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Published in:
Pharmacogenomics and personalized medicine

DOI:
10.2147/PGPM.S327353

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
2021

Link to publication in University of Groningen/UMCG research database

Citation for published version (APA):
Boiko, A. S., Pozhidaev, I. V., Paderina, D. Z., Bocharova, A. V., Mednova, I. A., Fedorenko, O. Y., Kornetova, E. G., Loonen, A. J. M., Semke, A. V., Bokhan, N. A., & Ivanova, S. A. (2021). Search for Possible Associations of FTO Gene Polymorphic Variants with Metabolic Syndrome, Obesity and Body Mass Index in Schizophrenia Patients. *Pharmacogenomics and personalized medicine*, *14*, 1123-1131. https://doi.org/10.2147/PGPM.S327353

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ORIGINAL RESEARCH

Search for Possible Associations of *FTO* Gene Polymorphic Variants with Metabolic Syndrome, Obesity and Body Mass Index in Schizophrenia Patients

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Purpose: Metabolic syndrome (MetS) is characterized by abdominal obesity, hyperglycaemia, dyslipidaemia and hypertension. FTO gene has been implicated in the pathogenesis of obesity, but the available scientific data concerning their relationship to antipsychotic drug-induced obesity and metabolic syndrome is still incomplete and inconsistent, which indicates that continuing the investigation of this gene's role is necessary.

Patients and Methods: In the present study, 517 patients with schizophrenia underwent antipsychotic drug treatment, and two groups were identified: patients with MetS and without MetS. Genotyping of 6 SNPs in the FTO gene was performed, and the results analyzed using R-programme.

Results: We performed a statistical analysis to identify possible associations of the frequencies of genotypes and alleles of the studied polymorphisms with the presence of metabolic syndrome in schizophrenia patients, with the presence of abdominal obesity, and with an increased body mass index. The rs7185735 polymorphism did not meet the Hardy-Weinberg criterion and was excluded. After correcting for differences in age, gender and duration of illnesses, none of the variants was shown to be related to metabolic syndrome or abdominal obesity, but rs9939609, rs1421085, rs3751812 and rs8050136 were associated with body mass index.

Conclusion: The present study provides additional support for these SNP's roles as a pharmacogenetic biomarker that may become useful in the framework of the personalized medicine approach.

Keywords: schizophrenia, gene polymorphism, body weight, waist circumference, fat mass and obesity associated gene

Introduction

Antipsychotics are an important therapeutic agent for patients with schizophrenia and bipolar disorder, but long-term usage of these drugs increases the risk of developing type 2 diabetes mellitus, hyperlipidemia and hypertension.[1–3] Together with central obesity, these phenomena form the so-called Metabolic Syndrome (MetS), which is a clustering of well-known cardiovascular risk factors.[4,5] Apart from increasing the likelihood of serious cardiovascular[6,7] and malignant pathology,[8,9] significant weight gain can also affect compliance and a decrease in the quality of life of patients with schizophrenia, since, in addition to the stigma of

Received: 1 July 2021
Accepted: 20 August 2021
Published: 7 September 2021

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schizophrenia, the stigma of obesity is added.[10] The prevalence of MetS and obesity in patients with schizophrenia is high, so according to studies, the incidence of MetS in schizophrenia patients taking antipsychotics ranges from 28%[11] to 46%,[12] and obesity from 16.4%[13] to 48.9%.[14]

The *FTO* gene was identified in 1999 as "Fatso" when tracing the genes lost in a mouse mutant with fused toes (Ft mutant).[15,16] After two independent Genome-Wide Associations Studies (GWAS) found that this gene had something to do with obesity,[17,18] a flood of research has begun to further specify its role, now labelled as "fat mass and obesity associated" (*FTO*) gene.[19,20] FTO protein function was first described as an N6-methyladenosine (m6A) demethylase dependent on iron and 2-oxoglutarate.[21,22] Then, the *FTO*-deficient mouse model was studied to understand its physiological function. These mice display postnatal growth retardation and reduced food intake, with a reduction of adipose tissue.[23,24] In line with this, overexpression of *FTO* induced an increase of adipose tissue.[25] The protein coded for by the *FTO* gene can be considered one of the most important enzymes that remove the methyl-labelling of N6-methyladenosine residues from the RNA molecule.[26,27] The activity of this RNA demethylase partly determines the post-transcriptional gene expression regulation and thus influences numerous (patho)physiological functions,[26,27] linking the *FTO* gene to cancer, obesity and neuropsychiatric disorders.[28–30] However, although the human *FTO* gene, which is located on chromosome 16q12.2,[31] encodes for RNA demethylase, this is probably not its primary role in causing obesity.[32] In contrast, *FTO* intronic variant rs1421085, which is the causal single nuclear polymorphism (SNP) associated with obesity, does not regulate *FTO* expression.[32] In fact, this variant disrupts the binding site of the ARID5B repressor, which regulates IRX3 and IRX5 expression, homeobox genes involved in morphogenesis during early embryonic development.[32–35] It has been suggested that this results in a shift between the development of beige (energy-wasting) and white (energy-storing) adipocytes.[34] Although a critical significance of IRX3 in the differentiation of preadipocytes has been demonstrated,[36] other mechanisms also exist that may be applicable.

The significance of polymorphisms of the *FTO* gene for obesity has been extensively investigated. In the first GWAS of the relationship between BMI and the *FTO* gene, rs9939609 was chosen to represent ten variants of the gene's first intron.[17] This variant was also found by Scuteri et al, but in their study,[18] rs9930506 showed the greatest association with increased BMI, hip circumference and body weight. At approximately the same time, obesity was found with a case-control design to be associated with rs1421085 and rs17817449 in different patient populations.[31] The findings for rs9939609, rs1421085, and rs17817449 were later confirmed in a Mexican population[37] and for rs9939609 with type 2 diabetes.[38] In a recent meta-analysis of GWASs, 29 SNPs in FTO were significantly associated with lean soft tissue (nonfat, nonbone), including rs9939609, rs9930506, rs1421085, and rs17817449.[39] Rs1421085 is in perfect linkage disequilibrium with rs1558902,[34] which in turn is the most associated SNP in the GWAS of Locke et al.[40] The rs1861868 variant is much less well studied, but an association with BMI in Old Order Amish individuals,[41] as well as Spanish,[42] German Sorbian,[43] African American,[44] Emirati,[45] and Saudi populations[46] has been described.

The involvement of the *FTO* gene in the development of obesity may be clear, but its contribution concerning weight gain in users of antipsychotic drugs is less evident.[47–51] An association between variants of the *FTO* gene is not observed by all researchers and is rather modest in many other cases. The relationship between polymorphisms of the FTO gene and metabolic syndrome has only once been investigated.[52]

The previous uncertainties led us to investigate the association between six variants of the *FTO* gene (rs7185735, rs9939609, rs1421085, rs1861868, rs3751812, rs8050136) and BMI or MetS in schizophrenia patients from three hospitals in Siberia.

Materials and Methods

Study Subjects

The study complied with the Declaration of Helsinki (1975, revised in Fortaleza, Brazil, 2013). The study protocol was approved by the Bioethical Committee of the Mental Health Research Institute of the Tomsk National Research Medical Center of the Russian Academy of Sciences (Protocol 187, approval on 24.04.2018). The patient population and design of the study particular have been described before.[53,54] After obtaining informed consent, we recruited 517 inpatients with schizophrenia from the clinics of the Research Institute of Mental Health of the Tomsk National Research Medical Center, the Tomsk Clinical Psychiatric Hospital, the Hospital of the Siberian State Medical University, the Kemerovo Regional Clinical

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Psychiatric Hospital and the N.N. Solodnikova Clinical Psychiatric Hospital of Omsk in the Russian Federation.

The study included patients with a verified diagnosis of schizophrenia according to ICD-10 (International Classification of Diseases 10th revision)[55] criteria, age 18–65 years, the patient's informed consent, Caucasian appearance, the absence of severe organic pathology or somatic disorders in the stage of decompensation, and usage of a stable antipsychotic treatment. The severity of psychopathology was measured by applying the Positive And Negative Syndrome Scale (PANSS).[56]

The antipsychotic and concomitant therapy received at the time of the examination (drugs, dosages used, duration of current drug use) were assessed, as well as previous antipsychotic and concomitant somatic therapy during the preceding six months. The study used a chlorpromazine equivalent (CPZeq) daily dosage to standardize the dose, efficacy, and side effects of antipsychotics.[57]

MetS was diagnosed according to the criteria of the International Diabetes Federation (IDF, 2005),[58] including the definition of abdominal obesity (waist circumference more than 94 cm in men, more than 80 cm in women) and the presence of any two of the following four signs:

1. Concentration of triglycerides (TG) above 1.7 mmol/L or lipid-lowering therapy;
2. Concentration of high-density lipoproteins (HDL) less than 1.03 mmol/L in men and 1.29 mmol/L in women;
3. Blood pressure (BP) greater than or equal to 130/85 mm Hg or usage of antihypertensive therapy;
4. The concentration of glucose in the blood serum is higher than or equal to 5.6 mmol/L or previously diagnosed type 2 diabetes mellitus.

Anthropometric parameters included waist circumference, height and body mass index (BMI).

Laboratory Examination

Blood Sampling

Blood samples were taken by antecubital venipuncture in vacutainer tubes with a clot activator (CAT) (to obtain serum) or with EDTA (to isolate genomic DNA by the standard phenol-chloroform method). Blood samples with CAT were centrifuged for 30 min at 2000 g at four °C to separate serum; the serum was stored at −20°C (or −80°C) until analysis.

Biochemical Parameters

The concentration of total cholesterol, high-density lipoproteins, triglycerides and glucose in blood serum was determined by colorimetric enzymatic methods applying commercial kits (Cormay, Łomianki, Poland).

Genotyping

Genotyping of six single nucleotide polymorphisms of *FTO* gene (rs7185735, rs9939609, rs1421085, rs1861868, rs3751812, and rs8050136) was carried out using the mass spectrometer MassARRAY® Analyzer 4 (Agena Bioscience™) and a QuantStudio ™ 3D Digital PCR System Life Technologies (Applied Biosystems) amplifier using TaqMan Validated SNP Genotyping Assay kits (Applied Biosystems), on the base The Core Facility "Medical Genomics", Tomsk NRMC. The criteria for selecting the variants mentioned were a) their citation in the relevant scientific literature as described in the introduction and b) a minor allele frequency (MAF) of at least 5%. Basic information of these SNPs is described in Supplementary Table 1.

Statistical Procedures

The analysis was carried out with software R version 4.0.4 using standard functions, as well as additional packages "SNPassoc", "psych" and "dplyr". The Hardy-Weinberg equilibrium (HWE) of genotypic frequencies was tested by the chi-square test. Pearson's chi-squared test was used for the between-group comparison of genotypic and allelic frequencies at the significance level $p < 0.05$. Assessment of the association of genotypes and alleles of the studied polymorphic variants of genes with a pathological phenotype was carried out using the odds ratio (OR) with a 95% confidence interval for the odds ratio (95% CI).

Logistic regression analysis was performed via standard "glm" function in R environment. Assessment of linkage disequilibrium and haplotype analysis was performed by Haploview software. The standardized measure of linkage disequilibrium (D') based on Lewontin.[59] The high linkage between loci has accorded to D'=1 and LOD≥2 (LOD-score; logarithm of odds ratio). Blocks were identified by the Solid Spine algorithm. To count the frequencies of haplotypes, we used EM-algorithm, which is realized in Haploview software.

Results

A total of 517 patients receiving long-term antipsychotic therapy were examined. Table 1 presents the main demographic and clinical parameters of the studied patients.

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Table 1 Demographic and Clinical Parameters of the Studied Patients

Sample Size, n	**517**
Gender, n (%)	Men: 269 (52.0%) Women: 248 (48.0%)
Age, years, Me [Q1; Q3]	39 [31; 49]
Age at onset, years, Me [Q1;Q3]	24 [20; 30]
Duration of illness, years, Me [Q1; Q3]	13 [7; 21]
PANSS, Me [Q1;Q3]	PANSS total score: 100 [88; 110] PANSS negative score: 25 [21;28] PANSS positive score: 22 [18;26] PANSS general score: 52 [44;58]
Duration of taking antipsychotics, years, Me [Q1;Q3]	9 [3;17]
CPZeq, dose, mg, Me [Q1; Q3]	450 [230;750]
Antipsychotics generations, n (%)	Conventional antipsychotics: 318 (61.5%) Atypical antipsychotics: 199 (38.5%)

Note: Me [Q1; Q3] – median and quartiles (first and third).
Abbreviation: CPZeq, chlorpromazine equivalents.

Table 2 Demographic and Clinical Parameters of Patients with and without MetS

Parameter		**Patients without MetS, n=378 (73.1%)**	**Patients with MetS, n =139 (26.9%)**	**p value**
Gender, n(%)	Women Men	165 (43.7%) 213 (56.3%)	83 (59.8%) 56 (40.2%)	**0.001**
Age, years, Me [Q1; Q3]		37 [30;47]	44 [34;54]	**0.000025**
Duration of illness, years, Me [Q1; Q3]		12 [6;20]	17 [9;23]	**0.0007**
CPZeq, dose, mg, Me [Q1; Q3]		450 [250;750]	434.8 [225;687.5]	0.962
Body mass index (BMI), Me [Q1; Q3]		23 [21.2;26.3]	30.5 [26.9;34.4]	**<0.0001**
Waist circumference, cm, Me [Q1; Q3]		83 [76;90]	102 [95;110]	**<0.0001**

Notes: Me [Q1; Q3] – median and quartiles (first and third); in bold: significant difference.
Abbreviation: CPZeq, chlorpromazine equivalents.

According to the criteria of the IDF (2005), metabolic syndrome was diagnosed in 139 patients (26.9%). Patients with metabolic syndrome had an older age and a longer duration of the disease (Table 2).

Checking the frequency distribution of genotypes in the study group of patients showed that the frequency distribution corresponds to the Hardy-Weinberg equilibrium except for rs7185735 polymorphism (Supplementary Table 2). This polymorphism was excluded from further analysis.

None of the polymorphisms studied showed a significant association with the presence of metabolic syndrome (Supplementary Table 3).

We divided the patients' group into two groups: patients with and without abdominal obesity according to the definition of abdominal obesity according to IDF (2005) criteria (waist circumference more than 94 cm in men, more than 80 cm in women). Our results demonstrate the tendency to the statistical association between genotypes frequency rs9939609 and rs1421085 and abdominal obesity (p=0.051 and p=0.052 accordantly). (Supplementary Table 4) However, this tendency was lost after correcting for differences in gender, age and duration of illness.

Results of associative analysis genotypes/alleles frequency and body mass index in patients with schizophrenia show that all variants were significantly associated with BMI apart from rs1861868 (Table 3). The logistic regression with adjustment for covariates was applied to test for association between the SNPs and BMI. Age, gender and duration of schizophrenia were used as covariates, and significant effects for rs9939609, rs1421085, rs3751812 and rs8050136 remained.

The next step in our data analysis was to assess linkage disequilibrium and make a haplotype analysis. Strong linkage was identified in Block 1 between four SNPs of the FTO gene (Figure 1). Haplotypes TCGT and CATA were associated with increased BMI in patients with schizophrenia and may have a linkage through heredity.

Then, we performed association tests for haplotypes and BMI based on observed frequencies and applied permutation test (10,000 times) to assess how real significance of our results in haplotypes (Table 4).

After the permutation test, all significances were gone, except TCGT-haplotype, which shows the best values, and we can conclude about the tendency to associate this haplotype with BMI. Possibly, further studies with more

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Table 3 Results of Associative Analysis Genotypes/Alleles Frequency and Body Mass Index in Patients with Schizophrenia

SNP	Genotypes/ Alleles	Patients with BMI ≤ 25	%	Patients with BMI > 25	%	OR	CI 95% (Lower)	CI 95% (Upper)	χ^2	P
rs9939609	T/T	75	30.4	55	24	0.72	0.48	1.09	7.989	**0.018**
	T/A	136	55.1	122	53.3	1.22	0.8	1.87		
	A/A	36	14.6	52	22.7	1.97	1.14	3.41		
	T	0.579	–	0.507	–	0.75	0.58	0.96	5.022	**0.025**
	A	0.421	–	0.493	–	1.34	1.04	1.73		
rs1421085	T/T	83	33.6	60	25.9	0.69	0.46	1.02	6.859	**0.032**
	T/C	123	49.8	120	51.7	1.35	0.89	2.05		
	C/C	41	16.6	52	22.4	1.75	1.04	2.97		
	T	0.585	–	0.517	–	0.76	0.59	0.98	4.445	**0.035**
	C	0.415	–	0.483	–	1.32	1.02	1.70		
rs1861868	C/C	83	33.6	64	27.6	0.75	0.51	1.11	0.608	0.738
	C/T	117	47.4	133	57.3	1.47	0.98	2.22		
	T/T	47	19	35	15.1	0.97	0.56	1.67		
	C	0.573	–	0.563	–	0.96	0.74	1.24	0.105	0.746
	T	0.427	–	0.438	–	1.04	0.81	1.35		
rs3751812	G/G	85	34.4	61	26.3	0.68	0.46	1.01	7.638	**0.022**
	G/T	126	51	123	53	1.36	0.9	2.05		
	T/T	36	14.6	48	20.7	1.86	1.08	3.2		
	G	0.599	–	0.528	–	0.75	0.58	0.97	4.931	**0.026**
	T	0.401	–	0.472	–	1.34	1.03	1.73		
rs8050136	C/C	87	35.2	61	26.3	0.66	0.44	0.97	8.298	**0.016**
	C/A	124	50.2	123	53	1.41	0.94	2.13		
	A/A	36	14.6	48	20.7	1.9	1.11	3.27		
	C	0.603	–	0.528	–	0.74	0.57	0.95	5.514	**0.019**
	A	0.397	–	0.472	–	1.36	1.05	1.76		

Note: In bold: significant difference.

numbers of patients can help to investigate this haplotype completely.

Discussion

We undertook the current investigation to gain a better understanding of the possible significance of the FTO gene for the development of metabolic syndrome during (and possibly due to) the long-term use of antipsychotics. We found no relationship with metabolic syndrome itself nor with central obesity as its principal component. A relationship with BMI existed, however, and therefore presumably also with antipsychotic drug-induced body weight gain. This was more specifically true for rs9939609, rs1421085, rs3751812, and rs8050136 polymorphisms, which were also significantly related after correcting for the difference in age, gender and duration of illness. Age and duration of illness can be considered as proxies for the duration of antipsychotic drug treatment but may also contribute to the risk of developing a metabolic syndrome as such, ie for other reasons.[60,61]

Although this is an exploratory study, the results can be regarded as useful. To our knowledge, the variants rs1861868 and rs3751812 have not been previously studied in a population of persons with schizophrenia treated with antipsychotics. Rs7185735 has been shown to be associated with weight gain due to antipsychotics,[62] but this variant had to be disregarded due to its failure to meet the HWE criterion. With rs1421085, rs8050136 and rs9939609, the possible contribution is still obvious. A relationship with (increase in) body weight was found for rs1421085,[63,64] rs8050136,[63,65–67] and rs9939609[62,63,66–68] by some authors and not by others (for rs1421085;[66,69,70] resp. for rs8050136;[64,69,70] resp. for rs9939609).[68–73] These researchers, by the way, examined people with different diagnoses and ethnicities, and the medication used also showed considerable differences. Only Roffeei et al investigated the relationship with metabolic

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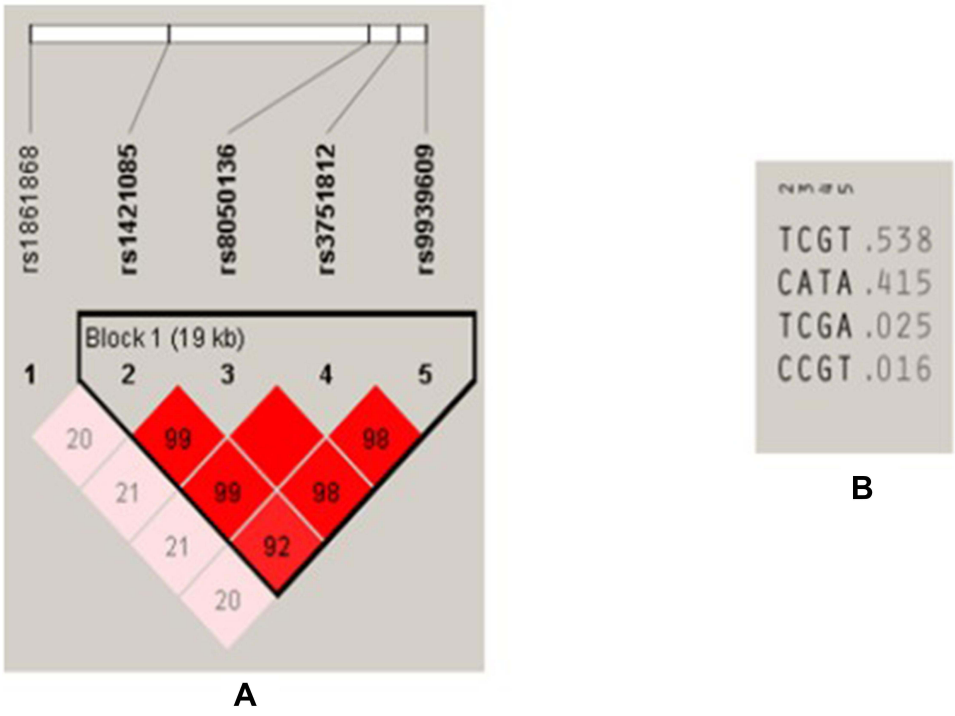

Figure 1 (**A**) Structure of linkage disequilibrium, investigated between 5 SNPs of FTO gene for patients with schizophrenia with metabolic syndrome. (**B**) Identified haplotypes in Block 1 with frequencies.
Notes: colour scheme is in accordance with official documentation; D'=1 and LOD≥2 – strong linkage (bright red); D' <1 and LOD>2 – average strength of linkage (shades of pink/red); D' <1 and LOD<2 – weak linkage (white colour).

syndrome and found an association with rs9939609 with Malaysian persons with schizophrenia who were treated with antipsychotics.[52]

The exact nature of the involvement of Fat Mass and Obesity Associated (FTO) Gene in the development of the metabolic syndrome from the use of antipsychotics in schizophrenia patients is unclear. It has been suggested that the FTO gene would mainly influence the differentiation of white and beige adipocytes during early embryological development.[34] This is an attractive thought, as it could explain why some individuals may be prone to overweight from an early age regardless of environmental influences. An excess of white (energy-storing) adipocytes could cause that the effects of (second generation) antipsychotics more easily result in body weight gain regardless of its localization (which is mainly reflected by BMI), only intra-abdominal fat contributes to metabolic syndrome by increasing waist circumference. This is somehow consistent with our findings; obesity itself seems to be associated with variations in the FTO gene, but metabolic syndrome (which is mainly determined by waist circumference and possible metabolic consequences of obesity) is not.

Although our study included a far larger number of patients than other research groups, it has several limitations. We applied an observational and transsectional design, our patients were treated with a variety of first and/or second generation antipsychotic drugs, and we cannot be certain about the previous long-term stability of drug intake causing the metabolic effects. However, in combination with the results of other researchers, our study provides a good indication that variants of the FTO gene only indirectly influence the development of the metabolic syndrome.

Table 4 Results of Association Test Between Haplotypes and BMI in Patients with Schizophrenia

Haplotype/Block 1	Frequencies	Case, Control Frequencies	χ^2	P	χ^2-Perm	p-value Perm
TCGT	0.538	0.489, 0.563	5.295	0.0214	5.295	0.0574
CATA	0.415	0.463, 0.400	3.898	0.0483	3.898	0.1427
TCGA	0.025	0.024, 0.020	0.148	0.7006	0.148	0.9935
CCGT	0.016	0.015, 0.016	0.024	0.8777	0.024	0.9993

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Conclusion

Variants rs9939609, rs1421085, rs3751812, and rs8050136 show a significant association with the body mass index of 517 people with schizophrenia who were treated with antipsychotic drugs. Statistical trends were only found with regard to the association with waist circumference (reflecting central obesity), and no association was found with the occurrence of metabolic syndrome. Combined with data published by others, our findings suggest that variations of the FTO gene have significance for the occurrence of obesity and weight gain but less directly for antipsychotic drug-induced metabolic syndrome.

Acknowledgments

The authors are grateful to the Tomsk Clinical Psychiatric Hospital (chief physician – Dr Sergey M. Andreev), the Kemerovo Regional Clinical Psychiatric Hospital (chief physician – Dr Veronika A. Sorokina) and the N.N. Solodnikova Clinical Psychiatric Hospital of Omsk (chief physician – Dr Andrey I. Cheperin) for their help in recruiting patients for this investigation.

Funding

This work was supported by the Russian Science Foundation (project no. 19-75-10012).

Disclosure

The authors report no conflicts of interest in this work.

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