Analysis of Associations between *5-HTT*, *5-HTR2A*, and *GABRA6* Gene Polymorphisms and Health-Associated Personality Traits

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The development of personality traits united by the notion of conscientiousness, should promote, along with reduction of anxiety, the physical and mental health. In order to detect the sources of conscientiousness and neurotism formation, we evaluated associations between polymorphic markers of *5-HTT*, *5-HTR2A*, and *GABRA6* genes and relevant scores of TCI questionnaire in a group of 369 volunteers. Associations of markers *VNTR* and *LPR* of *5-HTT* gene and marker *T1521C* of *GABRA6* gene with "self-directedness" and the effects of *5-HTR2A* gene marker *T102C* and its interactions with the *GABRA6* gene on the "harm avoidance" were detected.

Key Words: *health; personality; gene; serotonin; γ-aminobutyric acid*

Mental and physical health and life span are determined by two basic characteristics of personality: neurotism and conscientiousness [10]. Neurotism is liability to negative emotions and depression. Conscientiousness is liability to plan one's actions and orientation to delayed targets. The relationship between personality traits and health is realized through behavior promoting stable family life and well-being, through abstinence from harmful habits (*e. g*. tobacco smoking and dangerous driving), and through behavior directly aimed at health protection (personal hygiene, exercises, *etc.*). The development of conscientiousness is considered as a prospective trend of psychotherapy, which, along with anxiety reduction, will promote health preservation [6].

In order to modulate personality characteristics, we should understand the sources of their formation. It is known that genetic factors are important determinants of neurotism and conscientiousness [2]. Numerous molecular genetic studies of neurotism revealed its relationships with genes involved in serotonin (5-HT) metabolism in the CNS [12], while gene prerequisites of conscientiousness are discussed in just few of these studies. Analysis of biological studies led some authors to a hypothesis that the levels of 5-HT in the CNS are most likely associated with conscious regulation of behavior and impulses, but not with avoidance of potentially hazardous actions, caused by anxiety [5].

We searched for associations of neurotism- and conscientiousness-related personality characteristics with genes encoding 5-HT receptor 2A (*5-HTR2A*), 5-HT transporter protein (*5-HTT*) realizing 5-HT reuptake from the synaptic cleft, and GABA receptor A subunits α6 (*GABRA6*).

MATERIALS AND METHODS

The study was carried out on two samples. One (the main one) included 273 individuals from the common population (mean age 32±12 years, 65% women), the other consisted of 96 relatives of patients with psy-

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choses (mean age 46±11 years, 53% women). The specific stress situations, to which relatives of patients are exposed, often stimulates anxiety cluster or conscientiousness characteristics in them [4], in other words, can promote manifestation of genetic effects on these features through the genotype–environment interactions. All 369 volunteers were mentally healthy, answered the psychological questionnaire, donated blood for DNA isolation, and gave informed consent to participation in the study.

Personality characteristics were evaluated using Cloninger Temperament and Character Inventory (TCI) [7] including 7 dimensions. The dimensions related to neurotism and conscientiousness are called "Harm avoidance" (HA: anticipatory worry, fear of uncertainty, shyness, and fatigability) and "Self-directedness" (SD: responsibility, resourcefulness, purposefulness, self-acceptance, and congruent second nature).

DNA was isolated from venous blood by the phenol chloroform method. Amplification and identification of allele variants of *5-HTR2A* and *5-HTT* genes were carried out as described previously [1,3], of *GABRA6* gene by 5'-endonuclease analysis. The data on genotypes of *5-HTT* gene markers were obtained for 351 volunteers, of *5-HTR2A* gene markers for 301, and of *GABRA6* gene markers for 280 volunteers.

T102C polymorphism caused by thymine for cytosine substitution in position 102 was studied in *5-HTR2A* gene. Two polymorphisms were analyzed in *5-HTT* gene. *5-HTT LPR* polymorphism is presented by different numbers of repeated DNA sequences in the gene promoter region. The allele is called long (*L*), if the number of repeats is 16 and short (*S*), if their number is 14. The other polymorphism (*VNTR*) is caused by different numbers of repeating sequences forming a tandem in intron 2 of the gene. The most incident variants contain 10 and 12 repeats (alleles *10* and *12*). In addition, *GABRA6* gene polymorphism *T1521C* was studied. Some authors suggest an impact of *GABRA6* gene for neurotism, including the effect mediated through interactions with *5-HTT* gene [13].

The relationships between polymorphic markers and HA and SD were evaluated by the MANOVA. Genotype, gender, sample, and interactions between the above factors served as the intergroup factors. Significant effects were then analyzed by ANOVA and LSD test with Bonferroni correction for multiple comparisons.

RESULTS

The samples differed by age (t=10.15, p=0.00) and gender (χ^2=4.13, p=0.04). The SD in the group of relatives was higher than in the main group (t=3.30, p=0.00). The HA and SD scores correlated between each other (r=-0.37, p=0.00) in the total sample, did not depend on the age, and differed by gender. Women had higher HA scores than men (t=4.61, p=0.00) and a trend to lower SD scores (t=1.70, p=0.09).

Significant effects of *5-HTT VNTR* (F=4.61, p=0.00) and *GABRA6 T1521C* markers (F=2.49, p=0.04) and the impact of the relationship between *5-HTR2A T102C* and the sample (F=2.35, p=0.05) for personality traits were detected (Table 1). The *5-HTT VNTR* polymorphism was associated with SD (F=8.07, p=0.00). The *10*/*12* heterozygotes differed significantly from *10*/*10* (p=0.00) and *12*/*12* homozygotes (p=0.03). Heterozygotes had the lowest SD scores, while subjects with the *10*/*10* genotype had the highest values. This relationship was observed in the total group and in each sample. In addition, the impact of *VNTR+LPR* diplotypes for this trait was detected (F=2.55, p=0.04). Double heterozygotes *10*/*12+LS* had the lowest SD in comparison with other genotype combinations. *GABRA6 T1521C* polymorphism was also associated with SD (F=3.86, p=0.02). *CC* homozygotes were characterized by low SD, differing significantly from the *T* (*TT+TC*) allele carriers (F=5.93, p=0.02).

5-HTR2A gene was associated with HA (F=3.98, p=0.02). The HA scores in *TC* heterozygotes in the main sample were lower than in *TT* homozygotes (p=0.03). The effect of interactions between *5-HTR2A* and *GABRA6* genes on this trait was detected for the total sample (F=3.16, p=0.01). The relationship between HA and *GABRA6* genotypes manifested only in the carriers of two *5-HTR2A* gene alleles *C*. The HA scores were lowest in subjects with the *TT+CC* diplotype.

Hence, HA was associated with 5-HT transporter gene and SD with 5-HT 2A receptor gene. On the other hand, *GABRA6* gene polymorphism was essential for both HA and SD. It is known than *5-HTT* gene alleles *10* and *S* is characterized by low activity and are associated with increased anxiety and risk of depression, while such forms of impulsive behavior as liability to suicide, tobacco smoking, and ethanol consumption are associated with alleles *12* and *L* [9,12]. A negative correlation with heterozygotic state (negative heterosis) was observed for SD. These results confirm the concept according to which different genotypes by the same gene can be associated with different signs [8]. Interestingly, that the negative heterosis phenomenon for *5-HTT VNTR* was reported previously: the results of treatment with 5-HT reuptake inhibitors were worse in depressive patients with the *10*/*12* genotype than in those with the *12*/*12* genotype [14].

TABLE 1. SD and HA Scores and Genotypes

Sign	Genotype		Score
SD	*5-HTT VNTR***	10/10 (*n*=59)	16.51±5.16
		10/12 (*n*=136)	14.22±4.58
		12/12 (*n*=143)	15.66±4.50
	*5-HTT VNTR+LPR**	10/10+LS (*n*=17)	17.35±4.80
		10/12+LS (*n*=64)	13.45±4.91
		12/12+LS (*n*=70)	16.47±4.47
	*GABRA6 T1521C**	TT (*n*=92)	15.08±4.69
		TC (*n*=141)	15.33±4.81
		CC (*n*=47)	13.64±4.71
HA	*5-HTR2A T102C**	TT (*n*=44)	11.66±4.99
		TC (*n*=89)	9.15±4.08
		CC (*n*=86)	11.05±4.50
	*GABRA6+5-HTR2A***	TT+CC (*n*=37)	8.65±4.61
		TC+CC (*n*=52)	11.79±3.97
		CC+CC (*n*=13)	12.77±5.04

Note. Only statistically significant effects of the genes are presented. The genotype effect is significant at the levels of $^{**}p<0.01$ and $^{*}p<0.05$.

The data on lower HA scores in *5-HTR2A* heterozygotic patients are in line with our data obtained with other questionnaires [1]. In addition, they are in line with the results of studies demonstrating that the characteristics of receptors of this type in patients with suicidal attempts, characterized by high HA and low SD, were associated with HA alone [11]. On the other hand, other authors observed reduction of neurotism and elevation of conscientiousness in carriers of *5-HTR2A TT* genotype [15]. The discrepancy in the results can be due to differences in evaluation of personality traits and to genetic characteristics of the studied populations. Our data on the *GABRA6* gene confirm the hypothesis on its role in interactions between the 5-HT-ergic system and anxiety features [13], but ample interpretation of associations is impossible without detection of functional significance of alleles *T* and *C*.

Hence, genetically determined peculiarities of 5-HT and GABA metabolism are detected for the anxiety cluster characteristics associated with reduced mental and physical well-being, and for conscientiousness essential for health protection. Though these personality traits correlate, associations with different genotypes by the 5-HT-ergic system were revealed for them, which fact indicates different biochemical mechanisms of their formation.

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