severe form. It can lead to significant

Table 3. *Comparative analysis of OR of depression in population aged 25–44 years with different COMT polymorphism*

Indicator	Depression, n (%)	
	High level	No depression
Genotype:		
A/A	13 (38,2)	74 (60,7)
G/G	21 (61,8)	48 (39,3)
	χ^2=5,419; df=1; p=0,020	
Two-tailed Fisher's exact test	0,031	
OR (95% CI (confidence interval)	0,402 (0,184–10,877)	
Genotype:		
A/A	13 (23,6)	74 (40)
G/A	42 (76,4)	111 (60)
	χ^2=4,912; df=1; p=0,027	
Two-tailed Fisher's exact test	0,037	
OR (95% CI)	0,464 (0,233–0,924)	
Genotype:		
A/A	13 (17,1)	74 (31,8)
All other genotypes	63 (82,9)	159 (68,2)
	χ^2=6,084; df=1; p=0,014	
Two-tailed Fisher's exact test	0,013	
OR (95% CI)	0,443 (0,230–0,856)	
Allele:		
A	68 (44,7)	259 (55,6)
G	84 (55,3)	207 (44,4)
	χ^2=5,408; df=1; p=0,02	
Two-tailed Fisher's exact test	0,025	
OR (95% CI)	0,647 (0,448–0,935)	

Table 4. *Comparative analysis of OR of depression in men aged 25–44 years with COMT polymorphism*

Indicator	Depression, n (%)	
	High level	No depression
Genotype:		
A/A	3 (15,8)	49 (41,5)
G/A	16 (84,2)	69 (58,5)
	χ^2=4,603; df=1; p=0,032	
Two-tailed Fisher's exact test	0,041	
OR (95% CI)	0,264 (0,073–0,956)	

Table 5. *Comparative analysis of OR of depression in COMT female carriers*

Indicator	Depression, n (%)	
	High level	No depression
Genotype:		
A/A	10 (34,5)	25 (61)
G/G	19 (65,5)	16 (39)
	χ^2=4,769; df=1; p=0,029	
Two-tailed Fisher's exact test	0,05	
OR (95% CI)	0,337 (0,125–0,907)	
Аллель:		
A	46 (41,8)	92 (55,4)
G	64 (58,2)	74 (44,6)
	χ^2=6,658; df=2; p=0,01	
Two-tailed Fisher's exact test	0,01	
OR (95% CI)	0,432 (0,227–0,825)	

Table 6. *Logistic regression results*

COMT	Regression Coeff. B	St.Error	Wald' Statistics	Degree of freedom	Sig.	Exp.(B)	95%CI for Exp.(B)
Val/Val (general population)	0,466	0,217	4,600	1	0,032	1,594	1,041–2,442
Constant	-0,454	0,187	5,922	1	0,015	0,635	
Allel G (general population)	0,320	0,135	5,598	1	0,018	1,378	1,057–1,796
Constant	-0,269	0,094	8,093	1	0,004	0,764	
Allel G (female population)	0,443	0,199	4,958	1	0,026	1,557	1,054–2,298
Constant	0,257	0,139	3,436	1	0,064	1,293	

human suffering and lack of performance at work, school and in the family. Women are more vulnerable to depression than men [19]. In our study both high and moderate depression levels among women (16.3% and 26.6%) were higher than among men (9% and 20.9%). The gender difference in the prevalence of depression tends to show that twice as many women suffer from severe depression as men. This represents a serious health disparity [20]. The possible cause is in the biological basis of depression in men and women.

We analyzed different polymorphic variants of the *COMT* gene depending on the level of depression in both the general population and among men and women, since the polymorphic marker Val158Met (rs4680) of the *COMT* gene represents a variant of potential susceptibility to depression [21]. In the general population it was found that the G (Val) allele of the *COMT* gene prevailed among individuals with high levels of depression. Among carriers of the G/G (Val/Val) genotype of the *COMT* gene, high levels of depression were more common than among carriers of the A/A (Met/Met) genotype. A similar result was obtained in women. Female carriers of the G/G (Val/Val) genotype had high levels of depression more often than carriers of the A/A (Met/Met) genotype, and the G (Val) allele was more common among women with high levels of depression than the A (Met) allele. In contrast in the general population carriers of A/A (Met/Met) genotype had high levels of depression less than carriers of genotype G/A (Val/Met) and carriers of all genotypes did. A similar result was obtained among men: among carriers of the A/A (Met/Met) genotype of the *COMT* gene depression was less common than among carriers of the G/A (Val/Met) genotype.

Logistic regression analysis confirmed that the presence of the Val/Val polymorphism in the general population, as well as the G (Val) allele in both the general population and among women, contributes to the risk of depression.

Our results were confirmed in the works of our foreign colleagues Wang M's [22] and co-authors (2016), who conducted a meta-analysis of samples consisting of 2905 cases of persons with depression in comparison with 2403 persons of the control group. There was a significant correlation between Val/Val + Val/Met versus Met/Met (OR=1,180; 95% CI 1,019–1,367; p=0.027), Val/Met versus Val/Val (OR=1,18; 95% CI 1,038–1,311; p=0.013) and Val/Met versus Met/Met (OR=1,229; 95% CI 1,053–1,435; p=0.009). Further meta-analysis of samples of persons of caucasoid origin demonstrated a significant association of this SNP (single nucleotide polymorphism) with susceptibility to depression in Val/Val + Val/Met versus Met/Met (OR=1,231, 95% CI 1,046–1,494; p=0.013) and Val/Met versus Met/Met (OR=1,284, 95% CI 1,050–1,448; p=0.012).

One possible explanation for this phenomenon is that carriers of the Val/Val and Met/Met genotypes of the *COMT* gene are significantly different from each other by a strategy of the stress management. In the English literature Val158Met polymorphism is called «Warrior or Worrier». Each genotype has its pros and cons, and the Val/Met genotype is an averaged version between two extremes [23].

The advantage of the Val/Val (G/G) genotype carriers is that they cope better with stress and pain, are more susceptible to language learning, have more cooperativeness, empathy, higher emotional stability, fluency in speech, better memory capacity, large volume hippocampus. There are also disadvantages: the carriers of the aforementioned genotype have less enjoyment of life, low IQ (tested in people with schizophrenia), they can cope with information processing only under stressful conditions, fine motor skills are less developed, and depression often appears [23]. In our study, carriers of the G/G genotype or G allele had a high level of depression, both in the general population and among women.

Carriers of the Met/Met (A/A) genotypes have their positive aspects: they have more fun out of life, are more creative, have fluency in thinking (dopamine in the prefrontal cortex contributes to cognitive stability, being more resistant to distraction factors). They have higher IQ, better working memory and reading comprehension, more brain plasticity in old ages, better cognitive function when there is no stress, good ability to focus on the target, better fine motor skills. The disadvantages are that carriers of the Met/Met genotype are worse at coping with stress and pain, are more subject to anxiety and panic disorders, phobias. Possess reduced emotional stability, less extroverted [23]. In our population only among young men carriers of the A/A genotype even in comparison with carriers of the G/A genotype the depression were less common.

As mentioned before, young women-carriers of the G/G genotype are more likely to have a high level of depression, and among men, the presence of the A/A genotype reduces the frequency of depression. A possible reason is that the women have *COMT* gene activity that is reduced by estrogen, i.e. the total activity of COMT in the prefrontal cortex and other tissues is

approximately 30% lower for women than for men. This reduced activity of the *COMT* gene leads to an increase in the basic level of dopamine by about 30% higher for women than for men. Women have the basic level of dopamine that is close to the optimal value, while men have the baseline level of dopamine is initially too low, so indicators for men improve when dopamine levels increase slightly, while for women they do not. Therefore, the presence of a SNP that leads to a decrease in *COMT* (for example, the A allele for rs4680) will be more useful for men, but not for women. Indeed, men who carry the COMT polymorphic marker of the Met gene demonstrate the improved productivity in cognitive tasks that depend on the prefrontal cortex, while women do not [24].

Conclusion

1. In the open population at the age between 25 and 44 years, the prevalence of high-level depression was 13.2%, moderate-level depression was 24.4%. The high level of depression among men was 9%, The moderate level of depression was 20.9%; the high level of depression among women was 16.3%, the moderate level of depression was 26.6%.

2. A high level of depression in the open population of 25–44 years old carriers of genotype G/G of *COMT* gene was more common in comparison with carriers of the genotype A/A; also carriers of the genotype A/A rarely experienced high levels of depression in comparison with carriers of the genotype G/A and carriers of all genotypes. Carriers of the G allele were more likely to have high levels of depression compared to carriers of the A allele.

3. Among male 25–44 years old carriers of the genotype A/A of the *COMT* gene depression was less common than among male carriers of the genotype G/A.

4. In women of 25–44 years of age carriers of the G/G genotype experienced high levels of depression more often than carriers of the A/A genotype. The G Allele was more common among women with high levels of depression than the A allele.

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