

# **-759C/T polymorphism of the HTR2C gene is not correlated with atypical antipsychotics-induced weight gain, among Romanian psychotic patients**

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## **Abstract**

We aim to investigate whether the -759C/T polymorphism in 5-HTR2C gene was associated with weight change and hyperinsulinemia in Romanian pediatric patients with schizophrenia and bipolar disorders. The patients under investigation were enrolled between 2009 and 2014. A total of 81 schizophrenic and bipolar-disorder patients, aged between nine to 20 years (median age 15.74±4 years), who were following an atypical antipsychotic treatment (Risperidone, Aripiprazole, Olanzapine), were enrolled from University Hospital for Child and Adolescent Psychiatry and Neurology from Timisoara, Romania. The outcomes that we measured were the changes in Body Mass Index (BMI) from baseline to different time points: three months, six months, 12 months and 18 months, and the change in insulinemia over time, after atypical antipsychotic treatment. After carrying out the 5-HTR2C -759C/T polymorphism identification, we found that 22 patients presented the -759C/T polymorphism in 5-HTR2C gene. Between the patients exhibiting the 5-HTR2C -759C/T polymorphism and the patients having the wild type alleles, there was no significant statistical difference in changes of BMI from baseline to endpoints that indicates the lack of the protective effect of the T allele against atypical antipsychotics-induced weight gain. Interestingly, we found a statistically significant association between insulinemia and T alleles' carriers, after 18 months of treatment with the above-mentioned antipsychotics. Taking into consideration that atypical antipsychotics have been associated with elevated insulin levels and insulin resistance, maybe in the future the -759C/T polymorphism would find a role in the development of a more complex algorithm for prediction of diabetes mellitus risk, in patients taking atypical antipsychotics.

**Keywords:** pharmacogenetics, polymorphisms, antipsychotics, schizophrenia, bipolar disorder.

## **Introduction**

Although patients with psychotic disorders can benefit today from the effectiveness and real advantages of atypical antipsychotics, their prescription has to be preceded by a thoughtful risk/benefit evaluation because they are not without downfalls. Metabolic and endocrine side effects of atypical antipsychotics have become an increasing concern for clinicians and scientific researchers due to the fact that atypical antipsychotics are more and more prescribed to children and adolescents for psychotic and non-psychotic mental disorders and this category of patients seems to be very exposed to the risks associated with medication [1].

It has been stated that childhood adiposity and insulin levels are predictors of the occurrence of insulin resistance syndrome in adulthood and are responsible for increasing adult morbidity and mortality [2–5]. Therefore, trying to control excessive weight gain early in life could have a great impact on general public health.

All atypical antipsychotics could cause weight gain but in different proportions. Olanzapine causes the greatest increase in weight (an average of 2.3 kg/month), followed by Quetiapine (1.8 kg/month) and Clozapine (1.7 kg/month). Risperidone proved to cause a moderate increase in body weight (an average of 1 kg/month), Ziprasidone a slight increase (0.8 kg/month), and Asenapine, after three weeks of treatment, resulted in an increase of 0.9 kg [6], higher than placebo (0.1 kg), but less than Olanzapine (2.6 kg). Iloperidone, a relatively new atypical antipsychotic, was also associated with weight gain [6–8]. Interesting is the fact that a proportion of patients could experience a weight reduction after taking antipsychotics.

This interindividual variability, in developing weight gain after using atypical antipsychotics, opened the interest of this research. Knowing that the susceptibility of patient to develop this side effect after taking atypical antipsychotics has also a genetic component as well, the aim of this study was to identify a possible cause of this inter-

individual variability, but by using a pharmacogenetic approach, focused on possible pharmacodynamic causes.

Because weight gain is a side effect rather of an atypical antipsychotic than of a classical one, some researchers have linked it with their capacity to antagonize the 5HT<sub>2C</sub> [5-hydroxytryptamine (serotonin) receptor 2C, G protein-coupled] receptors [9–12].

Because the predictability value of 5-HTR2C -759C/T for atypical antipsychotics-induced weight gain is still controversial, we aim, through this study, to investigate whether the 5-HTR2C -759C/T polymorphism (rs3813929) was associated with weight change in Romanian pediatric patients with schizophrenia and bipolar disorders [13, 14]. Knowing that obesity is commonly linked to insulin resistance and compensatory hyperinsulinemia, we also wanted to explore the relation between this polymorphism and insulin levels [15, 16].

## ☞ Patients, Materials and Methods

### Subjects

A total of 81 patients with schizophrenia or bipolar disorder, aged between 9 to 20 years (median age 15.74±4 years) were enrolled between 2009 and 2014, from University Hospital for Child and Adolescent Psychiatry and Neurology from Timișoara, Romania.

All subjects were examined and diagnosed by experienced psychiatrists using DSM IV (Diagnostic and Statistical Manual), and K-SADS-PL (Kiddie Schedule for Affective Disorders and Schizophrenia – Present and Lifetime version). Only patients who had a baseline PANSS (Positive and Negative Syndrome Scale) ≥70 and those who were prescribed only atypical antipsychotics (Risperidone, Aripiprazole, Olanzapine) were included. We have to mention that some patients switched between antipsychotic therapies sometimes because of lack of efficacy, or because of adverse effects, but did not use other antipsychotics than the above mentioned ones. Exclusion criteria included: age >18 years or >21 years, if the patients were still studying in school, treatment with other antipsychotics and diabetes mellitus or family history of diabetes mellitus.

For each patient with ages less than 18 years, the informed consent was signed by the parents or legal guardians with assent of the child, and for those over 18 years the informed consent was signed by themselves.

The study protocol was approved by the Ethical Committee of the “Victor Babeș” University of Medicine and Pharmacy, Timișoara, and is in accordance with GCP (Good Clinical Practice) regulations.

The patients were weighed and their height was measured, based on which we calculated their Body Mass Index (BMI) for different time points: at baseline (BSL), three months, six months, 12 months and 18 months.

Fasting blood samples were also taken to measure insulinemia.

### DNA analysis

Genomic DNA was extracted from EDTA (ethylenediaminetetraacetic acid) blood using QIAamp DNA Mini

Kit (Qiagen, Germany). DNA samples were stored at -80°C. The allelic discrimination analysis was performed after the enrollment of the last patient and laboratory investigators were blind to patient's data. 5-HTR2C -759C/T polymorphism identification was carried out on a 7900HT fast real-time PCR (reverse transcription-polymerase chain reaction) instrument (Applied Biosystems, Foster City, CA, USA) by using TaqMan Genotyping Assay for Allelic Discrimination C\_\_27488117\_10 (rs3813929), TaqMan® PCR Master Mix and DNA probe according to the protocol provided by the producer. Two controls were used: AL-1, corresponding to the wild type (*wt*) was VIC™ dye-labeled, and AL-2 corresponding to 5-HTR2C -759C/T polymorphism was Fluorescein FAM dye-labeled. Genotypes were determined by measuring allele-specific fluorescence using the software for allelic discrimination (Applied Biosystems, Foster City, CA). For the female patients, we found homozygosity for the normal allele (CC) but also there were cases of heterozygosity (CT), while males being hemizygotes had only one allele, C or T on their genotype.

### Statistical analysis

The mean values of the BMI and insulinemia as well as the standard deviation were calculated. The *t*-test was used in order to establish the differences of association of biological parameters and it was considered that there is a statistically significant correlation, if *p*<0.05.

## ☞ Results

The 81 patients (34 males, 47 females) included in this analysis had a mean baseline BMI of 20.03±2.57 kg/m<sup>2</sup>. Weight gain was observed following antipsychotic treatment with a mean BMI increase of 0.65±0.03 at three months, 2.51±0.12 at six months, 3.71±0.76 at 12 months and 4.36±1.54 kg/m<sup>2</sup> at 18 months. In the same time, the mean baseline insulin values were 9.58±3.96 μU/mL, with a mean increase of 3.77±0.08 at six months, 8.69±6.34 at 12 months and 9.68±6.05 μU/mL at 18 months.

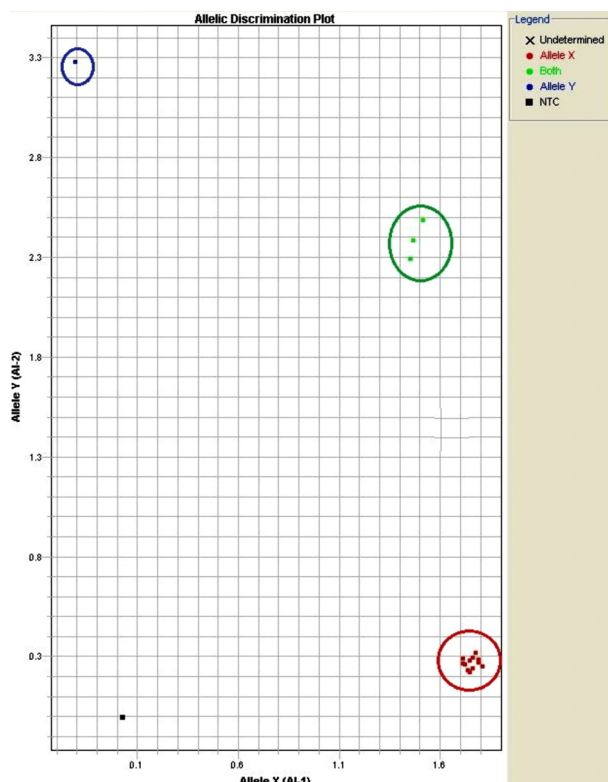
Because the 5HTR2C gene is located on the X chromosome, males can be hemizygous C or T, and females can be homozygote CC, TT or heterozygote CT, although we did not find the TT genotype in our sample.

From the study group, 22 patients presented the -759C/T polymorphism in 5-HTR2C gene. The results were analyzed by assessing the amplification curves and of the plots generated by the soft (Figure 1).

None of the female patients was identified as homozygote for the mutant allele T (there were no patients with TT genotype), so that two groups were formed: the first group included 59 patients with C/CC genotype and the second group included 22 patients with T/CT genotype.

The BMI was compared between the two identified groups based on the 5-HTR2C genotype (C/CC *versus* T/CT). The descriptive statistics of the study group are presented in Table 1.

It can be observed that there is no statistically significant difference in BMI evolution, from baseline through different timepoints until endpoint, in patients exhibiting the C/CC alleles and in patients with T/CT alleles (*p*>0.05).

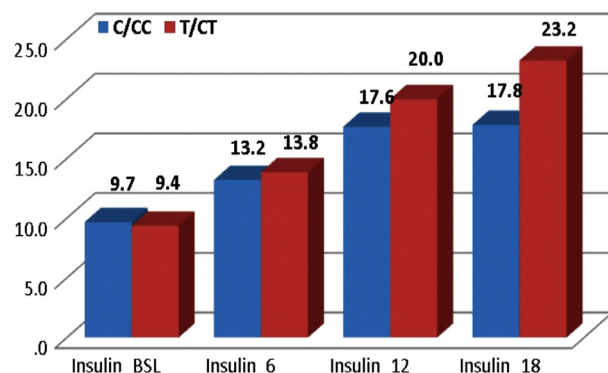


**Figure 1 – Plot for allelic discrimination for -759C/T (X: Wild type allele, Y: Mutant allele); the red group indicates the hemizygotes/homozygotes showing the wild type allele; the green group indicates the heterozygotes; the blue group represents the hemizygotes/homozygotes showing the mutant allele.**

**Table 1 – Comparison of the BMI between the studied groups at different time points**

Time point	Genotype	N	Mean BMI [kg/m <sup>2</sup> ]	SD	SEM	P	Significance level
BMI baseline	C/CC	59	20.6	2.2	0.29	0.226 <sup>ns</sup>	0.05
	T/CT	22	21.5	3.33	0.71		
BMI 3 months	C/CC	59	21.2	2.25	0.29	0.195 <sup>ns</sup>	0.05
	T/CT	22	22.1	3.37	0.72		
BMI 6 months	C/CC	59	23	2.52	0.33	0.119 <sup>ns</sup>	0.05
	T/CT	22	24.1	3.02	0.64		
BMI 12 months	C/CC	59	24.2	3.2	0.42	0.187 <sup>ns</sup>	0.05
	T/CT	22	25.3	3.62	0.77		
BMI 18 months	C/CC	59	24.7	3.89	0.51	0.076 <sup>ns</sup>	0.05
	T/CT	22	26.5	4.48	0.95		

BMI: Body Mass Index; SD: Standard deviation; SEM: Standard error of the mean; P: Significance level; <sup>ns</sup>Not significant.



**Figure 2 – Evolution of insulinemia after administration of atypical antipsychotics in correlation with 5HTR2C -759C/T genotype. BSL: Baseline; Insulin\_6: After six months; Insulin\_12: After 12 months; Insulin\_18: After 18 months.**

It was impossible to establish a correlation between BMI and the 5HTR2C genotype. The increase in body weight did not differ significantly between the T allele carriers and the C allele carriers.

From Figure 2, it can be observed an increase of insulinemia after administration of the antipsychotic treatment for both genotypes and we decided to analyze if this increase differs statistically significant between the two groups of patients.

When comparing for each time point the values of insulinemia for the two groups (C/CC and T/CT), there were no statistical significant differences observed at the baseline, six months and 12 months, while at 18 months from treatment initiation insulinemia was significantly increased in the T/CT genotype group ( $p=0.030$ ) (Table 2).

We consider that an increase with more than 7% of the initial weight is a significant weight gain with possible clinical consequences, so that we analyzed the distribution of the patients based on the BMI and their genotype.

Figure 3 presents the distribution of the patients for each time point, correlating the evolution of their BMI with their genotype, C/CC or T/CT, taking in consideration a 7% increase of BMI as a level of significance.

So that, the correlation between the genotype and BMI, at different time points, did not show any statistically significant differences at three months ( $p=0.724$ ,  $\alpha=0.05$ ), six months ( $p=0.949$ ,  $\alpha=0.05$ ), 12 months ( $p=0.939$ ,  $\alpha=0.05$ ) and not even at 18 months after the administration of antipsychotic treatment ( $p=0.593$ ,  $\alpha=0.05$ ).

Nor even when taking in consideration a level lower than 7% increase of the BMI as a significance threshold, we could not establish a protective action of T allele as regard the weight gain induced by atypical antipsychotics ( $p>0.05$ ).

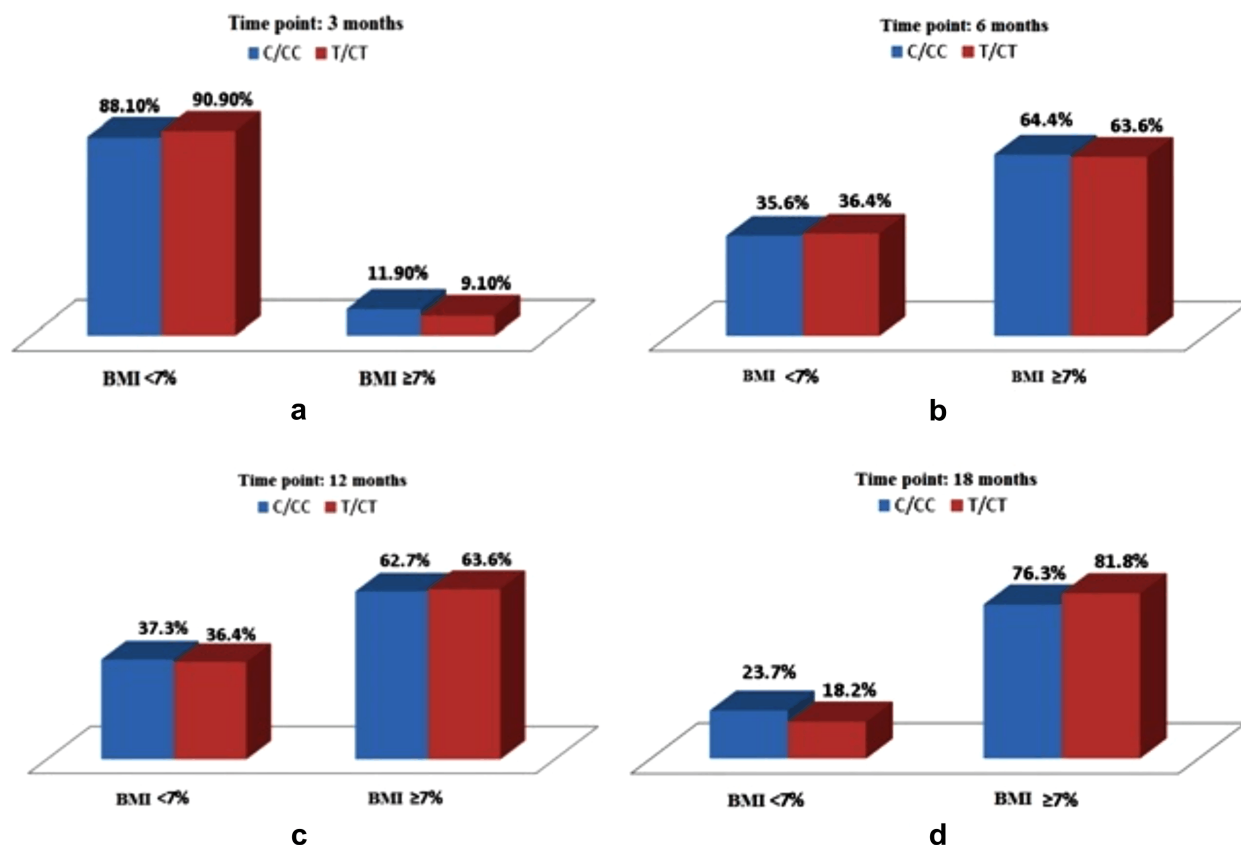
So that, the association between the T allele carriers and less BMI increase was not supported by our obtained results and findings in Romanian pediatric patients with schizophrenia and bipolar disorder.

Even when we evaluated the tendency of gaining weight below the threshold of 7% increase on BMI, we could not find a significant difference between the C/CC vs. T/CT genotype ( $p>0.05$ ), so that our study results did not support the protective effect of the T allele for weight gain induced by atypical antipsychotics.

**Table 2 – Comparison of the insulin blood levels' variation between the C/CC and T/CT genotypes at different time points**

Time point	Genotype	N	Insulinemia (mean) [μU/mL]	SD	SEM	P	Significance level
Insulinemia baseline	C/CC	59	9.7	3.83	0.5	0.765 <sup>ns</sup>	0.05
	T/CT	22	9.4	4.41	0.94		
Insulinemia 6 months	C/CC	59	13.2	4.32	0.57	0.530 <sup>ns</sup>	0.05
	T/CT	22	13.8	3.34	0.71		
Insulinemia 12 months	C/CC	59	17.6	11.11	1.45	0.372 <sup>ns</sup>	0.05
	T/CT	22	20	7.68	1.64		
Insulinemia 18 months	C/CC	59	17.8	9.73	1.27	0.030 <sup>s</sup>	0.05
	T/CT	22	23.2	9.9	2.11		

SD: Standard deviation; SEM: Standard error of the mean; P: Significance level; <sup>ns</sup>Not significant; <sup>s</sup>Significant.



**Figure 3 – Distribution of C/CC and T/CT genotypes taking in consideration a 7% increase of BMI as a level of significance: (a) Three months ( $p=0.724$ ,  $\alpha=0.05$ ); (b) Six months ( $p=0.949$ ,  $\alpha=0.05$ ); (c) 12 months ( $p=0.939$ ,  $\alpha=0.05$ ); (d) 18 months ( $p=0.593$ ,  $\alpha=0.05$ ). BMI: Body Mass Index.**

## Discussion

The studies regarding the distributions of different alleles in Romanian population are rare [16], and so are the pharmacogenetic studies in general. On the global scale, even-though there are some pharmacogenetic studies of antipsychotic medication, they have not yet offered sufficient sustainable data to widely integrate the pharmacogenetic tool in clinical practice, except for a few limited recommendations regarding the CYP2D6 testing included in Aripiprazole, Clozapine, Iloperidone and Risperidone labels [15–17]. Great efforts are also made for trying to evaluate the impact of candidate genes involved in the pharmacodynamic process of these drugs, but this approach has proved to be rather difficult because of contrasting results.

Atypical antipsychotics are not a homogenous class.

Aripiprazole and Ziprasidone have the lowest risk of weight gain and Clozapine and Olanzapine are more frequently associated with this side effect, probably because of different receptor affinities [17]. A recent meta-analysis, that included 307 studies, assessed the increase in BMI and the change in body weight that is clinically relevant (defined by 7% weight gain or loss), in relation with the duration of antipsychotic treatment (stratified in ≤6 weeks, 6–16 weeks, 16–38 weeks and >38 weeks). The study concluded that all antipsychotics increase body weight and BMI after prolonged treatment, and that, antipsychotic naïve patients are more sensible to this side effect. When only antipsychotic naïve patients were taking into consideration, and the outcome measured was the proportion of subjects gaining more than >7% weight after initiating antipsychotic treatment, even the

administration of Aripiprazole resulted in an elevated number of subjects with clinically relevant weight gain at each duration of exposure (15% of subjects had >7% weight gain after six weeks of starting Aripiprazole, while after >38 weeks, the proportion rose to 26%) [6–9]. Interesting is the fact, that a significant proportion of patients experienced a weight reduction after taking antipsychotics. The highest percentage of weight loss, of more than 7%, after initiation of antipsychotic treatment was observed in patients taking Aripiprazole (15% weight reduction after 16–38 weeks of treatment). Surprising was also the fact that even Olanzapine proved to be an atypical antipsychotic with the highest risk of inducing weight gain, a smaller proportion of patients did drop weight, after receiving this drug [8].

Physiologically, serotonin exerts an anorectic effect by acting on 5HT<sub>2C</sub> receptors in pro-opio-melanocortin neurons, increasing the  $\alpha$ -melanocyte-stimulating hormone release, which in turn acts to reduce appetite and food intake [10, 11]. Therefore, it can be expected that a 5HT<sub>2C</sub> agonist decreases food intake while a 5HT<sub>2C</sub> antagonist should produce the opposite effect, of increasing food intake [13]. After the mutant mice lacking 5HT<sub>2C</sub> receptor develop physiological changes similar to human obesity, it was suggested that this 5HTR2C gene can be a candidate gene in pharmacogenomics for studying antipsychotics-induced weight gain [12–14, 18–20].

Because there is also a different inter-individual susceptibility among patients to develop weight gain after antipsychotic treatment, it has been suggested that not only lifestyle and environmental factors, but genetic factors as well, play an important role in this inter-individual differences [19–21].

A candidate gene that has been intensively studied in association with antipsychotic weight gain is receptor 5HTR2C gene, located on X chromosome, which has a polymorphism -759C/T, in the promoter region, which may result in a different expression of the gene. Buckland *et al.* have found that the single nucleotide substitution C→T at -759 was associated with higher transcription activity of the 5HTR2C gene, leading possibly in an increased serotonin activity at 5HT<sub>2C</sub> receptor level in the hypothalamus, that offers a superior resistance to obesity and type II diabetes mellitus [18, 19, 22]. Several associations between -756C/T variants in the promoter region of the HTR2C gene and weight gain after antipsychotic treatment have been reported. Different studies involving -756C/T variant showed discordant results, in some studies it was reported that T allele is associated with reduced weight gain [21], in other an association between T allele and increased weight gain was found [23–27] or by contrary, in other studies no association was found [28, 29].

Finding a consensus about this polymorphism may be important:

(a) to bring a light on the mechanisms by which antipsychotic medications impact weight gain;

(b) for clinicians, to better choose an antipsychotic drug with a lower risk of metabolic side effects, if the patient proves to be at high risk;

(c) when one evaluates, in the process of releasing to market, an anti-obesity drug which is meant to prevent this side effect of antipsychotics; if the T allele proves to have a protective value against obesity, pharmacogenetic screening for 5HTR2C -759C/T can be a useful tool to rule out the T allele carriers from the studies, in order that the research drug could have a more powerful effect.

Our study is consistent with another pediatric study, which evaluated the role of -756C/T polymorphism in 124 children and adolescents (82% being Caucasian) treated with Risperidone for 2.8 years. They observed a significant increase in overall BMI z-scores but those were comparable across T(-) and T(+) group [29].

The contrast between findings of different studies has several possible explanations. The differences among the studies are likely due to the heterogenic variables such as ethnicity, type of antipsychotic prescribed, treatment duration, prior drug exposure and environmental and lifestyle factors. We included clinical samples from patients treated with heterogeneous atypical antipsychotics and there were cases where drugs have been switched between each other, although the medication and their doses did not differ significantly among genotype groups. This can have a positive side, because our result can thus be generalized to a whole pharmacological drug class, but can also disrupt the finding of a more specific significant association between a drug that is more predisposed to induce weight gain (Olanzapine or Clozapine) and C allele carriers.

Because of the discrepancies between the studies, it is unlikely that this polymorphism alone would become a future predictive biomarker of weight gain. Taking into consideration that weight gain is a trait in which multiple genes involved interact with environmental influences, the development of a haplotype model should have better chance to be implemented as a clinical tool and maybe -759C/T polymorphism would find a definite role in this model [30, 31]. Today, a major concern for physicians is the risk of development of a new onset type II diabetes mellitus in patients with schizophrenia or schizoaffective disorder treated with antipsychotics, which is in part related to the illness itself but also to the use of antipsychotics [5, 32, 33]. Diabetes mellitus can develop in susceptible patients because of the weight gain following antipsychotic treatment, but also can appear in patients who do not put weight, as an independent disorder and it is associated with high insulin concentrations and insulin resistance.

Any new information that could help build a consensus on the applicability of genetic testing in predicting antipsychotic outcome and dissipate controversy, it would be helpful, to guide clinicians in understanding and applying current knowledge in pharmacogenetics, and also researchers, which can develop and test new hypotheses starting on a clear and substantiated basis.

## ✎ Conclusions

Our positive result is the significant association between the increase of insulin levels and T allele carriers after 18 months of treatment with atypical antipsychotics



( $p=0.035$ ). This finding could emphasize the importance of lifestyle measures that have to be taken with special interest in T allele carriers, in order to diminish the metabolic risk. We recommend that further studies are needed, in order to investigate the -759C/T polymorphism, as a risk factor of antipsychotics to induce insulin resistance. So far, concerning the issue analyzed through the present study, the promise of psychiatric pharmacogenetics, that any patient being initiated on antipsychotic therapy, will be first genetically screened so that an individualized therapy could be prescribed, did not meet the expectations yet, more research being needed in this vast field.

### Conflict of interests

The authors declare no conflict of interests.

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