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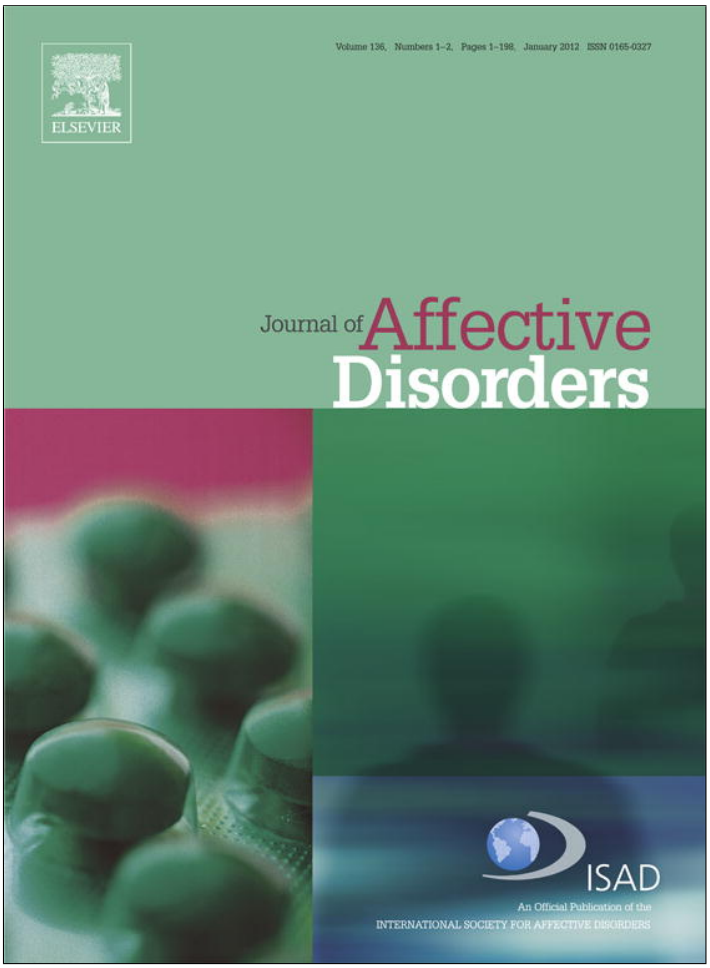

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Research report

Effect of the 5-HTTLPR polymorphism on affective temperament, depression and body mass index in obesity

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ABSTRACT

Background and aim: Many studies show high prevalence of affective disorders in obese patients. Affective temperament is a subclinical manifestation of such conditions. The 5-HTT gene encoding the serotonin transporter may be involved in both mood and eating dysregulation. The aim of this study was to investigate the influence of a polymorphism in the 5-HTT gene on affective temperament types, depressive symptoms and Body Mass Index (BMI) in obese patients.
Methods: This study involved 390 patients (237 females, and 153 males) with obesity. The TEMPS-A questionnaire, Beck Depression Inventory (BDI) and Hamilton Depression Rating Scale (HDRS) were used to evaluate affective temperaments and prevalence of depression. DNA was obtained for serotonin transporter gene-linked polymorphism (5-HTTLPR) genotyping.
Results: In obese patients S/S genotype was associated with depressive and L/L with cyclothymic temperament. Subjects with L/L genotype presented significantly higher BMI and greater intensity of depressive symptoms in BDI and HDRS. Females scored higher in anxious and depressive, while males in hyperthymic, cyclothymic and irritable temperaments. Females scored higher in BDI (subjective depression) while males in HDRS (objective depression).
Limitations: TEMPS-A, BDI and HDRS are frequently used in studies on affective disorders. However, these methods do not examine all dimensions of mood and personality.
Conclusions: In obese patients S allele of 5-HTTLPR was associated with development of depressive temperament while L allele corresponded with greater obesity and prevalence of depression. Different mechanisms may be involved in manifestation of depression in males and females with obesity.
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1. Introduction

The prevalence of obesity is growing across the world, particularly in countries of high socioeconomic development. Many studies show connection between obesity and mood disorders. Obese patients present elevated impulsivity and loss of impulse control (Kulendran et al., 2014). One study that consisted of 571 patients with major depressive disorders showed that obese (BMI > 30) individuals more frequently belonged to the bipolar group and had lower level of education compared to non-obese (BMI < 30) subjects (Vannucchi et al., 2014). Mood disorders, in particular depression and anxiety are important risk factors for obesity and contrarily, obesity is associated with higher risk for affective disturbances (Sachs-Ericsson et al., 2007; Luppino et al., 2010).

Recent studies shed new light on the link between obesity and it's psychiatric comorbidities along with their subclinical manifestations including affective temperament. The concept of affective temperament developed by Hagop Akiskal (Akiskal, 1992; Akiskal and Akiskal, 1992) is based on the idea that affective temperament and mood disorders are associated with similar genetic transmission and pathophysiological mechanisms (Akiskal, 1995). Moreover, current research indicate that affective temperaments could be utilized as phenotypes in order to identify

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susceptibility genes for bipolar disorder (BD) (Perugi et al., 2012). Results of these studies show that some pathological dimensions of affective temperament related to bipolar spectrum may predict loss of impulse control in obese patients. Amann et al. (2009) observed more psychiatric comorbidities in obesity compared to healthy subjects, especially in patients with morbid obesity. The scores in the "dark triad" (i.e. cyclothymic, irritable and anxious dimensions) were significantly more prevalent in the subgroup of obese patients.

Serotonin transporter (5HTT) plays a crucial role in control of serotonin transmission in regions of the brain associated with mood regulation, ingestion of food, energy expenditure and weight adjustment. This may indicate an important role of 5HTT in etiology of both mood and eating disorders.

The gene encoding 5-HTT is located on the long arm of chromosome 17 (17q11.1–17q12). The polymorphisms of 5-HTT influence transcriptional efficacy of the serotonin transporter gene. The S-allele (low-expressing) is linked to lower baseline transcriptional activity of the 5-HTT gene, resulting in lower efficiency of serotonin reuptake, while L-allele (high expressing) is associated with higher transcriptional gene activity and higher efficacy of serotonin reuptake (Lesch et al., 1996; Nakamura et al., 2000).

Many studies point to the association between 5-hydroxytryptamine transporter linked polymorphic region (5-HTTLPR) in the 5-HTT gene and sensitivity to stress as the etiology of mood disorders. S-allele has been associated with higher sensitivity to social and emotional stimuli, higher predisposition to depression and higher risk for suicide attempts (Caspi et al., 2010). In healthy population significant correlation between S-allele of 5-HTTLPR gene polymorphism, depressive temperament in TEMPS-A scale and high intensity in State Anxiety scale of the STAI questionnaire were found (Gonda et al., 2008). Moreover S-allele was related to anxiety, depression, hopelessness, guilt, hostility, aggression, neuroticism and self-directedness. Nevertheless, no association between the serotonin transporter gene polymorphism 5-HTTLPR and cyclothymic temperament measured with TEMPS-A was observed in healthy Korean and Norwegian populations (Landas et al., 2011).

In this study we assess the potential association between affective temperament dimensions measured with TEMPS-A scale and the serotonin transporter gene polymorphism 5-HTTLPR in obese patients.

2. Methods

2.1. Subjects

This study involved 390 subjects with obesity (BMI > 30 kg/m^2) of Polish nationality and Caucasian ethnicity, aged 20–76 years (Shapiro–Wilk test value – $W=0.945$; $p<0.001$) (mean, 52.5 ± 15.4). Two hundred and thirty seven females (aged 20–75, mean age 52.1 ± 16.0 years) and 153 males (aged 21–76, mean age 53.1 ± 14.3 years) were included. Male and female group did not differ in age.

The permission from the Bioethical Commission of the Nicolaus Copernicus University, Collegium Medicum in Bydgoszcz (No. 533/2008) was obtained for this research. All patients gave their written informed consent to participate in this project.

2.2. Methods

All subjects underwent neuropsychiatric assessment and physical examination. metric measurements were taken of body weight, waist circumference, hip circumference and waist-hip ratio (WHR). Patients with secondary obesity and addictions or severe somatic, psychiatric, or neurological disorders were excluded from this study. Severity in scores of depression symptoms was measured with Beck Depression Inventory (BDI) and Hamilton depression rating scale (HDRS). Depression was defined based on established cut-off score for Polish population. (i.e. BDI score greater than 12) (Parnowski and Jernajczyk, 1997).

For the assessment of affective temperament, the Polish version of Memphis, Pisa and San Diego Autoquestionnaire (TEMPS-A) was used (Borkowska et al., 2010). TEMPS-A is a self-report instrument of 110 (109 for males) items with hyperthymic (H), depressed (D), irritable (I), cyclothymic (C) and anxious (A) subscales requiring simple "yes" (score 1) or "no" (score 0) answers (Akiskal and Akiskal, 2005).

2.3. Genotyping

Genomic DNA was extracted from 7–10 ml of peripheral blood. Blood was collected and mixed with 0.5 ml of 0.5 Methylenediaminetetraacetic acid (EDETA) then frozen in liquid nitrogen (stored at -80 °C until isolation). The isolation procedure by Lahiri and Schnabel (1993) was used. 5-HTT gene fragments were amplified using the polymerase chain reaction (PCR) method with the following protocol: initial denaturation at 95 °C for 5 min, 30 cycles of denaturation at 95 °C for 1 min, annealing at 58 °C for 1 min, elongation at 72 °C for 1 min, and final extension at 72 °C for 2 min. The reaction mixture contained 0.2 U of Taq polymerase (Fermentas), 5 pmol of each primer, 1x$(NH_4)_2SO_4$ buffer, 4 mmol dNTP mixture, 100–200 ng of matrix DNA, 1.5 mM $MgCl_2$ and H_2O to final volume of 20 μl. Primers' sequences for 5-HTT were: 5′-GGCGTTGCCGCTCTGAATGC-3′ and 5′-GAGGGACTGAGCTGGACAACCAC-3′ (Lesch et al., 1996). Amplified products of 529 and 485 bp, corresponding to L and S allele respectively, were separated via electrophoresis in 2% agarose gel containing ethidium bromide and visualized under UV illumination with O′RangeRuler™ 50 bp DNA Ladder (Fermentas) as DNA length marker.

2.4. Statistical analysis

Shapiro–Wilk test was applied to check for normal distribution. Since the distribution of variables was non normal, nonparametric tests were used in subsequent analysis. Statistical significance of differences was calculated using Mann–Whitney U test, and for comparisons with three or more groups the Kruskal–Wallis ANOVA was applied. The R-Spearman test was used to determine correlations between variables.

STATISTICA 9.0 was used for statistical analyses and the computer program 'Utility Programs for Analysis of Genetic Linkage' (Copyright © 1988 J. Tot) was utilized to test for the goodness of fit to the Hardy–Weinberg equilibrium. A χ^2 value of 32.2 (p-value <0.001) indicates that the study population is not in Hardy–Weinberg equilibrium.

3. Results

In Table 1 the BMI and the intensity of depression symptoms measured with BDI and HDRS are presented. Males and females did not differ in BMI. Females scored higher on BDI (subjective complaints of depression), while males scored higher on HDRS (objective evaluation of intensity of depression symptoms performed by a psychiatrist).

Table 2 presents scores in five affective temperament subscales in obese subjects. In the whole study group, the highest scores were observed in hyperthymic subscale. Females scored higher in depressive and anxious, while males in irritable subscales.

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Table 1
Body Mass Index (BMI) and depressive symptoms (in BDI and HDRS) of the study participants. Data is presented as median and 25th and 75th quartiles.

Group	*N*	BMI	BDI	HDRS
Whole group [Values of Shapiro–Wilk test for normality]	389	35.5; (30.1–64.1) [$W=0.842$; $p<0.001$]	11.0; (0.0–34.0) [$W=0.928$; $p<0.001$]	5.0; (0.0–29.0) [$W=0.879$; $p<0.001$]
Females	237	37.2; (30.2–64.1)	12.0; (0.0–33.0)	4.0; (0.0–29.0)
Males	153	35.2; (30.3–63.0)	9.0; (0.0–34.0)[a]	10.0; (0.0–26.0)[a]

[a] Differences between males and females of $p<0.01$.

Table 2
Scores in affective temperament subscales in patients with obesity. Data is presented as median and 25th and 75th quartiles.

TEMPS-A	Whole group	Males	Females	Z score
Depressive	0.43 (0.33–0.52)	0.43 (0.24–0.43)	0.43 (0.38–0.52)	−4.63**
Cyclothymic	0.33 (0.24–0.52)	0.38 (0.29–0.62)	0.33 (0.29–0.52)	3.56**
Hyperthymic	0.48 (0.29–0.62)	0.50 (0.29–0.62)	0.48 (0.29–0.62)	1.82ns
Irritable	0.19 (0.05–0.29)	0.24 (0.14–0.33)	0.14 (0.05–0.24)	7.21**
Anxious	0.44 (0.24–0.60)	0.36 (0.21–0.52)	0.44 (0.24–0.60)	−2.37*

Differences between males and females of $^{*}p<0.05$ and $^{**}p<0.01$.

Table 3
Age, Body Mass Index (BMI), scores in depressive symptoms (BDI and HDRS) and affective temperament subscales of patients with obesity with BMI ≤ 40 and with morbid obesity BMI > 40. Data is presented as median and 25th and 75th quartiles.

	Obesity	Morbid obesity	*p* Value
	BMI ≤ 40	BMI > 40	Mann Whitney *U* Test
	N=240	*N*=149	
Age	63.5 56.0–70.0	43.0 38.0–50.0	< 0.001
BMI	32.4 30.9–35.3	50.2 43.4–56.5	< 0.001
BDI	11.0; 7.0–17.5	10.0 5.0–20.0	Ns
HDRS	3.0 1.0–11.0	8.0* 3.0–16.0	< 0.001
TEMPS-A			
Depressive	0.43; 0.36–0.52	0.38; 0.29–0.48	
Cyclothymic	0.26; 0.24–0.45	0.48; 0.29–0.62	0.011
Hyperthymic	0.43; 0.24–0.62	0.57; 0.38–0.62	< 0.001 < 0.001 ns
Irritable	0.19; 0.10–0.29	0.19; 0.05–0.33	0.008
Anxious	0.48; 0.25–0.64	0.42; 0.21–0.52	

In Table 3 comparison of BMI, age and scores in BDI, HDRS and TEMPS-A in patients with obesity (BMI ≤ 40) and with morbid obesity (BMI > 40) are shown. Subjects with morbid obesity were younger and presented higher scores in HDRS. In TEMPS-A they scored lower in depressive and anxious subscales, while their scores in cyclothymic and hyperthymic subscales were significantly higher.

Table 4
The genotype of 5-HTTLPR gene distribution in studied group.

Group	N	S/S genotype N (%)	S/L genotype N (%)	L/L genotype N (%)
Whole groupp	389	64 (16.5)	263 (67.6)	62 (15.9)
Females	237	51 (21.5)	141 (59.5)	45 (19.0)
Males	152	13 (8.5)*	122 (80.3)*	17 (11.2)
Obesity BMI ≤ 40	240	17 (7.1)	173 (72.0)	50 (20.9)
Morbid obesity BMI > 4–0	149	47 (31.5)	90 (60.4)#	12 (8.1)#

Difference of genotype distribution between males and females pf $^{*}p<0.01$.
Difference of genotype distribution between obesity and morbid obesity significant of $^{\#}p<0.01$.

Table 5
The BMI and depressive symptoms scores in obese patients with S/S, S/L and L/L genotypes of 5-HTTLPR gene. Data is presented as median and 25th and 75th quartiles.

	S/S genotype *N*=64	S/L genotype *N*=263	L/L genotype *N*=62	*p*
BMI	35.2** (30.3–36.9)	35.3** (31.1–43.9)	52.5 (34.5–56.5)	< 0.001
BDI	9.0** (0.0–9.0)	11.0* (7.0–20.0)	18.0 (7.0–19.0)	< 0.001
HDRS	2.0** (0.0–2.0)	6.0** (2.0–14.0)	12.0 (2.0–14.0)	< 0.001

Significance of differences between genotypes Kruskal–Wallis ANOVA
Difference in comparison to L/L genotype of $^{*}p<0.01$ $^{**}p<0.001$. The *U* Mann–Whitney Test.

The distribution of the 5-HTTLPR polymorphism is presented in Table 4. However, The distribution of genotypes (S/S, S/L, L/L) is different in male and female patients. S/S genotype was significantly more prevalent in females, while S/L genotype was more frequent in males.

Using Kendall's partial rank correlation technique it was found that both genotype and gender showed significant correlations with the results in BDI and HDRS (genotype vs. BDI and HDRS: $\tau=0.08$, $p=0.02$ and $\tau=0.12$, $p<0.001$ respectively; gender vs. BDI and HDRS: $\tau=0.14$, $p<0.001$ and $\tau=0.15$, $p<0.001$ respectively) after their mutual correlation had been partialled out. The association between 5-HTTLPR polymorphism, BMI and depression symptoms measured with BDI and HDRS are presented in Table 5. Obese patients with L/L genotype presented significantly higher BMI and intensity of depression symptoms measured with BDI and HDRS.

Scores in five affective temperament subscales of TEMPS-A in obese patients with S/S, S/L and L/L genotypes are presented in Table 6. As shown, there were significant differences in TEMPS-A results between the three genotypes of 5-HTTLPR. Subjects heterozygous for S/L genotype obtained significantly lower scores in all dimensions of affective temperament, compared to remaining genotypes, except for hyperthymic one in which their score was the highest. Subjects with S/S genotype scored significantly higher in depressive and anxious subscales, compared to S/L and L/L genotypes and lowest on hyperthymic temperament. Subjects with L/L genotype presented highest scores of cyclothymic temperament than other genotypes. Using Kendall's partial rank correlation technique it was found that genotype showed significant correlations with scores in depressive, cyclothymic and irritable subscale of TEMPS-A while gender showed significant correlations with all subscales of TEMPS-A.

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Table 6
Scores of affective temperament subscales in patients with obesity with S/S, S/L and L/L genotype of 5-HTTLPR. Data is presented as median and 25th and 75th quartiles. Kendall's tau and *p*-values for the correlation between genotype and gender and subscales of TEMPS-A. Kruskal–Wallis ANOVA.

TEMPS- A subscales	S/S genotype $N=64$	S/L genotype $N=263$	L/L genotype $N=62$	p	Partial tau for gender	Partial tau for genotype
Depressive	**0.52** (0.31–0.61)	0.38 (0.29–0.43)	0.48 (0.33–0.67)	<0.001	-0.22; $p<0.001$	-0.15 $p<0.001$
Cyclothymic	0.43 (0.24–0.48)	0.28 (0.24–0.48)	**0.55** (0.48–0.67)	<0.001	-0.24 $p<0.001$	0.18 $p<0.001$
Hyperthymic	0.29 (0.19–0.57)	**0.57** (0.38–0.62)	0.43 (0.33–0.62)	<0.001	0.21 $p<0.001$	0.02 $p=0.46$
Irritable	0.24 (0.05–0.29)	0.14 (0.05–0.29)	0.33 (0.19–0.38)	<0.001	-0.20 $p<0.001$	0.34 $p<0.001$
Anxious	**0.47** (0.25–0.60)	0.44 (0.25–0.60)	0.36 (0.20–0.52)	<0.001	-0.17 $p<0.001$	-0.05 $p=0.1$

4. Discussion

In the group of obese patients prevalence of depressive symptoms that met the cut-off for depression was about 50%. Females suffering from obesity scored significantly higher in BDI that measures subjectively experienced depression, while males presented significantly higher scores in HDRS that measures depression objectively. This indicates that female obese patients more often than men report depressive symptoms, contrary to the actual prevalence of depression. It is plausible that the display of depression in obese females plays an important part in their social support seeking. Different neurobiological mechanism may govern the perception of stress and depression in men and women. Beaver et al. (2012) found a connection between short allele of 5 HTTLPR gene and perceived stress in adolescent women, but not in men. Women homozygous for short allele of 5 HTTLPR gene were more likely to report depressive symptoms compared to women with long allele. In our study we observed higher prevalence of short allele of 5 HTTLPR gene in obese females.

Previous data showed comorbidity between obesity and mood disorders (Singht, 2014). In the USA adults with depression are more likely to be obese than adults without depression, this being especially apparent in females (Pratt and Brody, 2014). Emotional eating behavior correlated with depression is an important factor in etiology of obesity (Simon et al., 2006), while obesity is associated with increased risk of depression (Stunkard et al., 2003; Sachs-Ericsson et al., 2007; Luppino et al., 2010; Ma and Xiao, 2010).

Hyperthymic temperament (48%), anxious temperament (44%) and depressive temperament (43%) were the most common dominant affective temperaments in the studied group. Females and males presented a different profile of affective temperaments. Females scored higher in anxious and depressive temperaments, while males in hyperthymic, cyclothymic and irritable temperaments. In comparison, healthy Polish subjects (of both genders) similarly obtained highest scores in hyperthymic temperament, however males had significantly higher scores in hyperthymic and irritable temperament, while females scored significantly higher on cyclothymic and anxious temperaments (Borkowska et al., 2010). This may indicate different affective temperament profile in obese subjects due to gender differences. However, more research on this aspect is required. Interesting data comes from a Polish study performed in females with co-morbid bipolar disorder and bulimia. These patients were characterized by extreme dimensions of both cyclothymic and irritable temperaments (Rybakowski et al., 2014).

Comparing the results of patients with morbid obesity (BMI >40) and obesity (BMI ≤ 40) we found, that subjects with morbid obesity are younger, and score higher in HDRS, but not in BDI. They also score higher in hyperthymic and cyclothymic subscales of TEMPS-A and lower in other domains. This findings may suggest, that morbid obesity is more likely associated with increased risk of bipolar disorder. This partially confirms the findings of Amann et al. (2009), indicating that obesity (especially morbid obesity) is related to more psychiatric disorders. These authors further showed that scores in the "dark triad" (i.e. cyclothymic, irritable and anxious subscales) were significantly more prevalent in patients with morbid obesity. Contrarily, in our study patients suffering from morbid obesity did not differ from the remaining obese subjects in irritable temperament, and presented lower scores on anxious and depressive subscales.

The study population is not in Hardy–Weinberg equilibrium. The genotype distribution is atypical for a Caucasian population which usually displays allele frequencies of 57% for the L allele and 43% for the S allele, with a 5-HTTLPR distribution of 32% L/L, 49% L/S, and 19 S/S (Lesch et al., 1996). The frequency of the S/S allele was significantly higher in females, while S/L allele was more frequent in males. Additionally, compared to the remainder of the group, in patients with morbid obesity the L/L allele was more frequent, while S/L allele was more uncommon. This may indicate possible significance of the long 5-HTTLPR allele in the development of morbid obesity.

Our results show a significant correlation between the 5-HTTLPR polymorphism, depressive symptoms and affective temperament in obese patients. According to our hypothesis short allele of 5-HTTLPR was associated with depressive subscale of TEMPS-A. This corresponds with the data obtained by Gonda et al. (2008) from healthy subjects, which indicate that short allele of this gene may be related to the high risk of depression in general population and also with other disorders connected with emotional disturbances. Previous study of this research group (Gonda et al., 2006) showed an association between short allele of 5-HTTLPR and scores in the cyclothymic, depressive, anxious, and irritable subscales of TEMPS-A in women. This may imply a relationship between affective temperament and serotonin transporter gene polymorphism.

Interestingly, in our study the level of depressive symptoms measured by both self-assessment (BDI) and objective (HDRS) scales was associated with long allele, contrary to previous observations in affective disorders (Caspi et al., 2010; Gonda et al., 2008). One possible explanation of this phenomenon might be that patients suffering from affective and somatic disorders tend to develop different types of depression; in obesity the clinical manifestation of depression is mainly atypical. Moreover, the long allele of 5-HTTLPR was associated with higher BMI (Table 4) and, as was mentioned before, was significantly more prevalent in subjects with morbid obesity.

In morbid obesity it is likely, that sensitivity to external stimuli associated with long allele of 5-HTTLPR is lowered, resulting in lesser reactiveness to information regarding the increased risk of serious health problems connected with abnormally high BMI. This may be yet another factor impairing the change of pathological eating behavior. Moreover in obesity L/L genotype is strongly

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connected with cyclothymic temperament, and although the depressive temperament was mainly associated with short allele of 5-HTTLPR, subjects with L/L genotype obtained significantly higher results in depressive temperament in comparison to S/L genotype, while their scores were only slightly lower compared with patients with S/S genotype. This indicates that long allele of 5-HTTLPR may also be involved in etiology of depressive temperament and depression in obesity. This corresponds with previous data that pointed at an association between long allele of 5-HTTPLR and unipolar depression (Collier et al., 1996; Ogilvie et al., 1996).

The scores of subjects with S/L genotype of 5-HTTLPR were significantly lower in irritable, cyclothymic and depressive temperaments compared to remaining genotypes. This may point to a protective role of S/L genotype in the development of affective disorders in obese patients.

To summarize, we found that the short allele of 5-HTTLPR considered to be associated with higher sensitivity to life stress (Wilhelm et al., 2007), may play a crucial role in the development of depressive temperament in obese patients, while long allele of 5-HTTLPR was connected with the development of morbid obesity and depression in the studied population.

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Conflict of interest

None to declare.

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