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Association of the *HTR2A* T102C SNP with Weight Gain and Changes in Biochemical Markers in Patients Receiving Antipsychotics

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Abstract

The purpose of our research was to study the association of the *HTR2A* T102C (rs6313) SNP with anthropometric and biochemical markers in patients treated with typical and atypical antipsychotics in monotherapy mode.

Materials and methods: One hundred and seventeen white inpatients (95 men and 22 women) with F2 disorders (ICD-10, 1995) were enrolled in the study. All patients were divided into two groups by the antipsychotic class with which they were treated (Group 1 included 40 patients treated with typical antipsychotics; Group 2 included 77 patients treated with atypical antipsychotics) and two subgroups by weight change criteria during the study (Subgroup 1 included patients with weight change >6%; Subgroup 2 included patients with weight change <6%). The following examinations were performed: physical examination, anthropometric measurements (BMI, WC, TC), clinical examination, blood test, and genotyping for the *HTR2A* T102C (rs6313) SNP.

Results: There were no statistically significant differences in the distribution of genotypes of the *HTR2A* T102C (rs6313) SNP between Group 1 and Group 2 ($P>0.05$). Kruskal-Wallis one-way analysis of variance between subgroups showed statistically significant differences between carbamide levels in the second visit in Group 2 ($P=0.02$). We showed statistically significant differences between TT and CT genotypes of the *HTR2A* T102C SNP: carbamide level was greater in TT carriers ($P=0.02$). The strength of associations and risks between alleles of the *HTR2A* T102C SNP and antipsychotic-induced weight change were as follows: $OR_C=0.49$; $CI_C [0.25; 0.95]$; $RR_C=0.58$ $CI_C [0.35; 0.97]$; $OR_T=2.03$; $CI_T [1.05; 3.94]$; $RR_T=1.7$ $CI_T [1.02; 2.81]$.

Conclusion: Our results of the pilot pharmacogenetic studies show an association of the T allele carriage of the *HTR2A* T102C (rs6313) SNP with risk of antipsychotic-induced weight gain. The continuation of this study and an increase in the sample size will allow establishing valid pharmacogenetic markers for the risk of antipsychotic-induced weight gain. (**International Journal of Biomedicine. 2018;8(3):186-191.**)

Key Words: antipsychotics • single nucleotide polymorphism • serotonin receptor 2A • *HTR2A* gene • weight gain

Abbreviations

FPG, fasting plasma glucose; **FGAs**, first-generation antipsychotics; **HWE**, Hardy-Weinberg equilibrium; **HDL-C**, high-density lipoprotein cholesterol; **LDL-C**, low-density lipoprotein cholesterol; **MetS**, metabolic syndrome; **SGAs**, second-generation antipsychotics; **SNP**, single nucleotide polymorphism; **TC**, total cholesterol; **VLDL-C**, very-low-density lipoprotein cholesterol.

Introduction

Dysfunction of the dopamine system has been known to underlie the pathophysiology of schizophrenia since

the 1960s. FGAs, especially high potency drugs such as haloperidol, mainly bind to D2 receptors.⁽¹⁻³⁾ All SGAs tightly bind to serotonin (5-hydroxytryptamine, 5-HT) receptor 2A relative to the dopamine D2 receptor, and this

was once thought to be one of the defining characteristics of “atypicality” of SGAs.⁽¹⁾ In general, atypical agents have an enhanced 5-HT_{2A}/D₂ affinity ratio and that helps explain why typical and atypical agents may have different clinical effects.⁽⁴⁾ The atypical antipsychotics generally have additional affinities for a variety of neurotransmitter receptor subtypes (serotonergic, dopaminergic, histaminergic, adrenergic, and muscarinic acetylcholine receptor).⁽⁵⁾ FGAs are characterized by extrapyramidal symptoms, and hyperprolactinemia and, to a lesser extent, metabolic disorders; SGAs are more associated with weight gain, the appearance of type 2 diabetes, cardiovascular diseases, and the development of MetS.^(6,7) Results of numerous studies show that antipsychotic induced weight gain occurs in 12-16 weeks.⁽⁸⁾ It was found that patients with psychotic disorders are more likely to suffer from obesity than the general population.⁽⁹⁾ Epidemiological studies have shown that patients with schizophrenia are 2.5 times more likely to die from cardiovascular complications and their estimated life span is 20% less than the general population.⁽¹⁰⁾ The receptor antagonism at the central level of regulation, caused by taking antipsychotics, provokes an increased appetite and reduced possibility of feeling sated.⁽¹¹⁾

5-HT_{2A} is one of the most abundantly expressed serotonin receptors in the brain, with high levels in the cerebral cortical areas, hippocampus, nucleus accumbens, and caudate nucleus.⁽¹⁰⁾ This receptor belongs to G-protein-coupled receptors and is the primary excitatory receptor of serotonin, mainly acting at post-synaptic neurons. The 5-HT_{2A} receptor gene (*HTR2A*) is located on chromosome 13(13q14.2). The expression of *HTR2A* is regulated by several functional polymorphisms,^(13,14) among which T102C (rs6313) is the most studied SNP in the gene. Compared with the T allele, the C allele leads to lower receptor expressions⁽¹³⁾ and lower receptor binding potentials,⁽¹⁵⁾ and therefore reduces excitation at post-synaptic neurons.⁽¹⁶⁾ Significant association between the *HTR2A* T102C (rs6313) SNP and antipsychotic weight gain was found during treatment with olanzapine and risperidone in Japanese and Chinese populations.⁽¹⁷⁾

The purpose of our research was to study the association of the *HTR2A* T102C (rs6313) SNP with anthropometric and biochemical markers in patients treated with typical and atypical antipsychotics in monotherapy mode.

Materials and Methods

Participants

One hundred and seventeen white inpatients (95 men and 22 women) with ICD-10 Diagnosis Codes F20 (92/79%), F20.2 (1/0.85%), F20.6 (3/2.6%), F20+F10.2 (2/1.7%), F21.8 (2/1.7%), F22.8 (3/2.6%), F23 (6/5.1%), F23.1 (3/2.6%), and F25.1(4/3.4%) were enrolled in the study. Mean age of the disease onset was 24.56±1.95 years; mean age of the first medical help was 26.5±1.65 years; mean age of the first antipsychotic therapy was 25.7±1.7 years. The period of participation in the study was 8.36±1.13 weeks. Drugs taken by the patients are presented in Table 1.

All patients were divided into two groups (Table 2) by the antipsychotic class with which they were treated (Group 1

included 40 patients treated with typical antipsychotics; Group 2 included 77 patients treated with atypical antipsychotics) and two subgroups (Table 3) by weight change criteria during the study (Subgroup 1 included patients with weight change >6%; Subgroup 2 included patients with weight change <6%).

Table 1

Drugs taken by the patients in the study

Typical antipsychotics		Atypical antipsychotics	
Drug	Frequency (%)	Drug	Frequency (%)
Haloperidol	28 (70)	Olanzapine	15 (19.5)
Zuclopenthixol	6 (15)	Risperidone	17 (22.1)
Triptazinum	6 (15)	Quetiapine	12 (15.6)
		Asenapine	5 (6.5)
		Clozapine	11 (14.2)
		Paliperidone	6 (7.8)
		Aripiprazole	3 (3.9)
		Sertindole	5 (6.5)
		Sulpiride	1 (1.3)
		Amisulpride	1 (1.3)
		Aminasine	1 (1.3)

Table 2

The distribution of patients by the antipsychotic drugs

Patients	Group 1		Group 2	
	n	%	n	%
Total	40	34.1	77	65.9
Male	29	72.5	66	85.7
Female	11	27.5	11	14.3

Table 3.

The distribution of patients by weight change criteria during the study

Variable	Group 1		Group 2		Total	P- value
	Subgroup 1	Subgroup 2	Subgroup 1	Subgroup 2		
Sample size	8	28	17	46	99	0.63
Median age, yrs	33.4 (24.9;41.09)	34.1 (29.9;38.3)	29.0 (24.9;33.1)	35.1 (32.1;38.1)		0.25
Gender (M/F)	5/3	20/8	16/1	39/7	99	0.11
Median period of participation, weeks	5.6 (4.1;7.1)	7.2 (5.9;8.5)	8.4 (6.2;10.4)	9.2 (6.8;11.6)		0.84
Intake of benzodiazepine in anamnesis (Yes/No)	3/3	9/13	7/7	20/9	71	0.24
Smoking (Yes/No)	5/3	16/7	8/8	20/18	85	0.54

Study design

The research consisted of two visits: the first during enrollment in the study, the second when the observation was completed. All patients signed an informed consent document before enrolling in the project. The following examinations were performed: physical examination, anthropometric measurements (BMI, WC, TC), clinical examination, blood test (ALT, AST, FPG, VLDL-C, LDL-C, HDL-C, TC, triglycerides (TG), total protein, albumin, creatinine, uric acid, carbamide) and molecular-genetic evaluation. Genomic DNA was isolated from peripheral leukocytes with “Hemolytic” reagent (InterLabService, Russian Federation) for pre-processing of whole peripheral and umbilical blood and with extraction kit Ribo-prep (InterLabService, Russian Federation). Genotyping for the *HTR2A* T102C (rs6313) SNP was performed using real-time PCR by the RotorGene 6000 (Quagen, Germany) with an *HTR2A* kit according to the manufacturer’s protocol (Syntol, tge Russian Federation).

Statistical Analysis

Descriptive statistics were used to summarize the data. Shapiro - Wilk test was used for normality test. Chi-square and Fisher’s exact tests were used to determine the association between categorical measure including allele and genotype. T test or paired T test were used for comparison between two groups with a normal distribution of the quantitative characteristic. Wilcox test or paired Wilcox test were used as nonparametric alternative. Analysis of variance and Tukey post hoc test were used for comparison between 3 groups with a normal distribution of the quantitative characteristic and homogeneous dispersion (established by Levene test). Kruskal - Wallis one-way analysis of variance and Dunn post hoc test with Bonferroni adjustment were nonparametric alternative. Correlation was measured with Spearman rank correlation coefficient. The strength of the associations was expressed as odds ratio (OR) with 95% confidence interval (CI) and 95% credible interval (CrI), relative risk was expressed as risk ratio (RR). Binomial logistic model was also performed. The quality of the model (Area under the curve (AUC) specificity and sensitivity) was measured by receiver operating characteristic (ROC) analysis. For all tests, a probability value of $P < 0.05$ was considered statistically significant. Statistical analysis was performed by R programming language with IDE Rstudio. LePAC. Three exact probability tests for departure from HWE due to heterozygote excess, heterozygote deficit and omnibus probability test were carried out using GENEPOP (v. 4.7.0)

Results and Discussion

There were no statistically significant differences in the distribution of genotypes of the *HTR2A* T102C (rs6313) SNP between Group 1 and Group 2 ($P > 0.05$) (Table 4). It was not possible to reject HWE because of heterozygote excess ($P = 0.02$). Dynamics of the biochemical markers is shown in Tables 5 and 6 (P value for differences between the first and second visits in whole group).

Kruskal-Wallis one-way analysis of variance between subgroups showed statistically significant differences between

carbamide levels in the second visit in Group 2 ($P = 0.02$) (Tables 5 and 6). A Dunn post hoc test with Bonferroni adjustment showed statistically significant differences between TT and CT genotypes of the *HTR2A* T102C (rs6313) SNP: carbamide level was greater in TT carriers ($P = 0.02$).

Table 4.

Genotype distribution in the groups

Group	Genotype			Allele	
	CC	CT	TT	T	C
Group 1	6 (5.12%)	28 (23.93%)	6 (5.12%)	40 (17.0%)	40 (17.0%)
Group 2	11 (9.4%)	49 (41.9%)	17 (14.52%)	83 (36.0)	71 (30.0%)
Fisher exact test	$P = 0.70$				

Table 5.

Summarize data in Group 1, Me ($Q_{25}; Q_{75}$)

Variable	Genotype			P-value
	CC	CT	TT	
Weight, kg	FV 60.8(59.2;79.9)	68.5(62.2;81.8)	79(66.2;86.6)	0.7
	SV 60.0(56;83)	71(61;80)	77.4(70.7;86.6)	
FPG, mmol/L	FV 5.17(5.11;5.24)	4.96(4.66;5.48)	5.61(5.12;6.1)	0.5
	SV 5.61(4.87;5.89)	4.84(4.57;5.19)	4.89(4.68;5.31)	
TC, mmol/L	FV 3.98(3.69;4.18)	4.84(4.37;5.26)	4.42(4.06;4.60)	0.6
	SV 3.18(3.06;4.28)	4.51(4.24;5.20)	4.47(3.75;4.57)	
TG, mmol/L	FV 0.68(0.63;1.06)	1.47(1.02;1.90)	1.59(1.19;1.74)	0.1
	SV 0.73(0.69;1.00)	1.23(0.95;1.55)	1.52(1.49;1.58)	
VLDL-C, mmol/L	FV 0.31(0.28;0.48)	0.53(0.45;0.71)	0.62(0.55;0.68)	0.2
	SV 0.33(0.31;0.45)	0.54(0.35;0.58)	0.46(0.54;0.62)	
LDL-C, mmol/L	FV 2.30(2.22;3.10)	2.90(2.55;3.57)	2.66(2.43;3.20)	0.1
	SV 1.65(1.59;2.63)	2.74(2.48;3.62)	2.85(1.92;3.12)	
HDL-C, mmol/L	FV 1.20(0.95;1.46)	1.14(0.9;1.24)	0.77(1.01;1.16)	0.6
	SV 1.20(1.07;1.20)	1.10(0.94;1.22)	0.98(0.75;1.06)	
ALT, u/L	FV 16(14;20)	24.0(18.4;40.6)	17.5(13;30.17)	0.03
	SV 14(9;18)	25.0(18.3;28.6)	15.85(12.75;28.1)	
AST, u/L	FV 26(22;29)	31.0(22.7;42.8)	20.95(18.7;44.1)	0.004
	SV 17(16;19)	23.3(18.7;30.2)	20.8(18.15;23.07)	
Albumin, g/L	FV 51.0(48.0;51.1)	47.0(44.9;48.6)	48.8(46.87;50.5)	0.84
	SV 48(45.5;53.5)	47.0(44.5;49.8)	51.0(48.27;52.75)	
Total protein, g/L	FV 77(76;82)	73.0(69.75;76.9)	73.8(72.4;75.57)	0.3
	SV 73(71;75)	71.0(68.7;75.2)	74.55(71.52;75.07)	
Carbamide, mmol/L	FV 3.80(2.80;3.90)	3.45(3.11;3.91)	3.99(3.38;4.39)	0.4
	SV 3.00(2.60;4.00)	3.74(2.95;4.23)	3.79(3.45;4.13)	

FV – the first visit, SV – the second visit

Table 6

Summarize data in Group 2, Me (Q_{25} ; Q_{75})

Variable	Genotype			P-value	
	CC	CT	TT		
Weight, kg	FV	72.1(69.4;84)	69.3(62.0;81.1)	73(62;77)	0.004
	SV	74.0(71.2;84.5)	72.5(62.5;82.0)	75.5(67.3;77.9)	
FPG, mmol/L	FV	5.69(5.48;5.84)	5.30(4.87;5.68)	5.40(5.05;5.60)	0.01
	SV	5.18(4.85;5.31)	5.14(4.66;5.5)	4.88 4.47;5.27)	
TC, mmol/L	FV	4.33(3.91;5.93)	4.75(4.04;5.74)	4.44(3.66;6.19)	0.99
	SV	4.50(4.13;5.18)	4.82(4.20;5.48)	4.86(3.64;5.42)	
TG, mmol/L	FV	1.39(1.16;1.54)	1.39(1.07;1.95)	1.361.04;2.14)	0.1
	SV	1.82(1.17;2.02)	1.57(0.96;2.05)	1.5(1.07;2.52)	
VLDL-C, mmol/L	FV	0.53(0.45;0.54)	0.5(0.41;0.61)	0.49(0.34;0.69)	0.1
	SV	0.53(0.40;0.67)	0.52(0.35;0.73)	0.59(0.43;1.57)	
LDL-C, mmol/L	FV	2.56(2.10;2.98)	2.95(2.37;3.58)	2.55(2.01;3.65)	0.8
	SV	3.04(2.46;3.44)	2.93(2.67;3.60)	2.99(2.50;3.39)	
HDL-C, mmol/L	FV	1.30(1.00;1.56)	1.19(0.97;1.33)	1.33(1.24;1.40)	0.5
	SV	0.96(0.91;1.05)	1.15(0.95;1.32)	1.26(1.07;1.40)	
ALT, u/L	FV	32.45(19.8;53.07)	22.4(16.0;30.3)	25.2(17.7;31.0)	0.8
	SV	31.20(19.50;37.55)	22.55(14.47;32.25)	23.0(17.52;30.25)	
AST, u/L	FV	38.0(27.77;45.05)	28.5(21.0;35.2)	27.0(23.8;31.0)	0.4
	SV	26.0(18.25;33.5)	24.5(21.75;35.55)	21.0(19.5;30.65)	
Albumin, g/L	FV	50.2(46.6;50.9)	48.4(46.0;50.5)	47.0(46.45;49.40)	0.2
	SV	47.1(45.95;48.1)	48.6(45.4;50.7)	50.1(48.07;50.5)	
Total protein, g/L	FV	75.6(73.2;76.07)	73.5(70.0;77.0)	72.55(70.02;79.00)	0.7
	SV	77.0(72.05;77.50)	72.8(69.37;77.25)	71.85(69.55;74.75)	
Carbamide, mmol/L	FV	4.29 (3.45;5.17)	3.90 (3.35;4.30)	3.80 (3.40;4.1)	0.42
	SV	4.0 (3.74;4.21)	3.8 (3.48;4.40)	4.75 (4.35;5.17)	

FV – the first visit, SV – the second visit

Triglyceride levels in the second visit were correlated with LDL-C ($P=0.9$), HDL-C ($r=0.8$), and VLDL-C ($r=0.9$) levels in the first visit, and with glucose ($r=0.84$) and VLDL-C ($r=0.9$) levels in the second visit; TC levels in the second visit were correlated with LDL-C levels in the second visit ($r=0.91$).

The strength of associations and risks between alleles of the *HTR2A* T102C SNP and antipsychotic-induced weight change were as follows: $OR_C=0.49$; $CI_C [0.25; 0.95]$; $RR_C=0.58$ $CI_C [0.35; 0.97]$; $OR_T=2.03$; $CI_T [1.05; 3.94]$; $RR_T=1.7$ $CI_T [1.02; 2.81]$. In Bayesian statistics: $OR_C=0.499$. $CrI_C=[0.256; 0.951]$; $OR_T=2.003$; $CrI_T=[1.052; 3.904]$. Fisher exact test: $P=0.04$.

We also performed a binomial logistic regression (Table 7), where the dependent variable was the binomial factor (weight change >6% during research, Yes/No), and predictors were genotypes of the *HTR2A* T102C SNP and antipsychotics

(Haloperidol, Olanzapine, Risperidone, Quetiapine) and their daily dosage. The binomial logistic model was described by ROC analysis (Figure 1). Cutoff for specificity and sensitivity of the logistic model was 0.53. At this level, specificity of the model was 0.80 and sensitivity of the model was 0.80.

Table 7.

Binomial logistic regression coefficients

Variable	Estimate	Standard Error	z value	Pr (> z)
Intercept	3.4518	2.7262	1.266	0.20
rs6313 CT	2.6672	1.7791	1.499	0.13
rs6313 TT	4.8865	2.4338	2.008	0.04 *
Olanzapine	- 2.7532	5.2068	- 0.529	0.59
Risperidone	26.7116	4941.9003	0.005	0.99
Quetiapine	- 4.8765	3.5435	- 1.376	0.16
Dosage (in all)	- 0.6655	0.3143	- 2.118	0.03 *
Dosage of Olanzapine	0.3208	0.5887	0.545	0.58
Dosage of Risperidone	-7.9641	1235.4747	-0.006	0.99
Dosage of Quetiapine	0.6660	0.3149	2.115	0.03 *

Signif. codes: 0 '****' 0.001 '***' 0.01 '**' 0.05 '.' 0.1 ' ' 1
 Null deviance: 46.070 on 33 degrees of freedom
 Residual deviance: 28.018 on 24 degrees of freedom
 AIC: 48.018

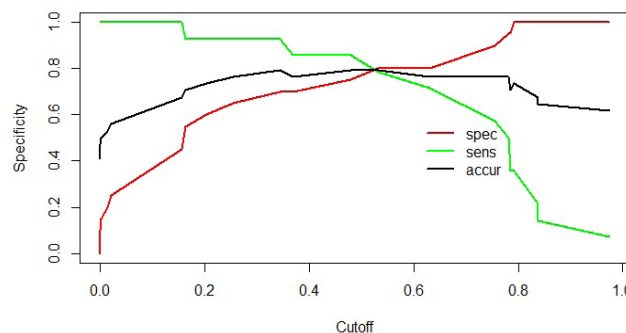


Fig. 1. ROC analysis curve: AUC = 0.88; Concordance = 0.86.

HWE was not observed in the prospective group, but it was observed ($P=0.34$) in the population group ($n=229$ patients) with same inclusion criteria (except monotherapy mod). Our assumption is that heterozygotes carriers of the *HTR2A* T102C (rs6313) SNP are more stable in monotherapy and needed changes in therapy less often. We are going to increase the prospective sample size to get more information. Received results showed that different classes (FGAs, SGAs) provided different changes in biochemical markers and weight. Atypical antipsychotics led to statistically significant differences in body weight and glucose concentration, which are considered as pre-diabetic changes and could be part of MetS. Mechanisms of these changes are widely

discussed. On the other hand, FGAs provided statistically significant differences in enzyme (AST, ALT) activity. We did not measure iso-enzymes of the hepatic fraction, so we cautiously put forward an assumption about hepatotoxicity of typical antipsychotics. TT genotype carriers of the *HTR2A* T102C (rs6313) SNP, who received atypical antipsychotics, had a higher concentration of carbamide. Carbamide is the chief nitrogenous end product and is dependent on protein intake. In another study, it was shown that the *HTR2A* T102C (rs6313) SNP affects food behavior and that TT carriers prefer high-protein food.⁽¹⁸⁾

Our study showed that the T allele carriers of the *HTR2A* T102C (rs6313) SNP have increased risk of antipsychotic-induced weight change. The intercept in our regression model consisted of the CC genotype of the *HTR2A* T102C (rs6313) SNP, haloperidol, and single dosage. Patients with the TT genotype of the *HTR2A* T102C (rs6313) SNP had significant differences in association with antipsychotic-induced weight change than CC carriers. Despite the synonymous substitution in this SNP, it can affect, by linkage, disequilibrium with the *HTR2A* 1438A/G SNP in the promoter region.⁽¹⁹⁾ Also, changing Haloperidol to Quetiapine leads to higher OR of antipsychotic-induced weight change, with a positive dose-dependent effect (mean dose of 318.75 mg/day). Similar results showed Brecher et al. (2007). Long-term treatment with quetiapine monotherapy was associated with moderate weight gain. Most weight gain occurs within the first 12 weeks of treatment and has no clear dose relationship.⁽²⁰⁾

Conclusion

Our results of the pilot pharmacogenetic studies show an association of the T allele carriage of the *HTR2A* T102C (rs6313) SNP with risk of antipsychotic-induced weight gain. The continuation of this study and an increase in the sample size will allow establishing valid pharmacogenetic markers for the risk of antipsychotic-induced weight gain.

Competing interests

The authors declare that they have no competing interests.

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