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Polymorphic Variant of *NQO1* rs1800566 and Antipsychotic-induced Metabolic Disorders in Patients with Schizophrenia

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ABSTRACT

Aim. To conduct an associative analysis between antipsychotic-induced metabolic disorders and the polymorphic variant *NQO1* rs1800566.

Materials and methods. The study included 603 patients with schizophrenia, who underwent a comprehensive clinical, anthropometric and laboratory examination. Metabolic syndrome (MetS) was established based on the 2005 International Diabetes Federation criteria. Genotyping of the polymorphic variant *NQO1* rs1800566 was performed in the studied sample of patients. Statistical processing of the results was performed using Statistica 12.0 software package (StatSoft, Russia).

Results. Among patients receiving basic therapy with atypical antipsychotics, the T allele had an effect predisposing to the development of MetS (odds ratio: 1.63, 95% confidence interval: 1.01–2.62), while the *C* allele was statistically significantly more common among patients without metabolic syndrome (odds ratio: 0.61, 95% confidence interval: 0.38–0.99). In carriers of the *TT* genotype, serum triglyceride levels are statistically significantly higher than in carriers of the *CC* or *CT* genotypes ($p = 0.049$).

Conclusion. The results of the study for the first time revealed associations of the polymorphic variant *NQO1* rs1800566 with MetS and hypertriglyceridemia in patients with schizophrenia receiving pharmacotherapy with second-generation antipsychotics. The results of this study confirm the contribution of the genetic component to the development of metabolic disorders in patients with schizophrenia and open up prospects for further search for genetic markers for the prevention and correction of this undesirable phenomenon.

Keywords: molecular genetics, *NQO1*, single nucleotide polymorphism, metabolic disorders, schizophrenia, antipsychotics, adverse effects of therapy

Conflict of interest. The authors declare no obvious or potential conflicts of interest related to the publication of this article.

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Conformity with the principles of ethics. All patients included in the study signed a voluntary informed consent. The study was approved by the Ethics Committee of Mental Health Research Institute of Tomsk NRMC (Minutes No. 165 dated September 18, 2023). .

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Полиморфный вариант *NQO1* rs1800566 и антипсихотик-индуцированные метаболические нарушения у пациентов с шизофренией

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РЕЗЮМЕ

Цель. Провести ассоциативный анализ между антипсихотик-индуцированными метаболическими нарушениями и полиморфным вариантом гена НАД(Ф)Н-хиноноксидоредуктазы-1 (*NQO1*) rs1800566

Материалы и методы. В исследование включены 603 пациента с шизофренией, у которых было проведено комплексное клиническое, антропометрическое и лабораторное обследование. Метаболический синдром (МС) устанавливался на основании критериев Международной федерации диабета (IDF), 2005. Проведено генотипирование полиморфного варианта *NQO1* rs1800566 в исследуемой выборке пациентов. Статистическая обработка результатов осуществлена с использованием программного обеспечения Statistica for Windows V.12.0 (StatSoft, Россия).

Результаты. Среди пациентов, принимающих базовую терапию атипичными антипсихотиками, аллель *T* обладал эффектом, предрасполагающим к развитию МС (отношение шансов (ОШ) 1,63; 95%-й доверительный интервал (ДИ): 1,01–2,62), в то время как аллель *C* статистически значимо чаще встречался среди пациентов без метаболического синдрома (ОШ 0,61; 95%-й ДИ: 0,38–0,99). У носителей генотипа *TT* уровни триглицеридов в сыворотке крови статистически значимо выше, чем у носителей генотипов *CC* или *CT* (p = 0,049).

Заключение. В результаты проведенного исследования впервые были обнаружены ассоциации полиморфного варианта *NQO1* rs1800566 с МС и гипертриглицеридемией у больных шизофренией, принимающих фармакотерапию антипсихотиками второго поколения. Результаты данного исследования подтверждают вклад генетической компоненты в развитие метаболических нарушений у больных шизофренией и открывают перспективы для дальнейшего поиска генетических маркеров с целью превенции и коррекции этого нежелательного явления.

Ключевые слова: молекулярная генетика, *NQO1*, однонуклеотидный полиморфизм, метаболические нарушения, шизофрения, антипсихотики, нежелательные эффекты терапии

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

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Соответствие принципам этики. Все пациенты, включенные в исследование, подписали добровольное информированное согласие. Исследование одобрено этическим комитетом НИИ психического здоровья Томского НИМЦ (протокол № 165 от 18.09.2023).

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INTRODUCTION

The ambiguity of the use of long-term antipsychotic pharmacotherapy lies in its dual effect on the organism of patients with mental disorders. On the one hand, these drugs successfully reduce the psychopathological symptoms of schizophrenia, which has been proven by numerous studies [1, 2]. On the other hand, antipsychotics, especially with long-term use, cause serious somatic, neurological, and other complications [2–4].

Both conventional and atypical antipsychotics can lead to weight gain, although the pathogenesis of this adverse effect is somewhat different. Conventional antipsychotics more often lead to hyperprolactinemia by blocking D2 dopamine receptors in the tuberoinfundibular pathway [5], while atypical antipsychotics cause dyslipidemia, increase insulin resistance [6], and thereby contribute to the development of obesity or metabolic syndrome (MetS). Increased body weight significantly reduces the quality of patients life, often leading to a decrease in their compliance and even to a complete treatment refusal [5].

Oxidative stress is characterized by increased synthesis of free radicals, in particular active forms of oxygen: singlet oxygen, superoxide radical, hydrogen peroxide, etc., as well as disruption of the prooxidant and antioxidant systems. Typically, free radical oxidation plays an important role in the bactericidal action of neutrophils, regulation of blood pressure, polymerization of proteins, and lipid peroxidation. In pathology, oxidative stress leads to the formation of atherosclerotic plaques, the development of coronary heart disease, hypercholesterolemia, carcinogenesis, and a predisposition to thrombosis [7].

One of the aspects of schizophrenia pathogenesis is considered to be the development of oxidative stress [8], which leads to impaired neuroplasticity and increased neurodegeneration and is detected regardless of whether patients have taken antipsychotics [9] or not [10]. There is evidence that oxidative stress is a probable mechanism for the development of tardive dyskinesia, one of the most severe adverse effects of conventional and some atypical antipsychotics [11, 12].

It has also been shown that lipid peroxidation processes occur rapidly in obesity [13], which in itself can cause oxidative stress. Progressive growth of adipose tissue leads to increased production of reactive oxygen species and pro-inflammatory mediators, disruption of the balance of prooxidant and antioxidant systems and, consequently, to the development of oxidative stress [14, 15], which forms a vicious circle [7].

The *NQO1* gene encodes the flavoenzyme NAD(P)H quinine oxidoreductase-1. This enzyme catalyzes the reduction of quinones to less toxic hydroquinones and is also involved in the detoxification of superoxide radicals to hydrogen peroxide. *NQO1* expression increases in oxidative stress [16]. There is also evidence that *NQO1* is found in the brain, where it is involved in dopaminergic neurotransmission [17] and neuroprotection [18].

Genetic factors have been proven to play significant role in the development of schizophrenia, the formation of its clinical picture and the severity of drug-induced side effects of antipsychotic therapy [19, 20]. The polymorphic variant *NQO1* rs1800566 is functional: it leads to the replacement of proline with serine and a significant decrease in enzyme activity [21]. In this regard, we hypothesized that polymorphic variants of the *NQO1* gene may participate in the formation of metabolic disorders in patients with schizophrenia when they are receiving antipsychotic therapy.

Thus, the aim of the study was to analyze the associations between antipsychotic-induced metabolic disorders and the *NQO1* rs1800566 polymorphic variant.

MATERIALS AND METHODS

Patients. The study was conducted at the Department of Endogenous Disorders of the Mental Health Research Institute of Tomsk National Research Medical Center. A total of 603 patients with schizophrenia (302 men and 301 women) were examined. All patients included in the study underwent in-patient treatment, signed a voluntary informed consent, and received antipsychotic therapy in the average therapeutic doses recommended by the manufacturer.

Inclusion criteria were as follows: age 18–55 years; follow-up history of at least 1 year; Slavic ethnicity; verified diagnosis of schizophrenia according to ICD-10 criteria; consent to participate in the study.

Exclusion criteria were as follows: the presence of organic, neurological, severe somatic diseases leading to organ failure; the presence of concomitant addictive or other mental disorders; refusal to participate in the study.

All subjects completed the “Basic card of socio-demographic and clinical-dynamic features for patients with schizophrenia” [22], which we had

previously tested in clinical trials.

*Mental status assessment***.** The severity of the mental state was verified using the Positive and Negative Syndrome Scale (PANSS) [23] in the adapted Russian version (SCI-PANSS) [24].

*Anthropometric study***.** All subjects underwent anthropometric measurement, which included the measurement of height, weight, and waist circumference, and the calculation of body mass index (BMI). Waist circumference was measured midway between the lower rib and the iliac crest.

*Laboratory parameters***.** Blood for biochemical tests was taken on an empty stomach between 8.00 and 9.00 a.m. Glucose, triglycerides (TG), and high-density lipoproteins (HDL) were measured in blood serum samples using standard biochemical methods.

*Metabolic syndrome***.** MetS was defined according to the criteria of the International Diabetes Federation (IDF) (2005) [25]:

– abdominal obesity: waist circumference ≥ 94 cm in men or ≥ 80 cm in women;

– dyslipidemia: elevated triglyceride (TG) levels ≥ 1.7 mmol/l;

– dyslipidemia: low HDL levels < 1.03 mmol/l in men or < 1.29 mmol/l in women;

– blood pressure ≥ 130/85 mm Hg;

– fasting plasma glucose levels ≥ 5.6 mmol/l.

*Molecular genetic analysis***.** Genotyping of the polymorphic variant *NQO1* rs1800566 was performed by real-time PCR using SNP Genotyping Assay kits (ThermoFisher Scientific, USA) on a StepOnePlus device (Applied Biosystems, USA).

Based on the genotyping results, patients were divided into 3 groups according to the identified genotypes for further comparison of quantitative indicators.

Statistical analysis was performed using Statistica for Windows V.12.0 software (StatSoft, Russia). The Shapiro–Wilk test was used to test whether data set was normally distributed. The obtained data did not obey the normal distribution law. Therefore, they are presented as the median with the interquartile range *Me* [Q_1; Q_3]. Qualitative data are presented as frequency indicators in absolute and relative units *n* (%). When comparing qualitative data, Pearson's $\chi 2$ was used, including taking into account the Yates correction, and Fisher's exact test (if one or more of the study groups had less than 5 people). Quantitative data were compared using the Kruskal–Wallis test (H). The odds ratio (OR) with the calculation of the 95% confidence interval (CI) was used as a quantitative measure of the degree of association of a genetic marker with MetS. The threshold level of statistical significance is $p = 0.05$.

This study did not use animals in the experiments. All the procedures performed comply with the ethical standards of the research institute and/or national Ethics Committee and the Helsinki Declaration of 1964 and its subsequent amendments or comparable standards of ethics.

RESULTS

Socio-demographic and clinical characteristics of patients are presented in Table 1.

Table 1

Socio-Demographic and Clinical Characteristics of the Examined Patients

Characteristic	Parameter
Sample size, *n*	603
Gender, *n* (%)	Men: 302 (50.1%)
	Women: 301 (49.9%)
Age, years, *Me* [Q_1; Q_3]	39 [31; 49]
Age of manifestation, years, *Me* [Q_1; Q_3]	24 [20; 30]
Duration of disease, years, *Me* [Q_1; Q_3]	13 [7; 21]
PANSS, points, *Me* [Q_1; Q_3]	Total score: 102 [92; 102]
	Positive symptoms: 23 [19; 27]
	Negative symptoms: 25 [22; 29]
	General psychological symptoms: 52 [46; 58]
Duration of basic therapy, years, *Me* [Q_1; Q_3]	8 [3; 17]
Chlorpromazine equivalent, mg, *Me* [Q_1; Q_3]	434.8 [225; 758.7]
Pharmacological profile of antipsychotics, *n* (%)	Conventional: 370 (61.4)
	Atypical: 234 (39.3)
Metabolic syndrome , *n* (%)	Yes: 156 (25.9%)
	No: 447 (74.1%)

At the first stage of the study, an association analysis was performed between the frequency of occurrence of genotypes and alleles of the selected single-nucleotide polymorphic variant *NQO1* rs1800566 and MetS. No statistically significant associations were found in the total sample of patients. At the second stage, patients were divided into groups depending on the pharmacological profile of the basic antipsychotic. In the case of using conventional antipsychotics, no relationship was found between the selected polymorphic variant and MetS. Among patients receiving basic therapy with atypical antipsychotics, the T allele had an effect predisposing to the development of MetS, while the C allele was statistically significantly more common among

patients without MetS (Table 2).

Anthropometric and laboratory parameters were compared among patients receiving basic atypical antipsychotic therapy, for which they were divided into subgroups with different genotypes of the studied polymorphic variant *NQO1* rs1800566. It was shown that in carriers of the TT genotype, serum triglyceride levels were statistically significantly higher than in carriers of other genotypes (Table 3).

Table 2

Comparison of Genotype and Allele Frequencies of the *NQO1* Rs1800566 Polymorphic Variant in the Group of Patients Receiving Basic Therapy with Atypical Antipsychotics, *n* (%)

Polymorphic variant			Without MetS	With MetS	OR		χ^2/F	*p*
					Value	95% CI		
General sample								
rs1800566	genotypes	*CC*	309 (65.7)	92 (57.1)	0.69	0.48–1.00	4.71	0.09
		CT	140 (29.8)	63 (39.1)	1.51	1.0 –2.20		
		TT	21 (4.5)	6 (3.7)	0.96	0.38–2.45		
	alleles	*C*	0.806	0.767	0.79	0.58–1.07	2.29	0.13
		T	0.194	0.233	1.26	0.93–1.72		
Patients receiving conventional antipsychotics as basic therapy								
rs1800566	genotypes	*CC*	182 (65.2)	52 (59.1)	0.77	0.47–1.26	2.91	0.23
		CT	84 (30.1)	34 (38.6)	1.42	0.86–2.34		
		TT	13 (4.7)	2 (2.3)	0.54	0.12–2.46		
	alleles	*C*	0.803	0.784	0.89	0.59–1.35	0.29	0.59
		T	0.197	0.216	1.21	0.74–1.69		
Patients receiving atypical antipsychotics as basic therapy								
rs1800566	genotypes	*CC*	111 (68.1)	37 (53.6)	0.54	0.30–0.96	4.34	0.11
		CT	46 (28.2)	28 (40.6)	1.83	1.00–3.32		
		TT	6 (3.7)	4 (5.8)	2.00	0.53–7.48		
	alleles	*C*	0.822	0.739	0.61	0.38–0.99	4.13	0.04*
		T	0.178	0.261	1.63	1.01–2.62		

* statistically significant differences (here and in Table 3).

Table 3

Comparison of Anthropometric and Biochemical Parameters in a Group of Patients Receiving Basic Therapy with Atypical Antipsychotics with Different Genotypes of the *NQO1* Rs1800566 Polymorphic Variant, *Me* [Q_1; Q_3]

Parameter	Genotype			*H*	*p*
	CC	CT	TT		
Waist size, cm	87 [78; 98]	87 [78; 100]	91 [83; 96]	0.61	0.73
BMI, kg/cm^2	26.2 [22.5; 31.1]	23.2 [20.5; 26.3]	27.6 [22.5; 31.5]	0.31	0.86
Glucose, mmol/l	4.91 [4.5; 5.48]	5.1 [4.5; 5.42]	5.2 [5; 5.8]	1.78	0.41
Triglycerides, mmol/l	1.32 [1; 1.92]	1.3 [0.9; 1.84]	1.94 [1.6; 2.3]	5.65	0.049*
HDL, mmol/l	1.01 [0.82; 1.25]	1 [0.82; 1.3]	1.09 [0.6; 1.45]	0.003	0.999

DISCUSSION

Along with the choice of the most effective pharmacotherapeutic tactics in the treatment of schizophrenia, the problem of genetic predisposition to the development of certain undesirable metabolic phenomena when using antipsychotic drugs has remained no less relevant for biological psychiatry for a long time.

It is assumed that *NQO1* acting as an antioxidant enzyme prevents the overproduction of reactive oxygen species, leading to vascular dysfunction, promoting the activation of adipocyte transcription factors and disruption of the regulation, and synthesis of fatty acids and lipids [26]. The results obtained in the course of the study may mean that carriers of the mutant allele have reduced *NQO1* activity and, consequently, a shift in the balance towards the prooxidant system. Together with the increased risk of cardiometabolic disorders when taking some atypical antipsychotics and the development of oxidative stress with increased formation of adipose tissue, which could explain the differences obtained.

There is no information in the literature on studies of the association of polymorphic variants of the *NQO1* gene with antipsychotic-induced metabolic disorders. The overwhelming majority of publications regarding the sought-after polymorphic variant are devoted to its association with cancer [26–28], since oxidative stress plays an important role in carcinogenesis processes. Therefore, we consider the present study to be a pilot. Anecdotal data on the presence or absence of an association of this polymorphic variant, as well as other polymorphic variants of the *NQO1* gene with the development of metabolic disorders, obesity, or MetS are presented.

A relationship was found between the T allele and hypertriglyceridemia, and reduced HDL levels in a Mexican population of patients suffering from MetS [30]. Elevated triglyceride levels were associated with carriage of the homozygous T allele [31]. Mice homozygous for the knockout of the *NQO1* gene have been shown to have increased TG levels [32]. While administration of beta-lapachone, a natural *NQO1* substrate that activates the enzyme, to mice was accompanied by a decrease in the concentration of TG, cholesterol, free fatty acids, leptin, glucose, insulin, and body weight in mice with an experimental model of obesity and diabetes mellitus [33].

A number of studies involving patients with type 2 diabetes mellitus have not revealed associations between this disease and the *NQO1* rs1800566 polymorphic variant [34, 35]. According to the authors, the lack of associations may be due to the influence of concomitant therapy with fibrates and statins [34]. This further emphasizes the importance of assessing the effect of antipsychotic therapy in our study.

It is worth mentioning that one of the limitations of this study is the fact that the sample was recruited from patients with chronic schizophrenia. Patients received long-term antipsychotic therapy; however, it cannot be confirmed that all patients had high compliance in the long term. However, the results were obtained on a sufficient sample size and through correct statistical processing and therefore reflect objective clinical data. In the future, they can form the basis for a more detailed study of the contribution of oxidative stress to the development of antipsychotic-induced obesity in patients with schizophrenia.

CONCLUSION

For the first time, we have found found associations of the polymorphic variant *NQO1* rs1800566 with MetS and hypertriglyceridemia in patients with schizophrenia receiving pharmacotherapy with second-generation antipsychotics. The obtained data confirm the contribution of genetics to the development of metabolic disorders in patients with schizophrenia and open up prospects for further search for genetic markers for the purpose of preventing and correcting this on-treatment adverse event.

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