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THE STUDY OF GENE POLYMORPHISMS IN NEUROTRANSMITTER SYSTEMS (*HTR1A* AND *SLC6A3*) AND MORPHOFUNCTIONAL CHARACTERISTICS IN STUDENTS WITH DEPRESSION SYMPTOMS

Introduction

In modern constitutional anthropology, the most interesting problem is the search for associations between different systems of the organism. Interdisciplinary projects, which combine two or more separate academic disciplines, are becoming more popular.

The present study combines the methods of three sciences: anthropology, genetics, and psychology.

In the last decades, due to the increasing level of stress, the study of different depressive states has been ever important for modern society. The increasing rate of depressive states necessitates the search of different markers of this disorder all over the world. These could be constitutional or functional characteristics, as well as genetic markers. Among university students, there are many individuals who experience the symptoms of anxiety or depression, particularly among first-grade students (Garanyan et al. 2007).

Depression may be of reactive or endogenous character. In the first case, the reason for it may be a very strong tragic event in one's life. The cause of endogenous depression may lie in a hereditary predisposition. As a rule,

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both, i.e. genetic factors and environmental conditions, contribute to the development of a depressive state.

The researchers who study predispositions of individuals to different psychotic disorders aim to reveal the tendency for depression in humans as early as possible. Early diagnosis helps prevent further development of this state and provide psychological support if necessary.

This paper is an interdisciplinary study of morphofunctional characteristics and the variability of genes in neurotransmitter systems (*HTR1A and SLC6A3)* in young men and women with signs of depressive symptoms.

One of the main physiological regulators of aggression is serotonin (Eichelman et al. 1979). It was found that aggressive and suicidal behavior in humans is accompanied by a low level of serotonin metabolite – 5-oxy indole acetic acid in blood (Asberg 1986). The level of 5-oxy indole acetic acid in cerebrospinal fluid was significantly lower in murderers and potential murderers than in the control group (Liniolla et al. 1983). It is suggested that suicidal persons have a deficiency (possibly genetic) in the serotonergic system in the brain (Simonov 1987, Roy et al. 1987). Receptor 1A (*HTR1A*) is defined as the most expressed serotonin receptor in mammal brain. Any change in the activity of those receptors is expressed in behavioural changes, such as increasing excitability, but also may be a result of depressive state.

In previous studies, researchers discovered and studied the promoter single-nucleotide polymorphism (SNP) G1019C (SNP rs 6295), which influenced the level of gene expression. It was shown that the presence of G-allele, if compared to C-allele, increases the transcription of the gene and consequently the content of receptor 1A in the organism. G-allele and the genotype GG happen to be associated with depression, suicidal behavior, and impulsivity (Lemonde et al. 2003, Huang et al. 2004, Benko et al. 2010).

The gene *SLC6A3* or *DAT1* is a transmitter of dopamine, limiting the activity of the dopaminergic system in the synapses by recapturing neuromediator in the presynaptic terminal.

Variable nucleotide tandem repeats (VNTR-polymorphism) were found in this gene in the 3'-non-coding region, with the number of repeats between 3 and 13 (3' UTR 40 bp VNTR) (Donovan et al. 1995). When studying the associations of the expression of gene dopamine transporter with allele variants, it was shown that the VNTR-polymorphism had an influence on the expression of the *DAT1* gene and that the highest level of expression was demonstrated by the allele with 10 repeats (Fuke et al. 2001).

It was also shown that the allele with 10 repeats was connected with the increased expression of transporter protein and, as a result, with a lower

accessibility of dopamine for the receptors (Asherson 2004). It was shown by numerous authors that there was a correlation between the VNTR-polymorphism of the *DAT1* gene and schizophrenia, attention-deficit hyperactivity disorder, a number of psychotic disorders (including depression), Parkinson's disease, and Tourette syndrome. *DAT1* was also connected with alcohol and drugs abuse (Cook et al. 1995, De Luca et al. 2006, Gill et al. 1997, Persico et al. 1997, Karama et al. 2008, Rowe et al. 2008, Vandenberg et al. 1992). It was shown that the genotype 9/9 and allele 9 were significantly associated with depression (Gafarov et al. 2012).

As for the associations of somatotypes with depressive state, contradictory results were presented in the literature. According to some authors, people with high BMI are more susceptible to psychic disorders (Starostina 2005). Other data indicate that depression could develop in people with both increased and decreased appetite (Sergeev et al. 2013). Some results show that women of picnic somatotype are more likely to "dramatize" their psychological state, to talk about their misfortunes and problems, even though in reality their situation is not so bad as it is described (Kokorin 2005).

The starting point for this article is the literature-based assumption that a predisposition to depression could be associated with polymorphisms in the *HTR1A and SLC6A3* genes, and possibly connected with the somatotypes. The study concentrates thus on the associations between polymorphisms in the indicated genes and morphofunctional characteristics of young men and women.

Materials and methods

Although the program of the research included some other approaches, only the results of the analysis of morphofunctional characteristics and psychological tests, were used for the present paper. Altogether, 372 students 16-23 years of age were observed in the cities of Saransk and Samara; among them, 170 men and 202 women, predominantly Russians.

Anthropometric program included the measurements of height, weight, waist and hip circumferences, skinfold thickness on the trunk and the extremities. Functional parameters, such as right-hand grip strength, blood pressure, heart rate, forced lung capacity, were also taken. Also, bioimpedance analysis was performed with the device "Medass ABC-01". Body mass components were measured: fat mass, active cell mass, skeletal-muscle mass, lean body mass, and specific metabolic rate.

The presence of depression symptoms in students was evaluated with the Beck questionnaire (Beck et al. 1961). The Beck Depression Inventory

is one of the most widely used tests for detecting depression symptoms. According to many specialists, the Beck scale helps separate most accurately between depression and apathy, and reveal the severity of depression symptoms (Levin 2006). The scale consists of 21 questions, each one assigned a value of 0 to 3 depending on the expression of the symptom. The total score varies between 0 and 63.

In this study, participants were classified along two categories: individuals with or without depression symptoms.

Buccal smears for molecular genetic analysis were taken from all the participants in order to determine polymorphisms of the *HTR1A and SLC6A3* genes.

All the materials used for the analysis in this research were collected in accordance with the bioethical procedure (protocol no. 55 from 26.03.2015, Bioethical Committee of Lomonosov Moscow State University), with signed informed consent of each participant and de-personification of data. The statistical analysis was performed with the software Statistica 10.0.

Results and discussion

Table 1 contains the means and standard deviations of the main morphofunctional characteristics in the men and women studied.

Table 1

Morphofunctional characteristics of young men and women under study

Characteristics	Men (N=170)		Women (N=202)	
	Mean	Std	Mean	Std
Weight (kg)	68.7	11.5	57.2	10.0
Height (cm)	176.2	7.2	163.9	5.4
Corpus length (cm)	76.2	2.8	71.4	2.7
Arm length (cm)	77.9	4.0	70.7	3.5
Leg length (cm)	100.0	5.7	92.4	4.4
Biacromial diameter (cm)	39.8	2.0	35.5	1.8
Biiliac diameter (cm)	28.4	1.8	27.6	1.7
Chest circumference (cm)	91.7	8.1	84.9	5.8
Waist circumference (cm)	76.9	7.6	69.5	7.2
Hip circumference (cm)	93.9	6.9	94.8	6.9
Upper arm circumference (cm)	28.5	3.3	25.9	3.1
Forearm circumference (cm)	26.0	2.2	22.6	1.7
Lower leg circumference (cm)	36.3	2.9	35.3	3.0

Subscapular skinfold (mm)	12.4	8.2	14.4	7.5
Triceps skinfold (mm)	10.4	7.0	16.5	7.1
Forearm	5.9	4.3	6.9	3.8
Abdominal	18.3	11.0	23.7	9.4
Lower leg skinfold (mm)	13.5	7.9	21.4	7.2
Systolic BP	135.3	14.2	120.0	11.2
Diastolic BP	74.8	10.4	74.9	8.3
Heart rate	75.1	14.7	77.2	12.3
Forced vital lung capacity (FVLC) (l)	4.6	0.8	3.3	0.5
Right hand grip strength (kg)	45.6	9.2	28.6	4.6
Fat mass (kg)	12.4	6.7	16.6	7.3
Active cell mass (kg)	34.1	4.6	22.7	2.3
Skeletal-muscle mass (kg)	31.1	3.5	19.8	2.0
Lean mass (kg)	56.4	6.6	40.6	3.8
Specific metabolic rate (kcal/m^2)	917.5	53.7	829.8	46.5

Source: own work.

To study morphofunctional characteristics of students in the groups with or without depression symptoms, as well as in the groups with different gene polymorphisms, the standardization procedure was used, and the data concerning men and women were combined to increase the number of participants in the groups under study.

As a result of comparative analysis, significant differences ($p < 0.05$) were found in the case of three morphofunctional characteristics in the students with or without depression symptoms. Lower values of fat mass and abdominal skinfold thickness were revealed in young people with depressive symptoms (Fig. 1 and 2). At the same time, they were characterized by higher values of specific metabolic rates. These results are in accordance with some known data (Kokorin 2005).

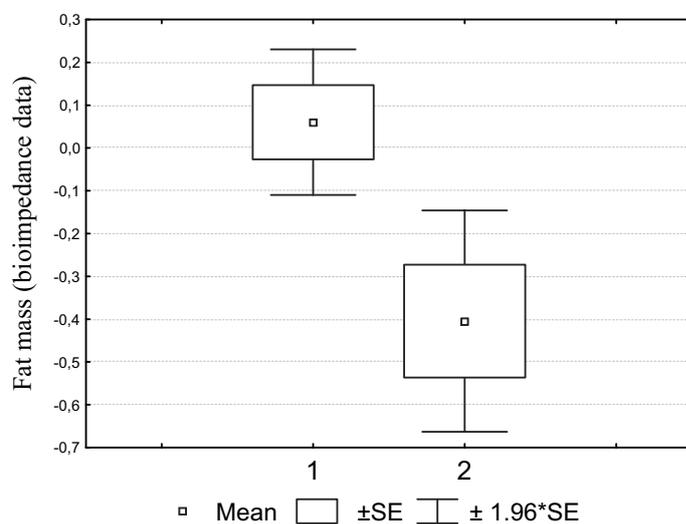In all the other morphofunctional characteristics, no intergroup differences were discovered.

Figure 1. Differences in mean values of fat mass (p<0.05) in the groups studied: 1 –
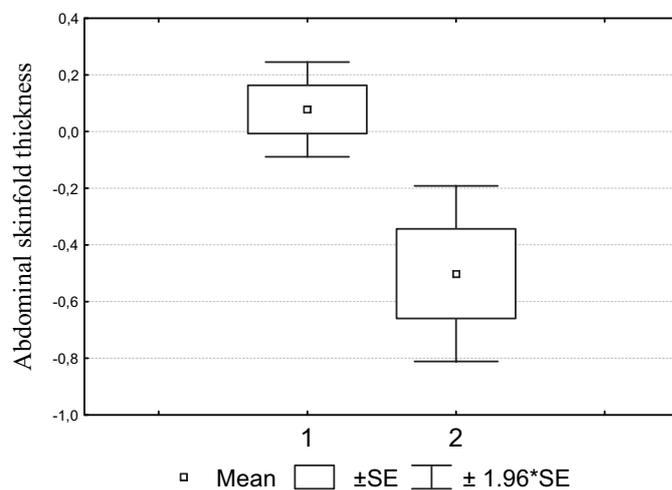without depression symptoms, and 2 – with depression symptoms.
Source: own work.

Figure 2. Differences in mean values of abdominal skinfold thickness (p<0.05) in the
groups studied: 1 – without depression symptoms, and 2 – with depression symptoms.
Source: own work.

Canonical discriminant analysis was used to study intergroup morphofunctional differences in the carriers of different genotypes. The results showed significant differences between the genotypes of the gene *SLC6A3* (p<0.05). Individuals with the genotype 9/9 of the *SLC6A3* gene were characterized by truncal adiposity (maximal values of abdominal and subscapular skinfolds). This trend may be interesting in the context of the understanding of genetical predisposition to depression symptoms as all the study participants were healthy young people, not diagnosed with any psychic disorders. However, due to a very small number of the genotype 9/9 representatives (4 people), further research is needed to verify the above data.

Significant associations of morphofunctional characteristics with the gene *HTR1A* polymorphism were not revealed in this study.

The comparative analysis of the frequencies of genotype and allele variants of the genes *DAT1 and HTR1A*in the groups with or without depression symptoms did not reveal any differences. However, this result also needs further investigation with a larger sample size and an increased number of the analyzed genetic markers.
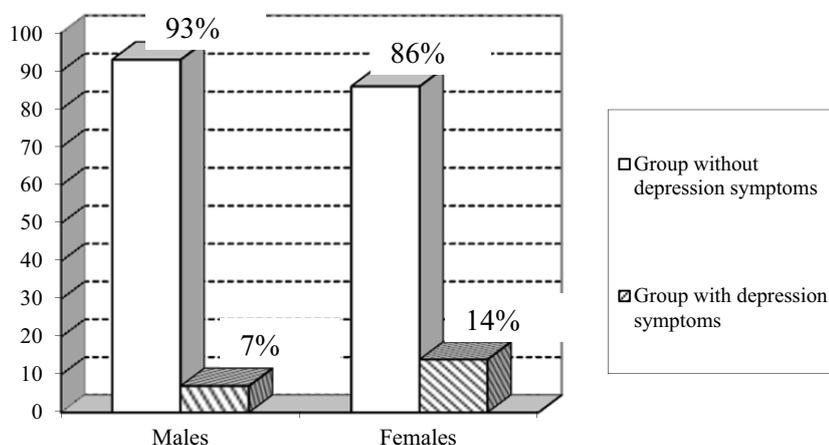

Figure 3. Percentage of the studied students in the groups with and without depression symptoms.
Source: own work.

Differences in the presence of depression symptoms between the two gender groups were found (Fig. 3). Subjects with symptoms of depression

are significantly more common among young women than men (p<0.05). This supports the data obtained by both Russian (Ilyin 2003, Topchy 2005, Pantyuk, Ermalenok 2007) and foreign authors (Vredenberg et al. 1986, Angold 1991). Some researchers (e.g. Piccinelli and Wilkinson 2000) explain higher susceptibility of women to depression and anxiety not only due to the influence of sex hormones but also to environmental, factors such as excessive social overloads, which may have serious negative effect on women's wellbeing.

As a result of the study, the following conclusions can be drawn:

– Young men and women with depression are characterized by significantly different morphofunctional characteristics (p<0.05): lower adiposity and abdominal skinfold thickness, relatively higher specific metabolic rate.

– No differences in the frequencies of the genotypes of the neurotransmitter systems genes (*DAT1*, *HTR1A*) were found between the groups of students with or without depression symptoms.

– Depending on the gender, differences in the number of individuals with depression symptoms were revealed (p<0.05): these symptoms were twice as high in women (14%) as in men (7%).

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Keywords: morpho-functional characteristics, depression symptoms, genes of neurotransmitter systems.

In the last decades, due to the increasing level of stress, the study of different depressive states and search for morpho-functional and genetic markers of depression have become important for modern society. This article is an interdisciplinary study of morpho-functional characteristics and variability of genes in the neurotransmitter systems (*HTR1A* and *SLC6A3*) in young men and women with the expression of depressive symptoms. The materials used include: morpho-functional characteristics (height, weight, body circumferences, skinfold thickness in the trunk and the extremities, and characteristics of cardiovascular and respiratory systems); evaluation of depression symptoms performed with the Beck questionnaire; determination of polymorphisms of the *HTR1A* and *SLC6A3* genes for 372 students from the cities of Samara and Saransk (170 men and 202 women aged 16-23, predominantly of Russian ethnicity. The results obtained are as follows: young men and women with depression symptoms are characterized by significantly different morpho-functional characteristics (p<0.05), lower adiposity and abdominal skinfold thickness, as well as a relatively higher specific metabolic rate. No differences in the frequencies of the genotypes of the neurotransmitter systems genes (*DAT1, HTR1A*) were found between the groups of students with or without depression symptoms. Differences in the number of individuals with the presence of depression symptoms were revealed (p<0.05) in relation to gender: these symptoms were twice as high in women (14%) as in men (7%).

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BADANIE GENOWEGO POLIMORFIZMU SYSTEMÓW NEUROTRANSMITERÓW (HTR1A ORAZ SLC6A3) ORAZ CHARAKTERYSTYKA MORFOFUNKCJONALNA U STUDENTÓW Z OBJAWAMI DEPRESJI

Słowa kluczowe: charakterystyka morfofunkcjonalna, symptomy depresji, geny i systemy neurotransmiterów.

W ostatnich dziesięcioleciach, ze względu na rosnący poziom stresu, badania nad różnymi stanami depresyjnymi i poszukiwanie morfofunkcjonalnych i genetycznych markerów depresji stają się coraz ważniejsze dla współczesnego społeczeństwa. Celem niniejszej pracy jest interdyscyplinarne badanie cech morfofunkcjonalnych i zmienności genów w układach neuroprzekaźników (HTR1A i SLC6A3) u młodych mężczyzn i kobiet z objawami depresyjnymi. Materiał: cechy morfofunkcjonalne (wysokość i masa, obwody ciała i grubości fałdów skórnych na tułowiu i kończynach, charakterystyka układu sercowo-naczyniowego i oddechowego); ocena objawów depresji za pomocą kwestionariusza Becka; określenie polimorfizmów genów HTR1A i SLC6A3 dla 372 uczniów z miast Samara i Sarańsk (170 mężczyzn i 202 kobiety w wieku 16 do 23 lat, głównie pochodzenia rosyjskiego). Wyniki: młode kobiety i mężczyźni z obecnością stanu depresyjnego charakteryzują się zmiennie odmiennymi cechami morfofunkcjonalnymi ($p < 0,05$); mniejszą otyłością i grubością fałdów skórnych brzucha, względnie wyższą specyficzną przemianą materii. Nie stwierdzono różnic w częstości genotypów genów systemów nerwowych (DAT1, HTR1A) pomiędzy grupami uczniów z objawami depresji lub bez nich. Różnice między płciami w liczbie osób z objawami depresji zostały pokazane ($p < 0,05$); objawy te były dwukrotnie wyższe u kobiet (14%) niż u mężczyzn (7%).