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Research article

The polymorphisms in serotonin-related genes (5-HT$_{2A}$ and SERT) and the prevalence of depressive symptoms in obese patients

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HIGHLIGHTS

- We examine the association between serotonin-related gene polymorphisms and the occurrence of depressive symptoms.
- The experimental group consists of obese patients.
- For the depressive symptoms measurement we use the Beck Depression Inventory (BDI) and Hamilton Depression Scale (HAM-D).
- 39% of patients are diagnosed with depressive symptoms.
- There are no significant associations between 5-HT$_{2A}$ and 5-HTT gene polymorphisms and depressive symptoms.

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ABSTRACT

As overweight and obesity are a growing problem in industrialized societies, they become a main focus of many studies. The aim of this study was to determine whether there is an association between the occurrence of polymorphisms in serotonin-related genes and the prevalence of depressive symptoms in obese patients. Two polymorphisms were tested: a 44-bp insertion/deletion in the serotonin transporter (SERT) gene and a single-nucleotide variation (1438G/A) in the serotonin 2A receptor (5-HT$_{2A}$) gene. The study involved 180 patients (41 men; 139 women) previously diagnosed as obese. All patients were subjected to clinical, biochemical, and neuropsychological evaluation and genotyping. Amplification of the gene fragments was obtained by the polymerase chain reaction (PCR) method. Products of the genotyping were separated via electrophoresis. The intensity of depressive symptoms was measured using the Beck Depression Inventory (BDI) and Hamilton Depression Scale (HAM-D). Clinically relevant depressive symptoms were diagnosed in 39% of subjects. The lowest intensities of depressive symptoms were ascertained in the group with the least advanced obesity, but this trend was statistically insignificant. Small differences were observed in obesity indicators among three groups of patients with various genotypes of the SERT gene, but these differences were also statistically insignificant. Furthermore, in the context of the intensity of depressive symptoms, no significant associations were observed in these two groups. Furthermore, no statistically significant differences were observed among specific obesity parameters and intensity of depressive symptoms as a function of the 5-HT$_{2A}$ gene polymorphism. To conclude, depressive symptoms were prevalent in obese participants: 39% of subjects experienced symptoms of clinical relevance. However, no significant associations were observed between 5-HT$_{2A}$ and SERT gene polymorphisms and depressive symptoms in this study group.

1. Introduction

The highest prevalence of obesity affects industrialized countries and societies, in which high-calorie diets are widespread. In Poland, the number of people living with this problem is increasing. Results obtained by the Pol-MONICA study in 1984, 1988, and 1993

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revealed that the percentage of obese women increased from 28% to 29% and that of obese men increased from 18.6% to 22.4% over this time period [1].

Overweight and obesity are also correlated with the occurrence of depressive symptoms. Prospective observational research has shown that occurrence of depression predicts the development of obesity, and also that the occurrence of obesity is a factor in the development of depression [2,3]. Data collected over the course of a national health program conducted in the USA from 2005 to 2006 revealed that BMI positively correlates with mild and moderate depressive symptoms, as well as with major depression, defined as having a score of ≥10 or meeting the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) diagnostic criteria for major depression on the nine-item Patient Health Questionnaire (PHQ-9). The increase in depressive symptoms as a function of weight starts at a BMI of 30 kg/m [2,4].

A large body of research indicates that serotonergic transmission plays a role in eating disorders. In humans, serotonin and its agonists cause moderation of food ingestion, weight loss, and increased energy expenditure. The activity of the serotonin transporter (SERT) is negatively correlated with BMI [5], possibly explaining the effectiveness of selective serotonin reuptake inhibitors (SSRI) for the treatment of obesity [6,7].

The gene encoding SERT is located on the long arm of chromosome 17 (17q11.1–17q12). Polymorphisms in the transcriptional regulatory region of this gene (5-HTTLPR: *SERT gene-linked polymorphic region*) involve a region of variable length that is rich in guanine–cytosine pairs. The absence or presence of a 44-bp fragment in this region results in the short (S) or long (L) variant, respectively; these variants differ in gene promoter activity [8]. The S-allele is linked to lower baseline transcriptional activity of the SERT gene, resulting in lower efficiency of serotonin reuptake [9,10]. To date, it remains unclear whether the 5-HTTLPR polymorphism is related to obesity.

The gene encoding the serotonin 2A receptor (5-HT_{2A}) is located on the long arm of chromosome 13 (13q14–q21). The most commonly investigated polymorphism of this gene is a single-nucleotide variation, 1438 G/A, in the promoter. Several studies have investigated the possible role of this polymorphism in obesity, but the results are ambiguous. Perez-Cornago et al. determined that DNA hypermethylation of 5-HT_{2A} is associated with a worse response to a weight loss intervention in subjects with metabolic syndrome [11].

Both of these polymorphisms have also been investigated in the context of their association with depressive symptoms. In a Scottish population, the S-allele positively correlated with unipolar disorder[12]; however, another study showed that the L-allele is associated with this disease [13]. A meta-analysis published in 2004 revealed a statistically significant association between the S-allele and unipolar disorder [14]. Analysis of the 1438G/A polymorphism did not reveal any significant correlation with the occurrence of major depression [15]. However, in a group of 67 persons with seasonal depression, the A-allele was more prevalent [16].

2. The aim of the study

We sought to assess the association between polymorphisms in serotonin-related genes (5-HT_{2A} and SERT) and the occurrence of depressive symptoms in obese patients.

3. Methods

The study involved 180 patients (139 women) of Polish nationality and Caucasian ethnicity, aged 18–73 years (mean, 43.7 ± 7.8). Demographic factors are shown in Table 1. The subjects were diagnosed as obese (BMI > 30 kg/m^2) and they were recruited from population hospitalized in Department of Endocrinology and Diabetology of Collegium Medicum of the Nicolaus Copernicus University (NCU) due to obesity. Patients with addictions or severe somatic, psychiatric, or neurological disorders were excluded, as were patients with secondary obesity. Permission for the study was obtained from the Bioethical Commission of the NCU, Collegium Medicum in Bydgoszcz (No. 533/2008). The subjects demonstrated their willingness to participate in the project by signing the Informed Consent Form.

3.1. Assessments

The first stage of the study was the clinical assessment, which consisted of obtaining a medical history and performing a physical examination. Aspects of obesity and psychological disorders mentioned in the medical history were emphasized. Metric measurements were taken of body weight, waist circumference, and hip circumference; waist-hip ratio (WHR) was also calculated.

The next step was assessment of the intensity of depressive symptoms. For this purpose, The Beck Depression Inventory (BDI) and the Hamilton Depression Rating Scale (HAM-D) were used. According to the BDI, patients scoring 12 or more points were diagnosed as having clinically important symptoms of depression. HAM-D is a multiple-choice questionnaire that is useful for measuring levels of depression among patients. The questionnaire is filled in by the clinician; therefore, it is an objective tool for measuring the intensity of depressive symptoms. HAM-D, which was designed for adults, defines the level of observed depressive symptoms, including low mood, insomnia, anxiety, and weight loss.

3.2. Isolation of genetic material

7–10 ml of peripheral blood was collected and mixed with 0.5 ml of 0.5 M ethylenediaminetetraacetic acid (EDTA), then frozen in liquid nitrogen and stored at −80 °C until isolation. The isolation procedure was followed using fast isolation procedure by Lahiri and Schnabel [17] and stored at −20 °C.

3.3. Genotype analysis

5-HT_{2A} gene promoter region and SERT gene fragments where 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, 1 × (NH4) 2SO4 buffer, 4 mmol dNTP mixture, 100–200 ng of matrix DNA, 1.5 mM MgCl2 and H2O to final volume of 20 μl.

Primers' sequences for 5-HT_{2A} were: F 5'-ACGAAGGGACTCCTGGTTTC-3' and R 5'-CTGGGTGGGATATTTCTGCT-3' [18]. Amplified product of 515 bp length (~100 ng) was digested overnight with 0.2 U of HpaII restriction enzyme (Fermentas) at 37 °C. Amplicons with −1438G allele were cut into 331 bp and 184 bp fragments, while those with −1438A remained undigested. The fragments were separated via electrophoresis in 3% agarose gel containing ethidium bromide and visualized under UV illumination with O'RangeRuler™ 50 bp DNA Ladder (Fermentas) as DNA length marker (Fig. 1).

Primers' sequences for SERT were: 5′-GGCGTTGCCGCTCTGAATGC-3′ and 5′-GAGGGACTGAGCTGGACAACCAC-3′ [19]. 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

Table 1
Demographic and clinical characteristics of the study participants undefined.

Group	*N*	Median BMI (range) [95%CI]	Median age, years (range) [95%CI]	Median BDI score (range) [95%CI]	Median HAM-D score (range) [95%CI]
Women	139	42.4char_ndash (30.1–64.1) [41,8 to 44,5]	40char_ndash (18–73) [37,5 to 42,0]	9char_ndash (0–34) [9,4 to 12,5]	4char_ndash (0–29) [5,0 to 8,4]
Men	41	47.3char_ndash (30.7–59.4) [43,2 to 48,1]	40char_ndash (19–63) [37,5 to 44,7]	11char_ndash (0–35) [8,5 to 15,7]	6char_ndash (0–20) [3,6 to 10,0]

BMI: body mass index; BDI: Beck Depression Inventory; HAM-D: Hamilton Depression Scale.

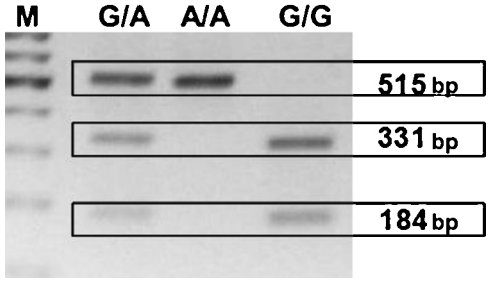

Fig. 1. Representative photo of the digested 5-HT_{2A} PCR products depending on the genotype: AA–only 515 bp band; G/A–515, 331 and 184 bp bands; GG–331 and 184 bp bands.

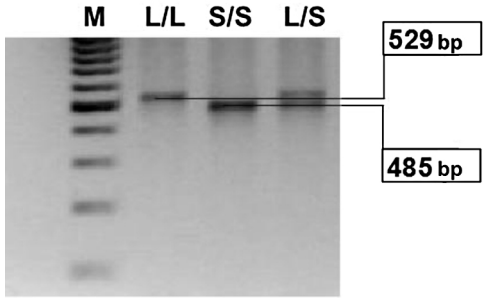

Fig. 2. Representative photo of separated SERT PCR products depending on the genotype: LL–only 529 bp band; S/S 485 bp band; L/S–529 and 458 bp bands M-DNA ladder.

O'RangeRuler™ 50 bp DNA Ladder (Fermentas) as DNA length marker (Fig. 2).

3.4. Statistical analysis

STATISTICA 9.0 was used for statistical analyses. The distribution of variables was analyzed using the Shapiro–Wilk test, which indicated that the variables were non-parametric. To assess the significance of the differences between groups, the Mann–Whitney *U* test was conducted for comparisons between two groups and the Kruskal–Wallis one-way analysis of variance by ranks test was used for comparisons among three groups. The R-Spearman test was used to determine correlations between variables. The computer program 'Utility Programs for Analysis of Genetic Linkage' (Copyright© 1988J. Tot) was utilized to test the goodness of fit of the genotypes to Hardy–Weinberg equilibrium. A p-value > 0.05 indicates agreement with Hardy–Weinberg equilibrium.

4. Results

The Mann–Whitney *U* test was performed to determine whether the BMI parameter differed significantly between male and female subjects. The mean BMI value was slightly higher in the male population, but this difference was not statistically significant.

The intensities of depressive symptoms determined by the BDI and HAM-D scales were highly positively correlated in both women (p = 1E-05) and men (p = 0.0001). Clinically relevant depressive symptoms were diagnosed in 39% of subjects. Because the data were non-parametric we calculated the R-Spearman rank correlation coefficient to investigate the correlation between age and BMI; these values were positively correlated (r = 0.329; p = 0.000022). No relevant correlations among age and BDI/HAM-D scores were observed. The lowest intensities of depressive symptoms (as measured by the BDI) were observed in the group with the lowest level of obesity, but this trend was not statistically significant.

Regarding the L/S (SLC6A4) polymorphism of the SERT gene, we used both the BDI and HAM-D to measure the intensity of depressive symptoms in L/L and S/S homozygotes and L/S heterozygotes in subgroups comprising male and female subjects (Table 2).

In addition, we examined the correlation between the L/S polymorphism and excessive body mass. (Table 2) presents the mean

Table 2
BDI, HAM-D and BMI results in relation to polymorphism L/S (SLC6A4) of the SERT gene.

	TOTAL			
	L/L (n = 63)	L/S (n = 89)	S/S (n = 25)	p-value
BDI	10.0 (0.0–34.0) [9,6 to 14,3]	8 (0.0–35.0) [7,6 to 11,7]	15.5 (0.0–32.0) [9,3 to 18,0]	0.11
HAM-D	6.0 (0.0–29.0) [5,1 to 10,7]	4.0 (0.0–25.0) [3,9 to 7,9]	5.0 (0.0–19.0) [2,11 to 10,9]	0.66
BMI	43.2 (30.1–61.9) [41,7 to 45,8]	42.4 (30.1–64.1) [41,8 to 45,3]	44.3 (33.2–59.4) [41,8 to 47,6]	0.85
FEMALES				
	L/L (n = 50)	L/S (n = 65)	S/S (n = 20)	p-value
BDI	9.0 (0.0–34.0) [9,4 to 14,8]	6.0 (0.0–25.0) [6,6 to 10,7]	15.5 (0.0–32.0) [9,2 to 18,5]	0.054
HAM-D	7.0 (0.0–29.0) [5,4 to 11,7]	3.0 (0.0–25.0) [2,7 to 7,0]	8.0 (0.0–19.0) [2,3 to 14,3]	0.08
BMI	41.5 (30.1–57.1) [40,1 to 44,6]	41.3 (30.1–64.1) [41,3 to 45,6]	43.9 (37.2–58.6) [41,2 to 46,4]	0.55
MALES				
	L/L (n = 13)	L/S (n = 24)	S/S (n = 5)	p-value
BDI	11.0 (0.0–27.0) [6,3 to 17,9]	9.0 (0.0–35.0) [6,9 to 17,4]	12.0 (3.0–21.0) [0,3 to 23,7]	0.99
HAM-D	3.5 (0.0–8.0) [-2,4 to 9,9]	9.5 (0.0–20.0) [4,6 to 14,4]	1.0 (1.0–5.0) [-3 to 8,0]	0.13
BMI	48.9 (31.7–59.2) [42,8 to 52,3]	43.9 (30.7–55.1) [41,1 to 17,4]	51.5 (33.2–59.4) [30,6 to 67,2]	0.42

Values are expressed as the median (range). [95%CI] – 95% confidence interval; BDI: Beck Depression Inventory; HAM-D: Hamilton Depression Scale.

Table 3
BDI, HAM-D and BMI results in relation to polymorphism 1438 G/A of the 5-HT_{2A} gene.

	TOTAL			
	A/A (n = 25)	A/G (n = 83)	G/G (n = 69)	p-value
BDI	9.0 (0.0–33.0) [6,2 to 15,6]	8.0 (0.0–35.0) [9,0 to 13,2]	11.0 (0.0–34.0) [9,5 to 14,0]	0.69
HAM-D	7.0 (0.0–21.0) [3,5 to 12,2]	3.0 (0.0–29.0) [3,8 to 8,6]	7.0 (0.0–21.0) [5,2 to 9,1]	0.38
BMI	43.2 (30.1–64.1) [40,8 to 48,6]	43.9 (30.8–61.9) [41,8 to 45,1]	43.2 (30.1–59.2) [42,1 to 46,0]	0.82
FEMALES				
	A/A (n = 19)	A/G (n = 59)	G/G (n = 57)	p-value
BDI	8.0 (0.0–33.0) [4,6 to 16,9]	8.0 (0.0–31.0) [8,0 to 12,5]	11.0 (0.0–34.0) [9,8 to 14,5]	0.21
HAM-D	7.0 (0.0–21.0) [3,3 to 14,9]	3.0 (0.0–29.0) [3,0 to 8,7]	6.0 (0.0–21.0) [4,7 to 9,1]	0.32
BMI	45.0 (30.8–61.9) [41,5 to 50,1]	41.5 (30.1–59.2) [40,7 to 44,5]	41.9 (30.1–64.1) [40,9 to 45,3]	0.47
MALES				
	A/A (n = 6)	A/G (n = 24)	G/G (n = 12)	p-value
BDI	11.0 (3.0–21.0) [5,3 to 17,6]	11.0 (0.0–35.0) [7,5 to 18,5]	10.0 (0.0–30.0) [4,2 to 18,2]	0.79
HAM-D	4.5 (0.0–9.0) [-2,9 to 11,9]	5.0 (0.0–20.00) [1,5 to 13,6]	7.5 (4.0–11.0) [2,5 to 12,4]	0.99
BMI	37.4 (31.7–59.4) [30,0 to 52,6]	47.6 (30.8–59.2) [42,5 to 49,3]	48.9 (36.6–55.4) [43,7 to 51,0]	0.99

Values are expressed as the median (range). M[95%CI] – 95% confidence interval; IBDI: Beck Depression Inventory; HAM-D: Hamilton Depression Scale; BMI: Body Mass Index.

values of the parameters describing obesity in three subgroups: L/L and S/S homozygotes and L/S heterozygotes. Analysis of these results indicated that there were no statistically significant differences among the three subgroups, BMI oscillated around similar values regardless of the allele type.

Among obese females, the associations between L-allele carrier and S-allele homozygote status and the intensity of depressive symptoms (measured with the BDI) were likewise not significant (Table 2). In L/L and L/S females the intensity of depressive symptoms was 9.0, and among S/S females it was 15.5, with the p-value of 0.077.

The most frequently studied polymorphism of the 5-HT_{2A} gene is the 1438 G/A promoter polymorphism. Therefore, we next investigated whether the occurrence of obesity differed among A/A and G/G homozygotes and G/A heterozygotes (in subgroups of women and men) (Table 3). However, the differences were not statistically relevant; BMI oscillated around similar values regardless of the allele type.

In addition, we investigated the association between polymorphisms in the 5-HT_{2A} gene and the intensity of depressive symptoms as measured by both BDI and HAM-D (Table 3). This analysis did not detect any significant differences in the intensity of depression in association with the 5-HT2A gene 1438 G/A polymorphism.

5. Discussion

Overweight and obesity have become serious problems in recent years; therefore, identifying the causes and developing new treatments are important scientific goals. Furthermore, psychological issues are a key aspect of eating disorders.

Many studies show that the most common problem affecting overweight and obese people is depression [2–4,20]. Here, we confirmed that the prevalence of depression in a cohort of obese patients was 39%. It is in agreement with previous studies which likewise indicated high prevalence of depression in obese subjects [2]. Previous studies report a correlation between perturbations of the serotoninergic system, obesity, and depression; consistent with this, serotoninergic antidepressants have been used successfully to treat some cases of obesity [21].

On the basis of these earlier findings, one of the main goals of the present study was to assess the interplay between polymorphisms in genes related to neurotransmitter activity, parameters of obesity, and depressive symptoms; certain interdependences were identified.

Previous studies [8,22,23] on the association between the L/S 5-HTTLPR polymorphism and obesity yielded conflicting results. Similarly, the results presented here do not demonstrate a specific correlation between BMI and L/S 5-HTTLPR. Therefore, this question requires additional study in other groups of obese subjects.

Studies conducted nearly 20 years ago suggest a correlation between the L-allele and unipolar disease [12,13]. However, a subsequent meta-analysis of three studies indicates that the S-allele is associated with unipolar disease [24]. The results presented herein are different from those of previous studies, which suggested that the S-allele is associated with a greater predisposition to depression [25]. Also in recent study Schulz et al. observed relevant correlation between S-allele and depression measured by Short Geriatric Depression Scale in group of 606 individuals [26].

Here, we observed no associations between 5-HTTLPR genotype and the intensity of depressive symptoms (as measured by BDI and HAM-D). This finding suggests that in these patients polymorphism of the serotonin transporter gene is not the most significant factor leading to depression.

As to the 1438G/A polymorphism in the serotonin 2A receptor, we observed no significant difference in obesity indicators in subjects carrying this allele. Similarly, no such differences were detected in a family study conducted in a Spanish population [29].

Likewise, we did not observe an association between the G and A alleles and the intensity of depressive symptoms in obese subjects. Therefore, it is likely that polymorphism of the 5-HT_{2A} gene does not play a significant role in the etiology of depression in obese people. Similar results were obtained in several studies of affective diseases assessed in two meta-analyses [15,16], in which major depression, unipolar and bipolar disorders ware diagnosed according to a standard diagnostic criteria (DSM, ICD).

The findings of global studies are not uniform: Japanese authors have demonstrated a statistically significant association between the 5-HT_{2A} A/G polymorphism and the intensity of depressive symptoms (as measured by the MADRS scale) [30].

The present results suggest, at least in this specific population, that it is unlikely that polymorphisms in the SERT and 5-HT_{2A} genes are significantly correlated with the intensity of depressive symptoms in obese subjects or with obesity itself. Thus, the results reflect the enormous complexity of the problem of obesity and depression. We must continue searching for the genetic mechanisms responsible for depressive symptoms in these patients.

Conflict of interest

The authors declare no conflicts of interest in association with this manuscript.

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References

[1] A. Pająk, R. Topór-Madry, A. Waśkiewicz, E. Sygnowska, Współczynnik masy ciała a ryzyko zgonu., Badanie POL-MONICA w populacji polskiej w średnim wieku Kardiol Pol., 2005; 62: 95–105.
[2] N. Sachs-Ericsson, A.B. Burns, K.H. Gordon, et al., Body mass index and depressive symptoms in older adults: the moderating roles of race, sex, and socioeconomic status, Am. J. Geriatr. Psychiatry 15 (2007) 815–825.
[3] F.S. Luppino, L.M. de Wit, P.F. Bouvy, et al., Overweight, obesity, and depression: a systematic review and meta-analysis of longitudinal studies, Arch. Gen. Psychiatry 67 (2010) 220–229.
[4] J. Ma, L. Xiao, Obesity and depression in US women: results from the 2005–2006 National Health and Nutritional Examination Survey, Obesity (Silver Spring) 18 (2010) 347–353.
[5] D. Erritzoe, V.G. Frokjaer, M.T. Haahr, et al., Cerebral serotonin transporter binding is inversely related to body mass index, Neuroimage 52 (2010) 284–289.
[6] C.C. Huang, C.Y. Chian, J.D. Lin, Short-term treatment of obesity with fluoxetine as a supplement to a low calorie diet, Changgeng Yi Xue Za Zhi 21 (March (1)) (1998) 50–56.
[7] H. Rezvanian, M. Hashemipour, R. Kelishadi, N. Tavakoli, P. Poursafa, A randomized,triple masked, placebo-controlled clinical trial for controlling childhood obesity, World J. Pediatr. 6 (November (4)) (2010 Nov) 317–322.
[8] H. Mergen, C. Karaaslan, M. Mergen, E. Deniz Ozsoy, M. Ozata, LEPR, ADBR3, IRS-1 and 5-HTT genes polymorphisms do not associate with obesity, Endocr. J. 54 (2007) 89–94.
[9] M. Nakamura, S. Ueno, A. Sano, H. Tanabe, The human serotonin transporter gene linked polymorphism (5-HTTLPR) shows ten novel allelic variants, Mol. Psychiatry 5 (2000) 32–38.
[10] K.P. Lesch, D. Bengel, A. Heils, S.Z. Sabol, B.D. Greenberg, S. Petri, J. Benjamin, C.R. Muller, D.H. Hamer, D.L. Murphy, Association of anxiety-related traits with a polymorphism in the serotonin transporter gene regulatory region, Science 274 (1996) 1527–1531.
[11] A. Perez-Cornago, M.L. Mansego, M.A. Zulet, J.A. Martinez, DNA hypermethylation of the serotonin receptor type-2A gene is associated with a worse response to a weight loss intervention in subjects with metabolic syndrome, Nutrients 6 (June 23 (6)) (2014) 2387–2403.
[12] A.D. Ogilvie, S. Battersby, V.J. Bubb, et al., Polymorphism in serotonin transporter gene associated with susceptibility to major depression, Lancet 16 (1996) 731–733.
[13] D.A. Collier, M.J. Arranz, P. Sham, et al., Serotonin transporter is a potential susceptibility factor for bipolar affective disorder, Neuroreport 7 (1996) 1675–1679.
[14] F.E. Lotrich, B.G. Pollock, Meta-analysis of serotonin transporter polymorphisms and affective disorders, Psychiatr. Genet. 14 (2004) 121–129.
[15] M. Anguelova, C. Benkelfat, G. Turecki, A systematic review of association studies investigating genes coding for serotonin receptors and the serotonin transporter: I. Affective disorders, Mol. Psychiatry 8 (2003) 574–591.
[16] M.A. Enoch, D. Goldman, R. Barnett, L. Sher, C.M. Mazzanti, N.E. Rosenthal, Association between seasonal affective disorder and the 5-HT2A promoter polymorphism, −1438G/A, Mol. Psychiatry 4 (1999) 89–92.
[17] D.K. Lahiri, B. Schnabel, DNA isolation by a rapid method from human blood samples: effects of MgCl2, EDTA, storage time, and temperature on DNA yield and quality, Biochem. Genet. 31 (1993) 321–328.
[18] I.S. Chee, S.W. Lee, J.L. Kim, S.K. Wang, Y.O. Shin, S.C. Shin, Y.H. Lee, H.M. Hwang, M.R. Lim, 5-HT2A receptor gene promoter polymorphism -1438 A/G and bipolar disorder, Psychiatric Genetics 11 (2001) 111–114.
[19] K.P. Lesch, D. Bengel, A. Heils, S.Z. Sabol, B.D. Greenberg, S. Petri, J. Benjamin, C.R. Muller, D.H. Hamer, D.L. Murphy, Association of anxiety-related traits with a polymorphism in the serotonin transporter gene regulatory region, Science 274 (1996) 1527–1531.
[20] T.M. Gadalla, Association of obesity with mood and anxiety disorders in the adult general population, Chronic. Dis. Can. 30 (2009) 29–36.
[21] A.J. Stunkard, M.S. Faith, K.C. Allison, Depression and obesity, Biol. Psychiatry 54 (2003) 330–337.
[22] A. Hinney, N. Barth, A. Ziegler, et al., Serotonin transporter gene-linked polymorphic region: allele distributions in relationship to body weight and in anorexia nervosa, Life Sci. 61 (1997) 295–303.
[23] M. Iordanidou, A. Tavridou, I. Petridis, et al., The serotonin transporter promoter polymorphism (5-HTTLPR) is associated with type 2 diabetes, Clin. Chim. Acta. 411 (February) (2010) 167–171.
[24] R.A. Furlong, L. Ho, C. Walsh, et al., Analysis and meta-analysis of two serotonin transporter gene polymorphisms in bipolar and unipolar affective disorders, Am. J. Med. Genet. 81 (1998) 58–63.
[25] K.S. Kendler, J.W. Kuhn, J. Vittum, C.A. Prescott, B. Riley, The interaction of stressful life events and a serotonin transporter polymorphism in the prediction of episodes of major depression: a replication, Arch. Gen. Psychiatry 62 (May) (2005) 529–535.
[26] C.J. Scholz, S. Jungwirth, W. Danielczyk, H. Weber, I. Wichart, K.H. Tragl, P. Fischer, P. Riederer, J. Deckert, E. Grünblatt, Investigation of association of serotonin transporter and monoamine oxidase-A genes with Alzheimer's disease and depression in the VITA study cohort: a 90-month longitudinal study, Am. J. Med. Genet. B. Neuropsychiatr. Genet. 165B (March (2)) (2014) 184–191.
[29] J.L. Santos, M.C. Ochoa, A. Patiño, C. Azcona, J.A. Martínez, A. Marti, No evidence of association between the serotonin 2A receptor–1438G/A promoter polymorphism and childhood obesity in a Spanish population: a case-parent study and a matched case-control study, Nutr. Neurosci. 8 (2005) 207–211.
[30] M. Kamata, A. Suzuki, K. Yoshida, H. Takahashi, H. Higuchi, K. Otani, Genetic polymorphisms in the serotonergic system and symptom clusters of major depressive disorder, J. Affect. Disord. 135 (2011) 374–376.