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Article

Single-Nucleotide Variant rs167771 of the *DRD3* Gene Does Not Increase the Risk of Developing Antipsychotic-Induced Parkinsonism in Schizophrenic Patients

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Abstract: Antipsychotic-induced parkinsonism (AIP) is a form of secondary parkinsonism that most often develops with blockade of dopaminergic receptors type D2. However, AIP can oc-cur not only while taking first-generation APs, but also new ones that have a wider receptor pro-file. There is a connection between the *DRD3* gene and the regulation of motor activity in associa-tion genetic studies of AIP; **Aim**: to study the role of single-nucleotide variant rs167771 of the *DRD3* gene, encoding dopaminergic receptors D3 type, with the risk of AIP in Caucasian patients with schizophrenia spectrum disorders (SSDs) of North-West Russia; **Methods**: The study in-volved 91 participants permanently residing in Saint Petersburg and the Leningrad region (North-West Russia), including: group 1 - 30 patients (SSDs with AIP); group 2 - 29 patients (SSDs without AIP); group 3 (control) - 32 healthy volunteers. All participants underwent: a neurological examination using scales and questionnaires (H&Y, MoCa, UPDRS, BARS, AIMS, ESRS) at two points (before and after 8 weeks on AP monotherapy) and an association genetic study of carriage of major and minor alleles and genotypes of rs167771 of the *DRD3* gene with a risk of developing AIP; **Results**: According to the study, it was shown that AIP is characterized by bradykinesia with a decrease in the amplitude of multidirectional movements. Mild/moderate asymmetry in the severity of action tremor according to the hemi-type on the left. The allelic frequency of the studied rs167771 of the *DRD3* gene in Caucasians of North-West Russia was comparable to that in the countries of Northern Europe, also in the countries of Southeast Asia and some regions of North and South America. The obtained clinical data are typical for the early stage of development of AIP, which is missed in more than 80% of cases by the 8th week from the start of taking AP. The major allele A of rs167771 of the *DRD3* gene is protective against the risk of SSDs (OR < 0.001), but not AIP (OR > 0.05); **Conclusions**: We have not found a significant association of rs167771 of the *DRD3* gene with the risk of developing AIP in Caucasians in North-West Russia.

Keywords: *antipsychotic-induced parkinsonism, gene DRD3; rs167771, dopaminergic receptor.*

1. INTRODUCTION

Drug-induced parkinsonism is secondary parkinsonism that occurs most often while taking antipsychotics (APs). At the same time, AP-induced parkinsonism (AIP) more often develops while taking first-generation APs [**1**], which block predominantly dopaminergic receptors D2 type [**2**]. However, a high risk of developing AIP has also been shown while taking new generations of APs. Dopaminergic receptors in the brain are

divided into two families: the D1 family (D1 and D5) and the D2 family (D2, D3 and D4). The leading theory for the development of AIP is the blockade of dopaminergic receptors type D2. All APs have a powerful ability to block these receptors and reduce dopaminergic neurotransmission [**3, 4**].

Also, there has been interest in the *D3* receptors, which encode the *DRD3* gene. The *DRD3* gene is similar to the *DRD2* gene, but differs from most other dopamine receptor genes. This gene contains 5 intronic regions, the position of two of which corresponds to the position of the introns of the *DRD2* gene. [**5**] The *DRD3* gene contains six exons and expresses five alternative mRNAs [**6**]. The most studied polymorphisms of this gene are rs6280 and rs1800828, while the least studied is the rs167771 polymorphism, the clinical and biological role of which is being actively studied as a predictor of Parkinson's disease (PD), but not as a predictor of AIP. However, Magistrelli et al. concluded that some single nucleotide variants (SNVs) of the *DRD1, DRD2, DRD3* genes may be involved not only in the development of the disease, but also in motor and non-motor complications (dyskinesias, visual hallucinations and cognitive decline), as well as in the pharmacological response and adverse reactions caused by dopaminergic agents [**7**].

Previously, the connection of the *DRD3* gene with the regulation of motor activity was shown in associative genetic studies of AIP [**5**]. Dopaminergic receptors D3 type are located in the ventral striatum and putamen of the basal ganglia - an area of the brain involved in locomotor control [**6**]. In rat models of parkinsonism, it was shown that a selective agonist the of D3 receptors inhibit motor activity in the nucleus accumbens [**7**], but selective antagonists of dopaminergic receptors type D3 increase motor activity [**8**]. Others studies were confirmed the role of D3 receptors in motor activity in an animal model (mouse) [**9**].

However, the results of clinical studies on the role of genetic predisposition to the development of parkinsonism are contradictory. Thus, Ivanova et al. [**8**] showed that the homozygous recessive genotype GG rs3773678 *DRD3* was significantly associated with the development of Parkinson's disease in the Caucasian population of Eastern Siberia (Russia), which is comparable to the results of previous studies in other countries of the world [**9, 10**]. A significant association was also identified between the variable alleles of SNVs rs167771 and rs324035 and the risk of developing PD in Caucasians from Eastern Siberia [**8**]. Pozhidaev et al. [**11**] demonstrated that rs167771 may play a prognostic role in the development of parkinsonism, but not drug-induced dyskinesia, in Caucasians in Russia.

Similar results were obtained by Spanish researchers Gasso et al. [**12**], who analyzed 70 SNVs in the *DRD3* gene and found a significant association of rs167771 with the risk of developing risperidone-induced parkinsonism.

However, there are studies that dispute the association of the risk of developing parkinsonism with rs167771 of the *DRD3* gene. Thus, Bakker et al. [**9**] concluded that this SNV is not associated with a predisposition to the development of extrapyramidal movement disorders in the studied population.

Polymorphisms of the *DRD3* gene can not only influence the formation of a therapeutic response to APs, but also increase the risk of developing certain neurological diseases and mental disorders, including PD [**8**], depression [**13**], schizophrenia [**14**], autism spectrum disorders [**15**], as well as the development of alcohol, nicotine and heroin addiction [**16**].

According to Ye et al. [**17**], genetically determined changes in the functioning of the dopaminergic system in humans predispose not only to the development of schizophrenia and primary PD, but also plays an important role in the development of AP-induced extrapyramidal adverse drug reactions (ADRs). The authors suggest that AIP can be interpreted from a systems perspective on dopamine homeostasis.

Thus, the above-mentioned studies, despite their contradictory nature, allowed us to hypothesize that rs167771 of the *DRD3* gene can be considered as a prognostic genetic marker for the development of AIP in schizophrenic Caucasians patients.

Aim of this research: to study the association of SNV rs167771 in the *DRD3* gene with the risk of AIP development in North-Western Russian Caucasian patients with SSDs.

2. MATERIALS AND METHODS

2.1. Data Collection

The study was open, observational, cross-sectional. It was carried out within the framework of the state assignment of the Ministry of Health of the Russian Federation. "Personalized approach to increasing the effectiveness of therapy and reducing the risk of somatic pathology in patients with affective and psychotic disorders» (Registration Number: 121040900046-5), subsection "Antipsychotic-induced extrapyramidal disorders: clinical and genetic predictors" (approved by the Local Ethics Committee of V. M. Bekhterev National Medical Research Centre for Psychiatry and Neurology (Saint Petersburg, Russia, protocol No. EC-I25/23 dated April 24, 2023). The study was carried out in the Institute of Personalized Psychiatry and Neurology of V. M. Bekhterev National Medical Research Centre for Psychiatry and Neurology (Saint Petersburg, Russia).

2.2. Study Participants

The study involved 91 participants, including: group 1 - 30 patients (SSDs with AIP); group 2 - 29 patients (SSDs without AIP); and group 3 - 32 healthy volunteers (**Table 1, Fig. 1**).

Table 1. The main pathways of metabolism and haloperidol

Group	Age of participants, M ± SE	Age of male participants, M ± SE	Age of female participants, M ± SE
Group 1	33.0 ± 9,74	32 ± 9,59	42 ± 6.66
Group 2	32.0 ± 8,36	32 ± 8,83	32.5 ± 6.89
Group 3	39.5 ± 10,2		45. 5 ± 9.75

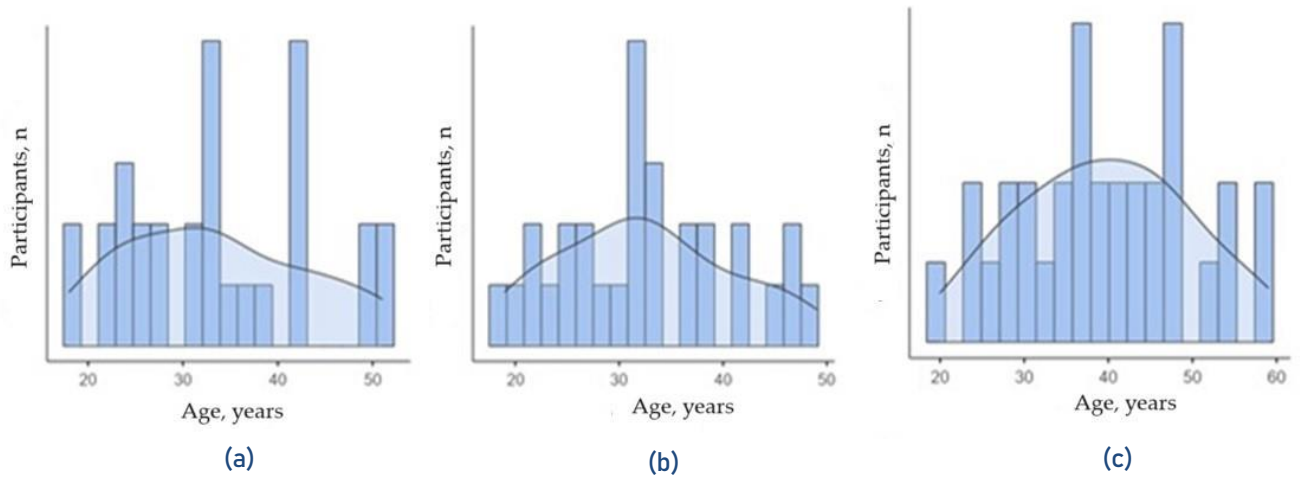

Figure 1. Distribution of groups by gender and age: (a) – group 1 (schizophrenic patients with antipsychotic-induced parkinsonism); (b) – group 2 (schizophrenic patients without antipsychotic-induced parkinsonism); (c) – group 3 – (healthy volunteers)

The minimum sample was calculated using an online calculator [**18**], we used Altman's formula to calculate the minimum sample size for two unrelated groups of participants in this study [**19, 20**].

Criteria for inclusion in the groups 1 and 2: male and female; age from 18 to 60 years; Caucasians; Russian speakers; permanent residence in Saint Petersburg and the Leningrad region; verified diagnosis F20 and F23 according to ICD-10 criteria (1995); taking APs in monotherapy mode; signing a voluntary informed consent by the patient to participate in the study.

Criteria for inclusion of participants in the group 3*:* male and female; age from 18 to 60 years; Caucasians; Russian speakers; permanent residence in St. Petersburg and the Leningrad region; healthy volunteers; signing a voluntary informed consent by a volunteer to participate in the study.

Criteria for excluding patients from the study: age less than 18 years and more than 60 years; Asians and Africans; pregnancy or lactation; neurodegenerative diseases; alcohol and drug addiction; PD; secondary parkinsonism due to acute and chronic intoxication (including exposure to industrial factors); diabetes; acute and chronic neuroinfection; infection caused by the human immunodeficiency virus; taking APs in polytherapy mode; questionable or unspecified clinical diagnosis of mental disorder; taking other psychotropic drugs; taking antiparkinsonian drugs; patient participation in another study; low patient compliance with the protocol of this study; patient refusal to participate in this study.

In all three groups, the number of male participants predominated: group 1 - 83.3%; group 2 - 79.3%; group 3 - 81.3%. The mean age was 34.0 ± 9.82 years old. Patients took APs of the first and new generations. In groups 1 and 2, olanzapine and paliperidone were more often prescribed: 6 patients (20.0%) and 7 patients (24.1%), respectively **(Fig. 2).**

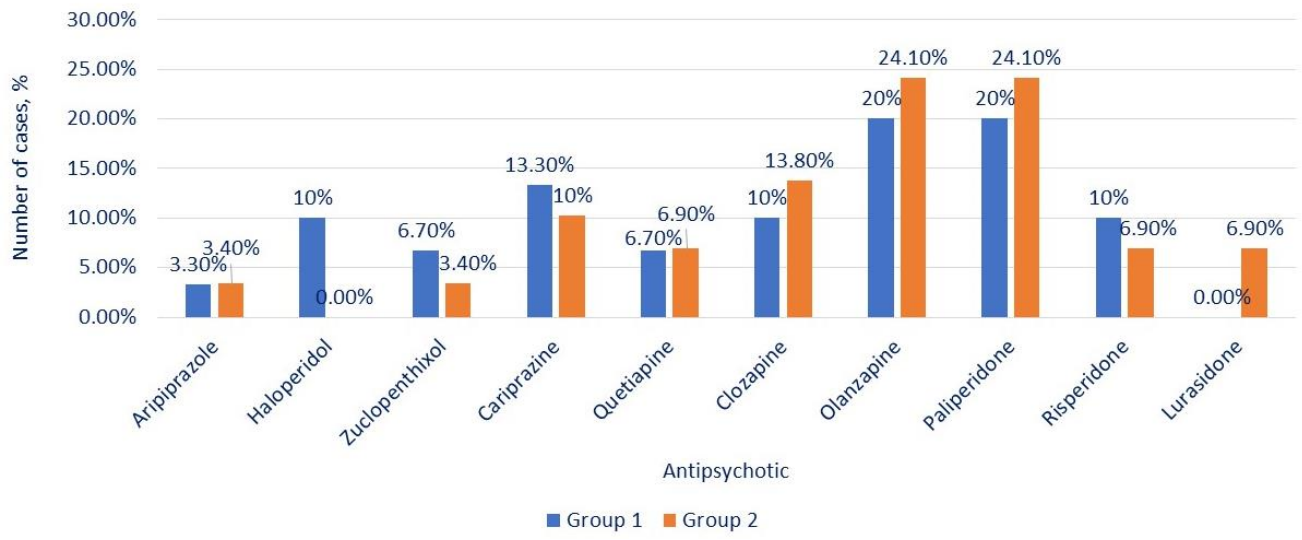

Figure 2. Antipsychotics taken in the groups 1 and 2

2.3. Clinical Analysis

During this study, all participants were examined by a neurologist three times: at the randomization stage, at the first visit (before start of APs prescription) and at the second visit (6 - 8 weeks after the start of APs prescription) using diagnostic scales and questionnaires (MoCa - Montreal Cognitive Assessment, UPDRS - Unified Parkinson's Disease Rating Scale (subscale II - Activities of Daily Living, and subscale III - Motor

Impairments), Schwab & England Scale - Schwab and England Activities of Daily Living Scale, BARS – Barnes Akathisia Rating Scale, AIMS - Abnormal Involuntary Movement Scale, ESRS - Extrapyramidal Symptom Rating Scale, H&Y - Hoehn and Yahr Scale) (**Fig. 3).**

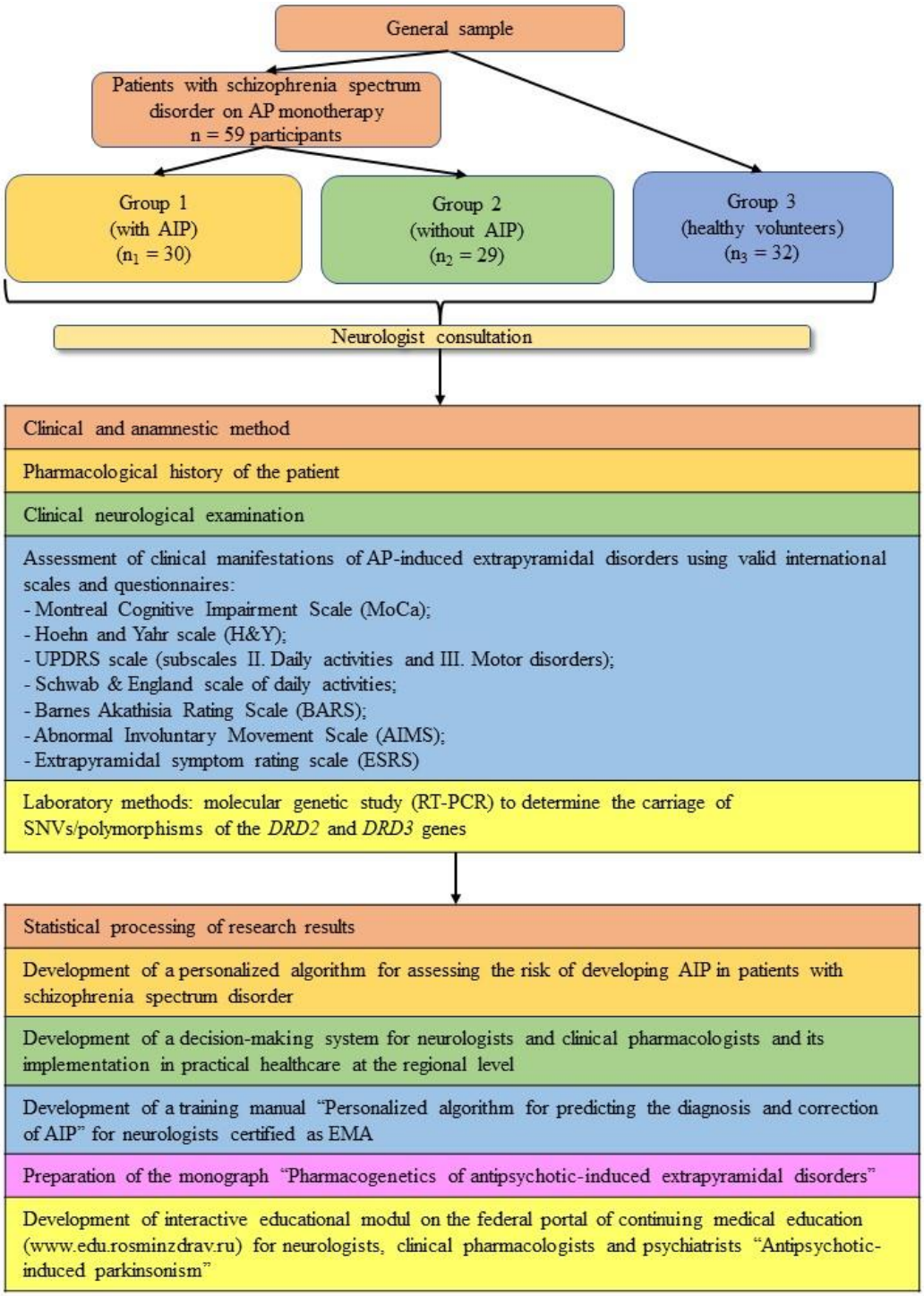

Figure 3. Study design

Note: AP - antipsychotic; AIP – antipsychotic-induced parkinsonism; RT-PCR - polymerase chain reaction in real time; EMA - educational and methodological association.

To diagnose AIP, we used the following scales: (1) UPDRS (subscale II (rated on a scale of grades from 1 to 3 points) - self-assessment of daily activities, including speaking, swallowing, handwriting, dressing, hygiene, falling, salivating, turning over in bed, walking and cutting food; and subscale III (rated with "yes" and "no" ratings) - controlled assessment of motor activity conducted by a neurologist) [**21**]; (2) ESRS (section I contains a search questionnaire concerning general information about the symptoms of parkinsonism, dystonia and dyskinesia and allows you to assess the 3 degrees of severity of their characteristics (mild, moderate, severe) or absence of signs, and the following sections contain an assessment of the symptoms of parkinsonism and their severity according to a 6-point system (section II), the symptoms of dystonia separately in hands and feet also with a 6-point assessment of their severity (section III) and dyskinesia with a detailed indication of their localization and a 6-point assessment; sections V and VI contain a scale of general clinical impression for assessing the severity of dyskinesia and parkinsonism) [**22**]; H&Y scale (to determine the degree of motor disorders in patients with AIP - from zero to the fifth)) [**23**] ; Schwab & England Scale (to diagnose the degree of daily activity of a patient with AIP, his dependence on other people when taking care of himself; the test has 11 levels and reveals the degree of self-care insufficiency as a percentage - from 100% (completely independent) to 0% (completely dependent on outside help, bedridden); the assessment was carried out by a neurologist) [**24**].

The MoCA (30 items) was used at the randomization stage to exclude patients with moderate to severe cognitive impairment (< 26 points) from the present study. The scale evaluates various cognitive functions: attention and concentration, executive functions, memory, speech, optical-spatial activity, conceptual thinking, counting and orientation. This is a simple test that allows you to quickly determine if there are any impairments in a person's cognitive functions, including their ability to understand, reason and remember [***и***].

We used BARS for the differential diagnosis of AIP and AP-induced akathisia in study participants at the randomization stage and two subsequent visits (visit 1 and visit 2). The BARS is a four-item scale that scores patients' akathisia based on: (a) brief observation by the clinician (ranked 0 to 3 points); (b) patient report of awareness of restlessness (ranked 0 to 3 points); (c) patient report of distress related to restlessness (ranked 0 to 3 points), which produces; (d) a global clinical assessment of akathisia [**26]**. The global clinical assessment contains five well-defined severity categories, which are considered clinically relevant: 0 points - absent of AP-induced akathisia; 1 point – questionable AP-induced akathisia; 2 points – mild AP-induced akathisia; 3 points – moderate AP-induced akathisia; 4 points – marked AP-induced akathisia; 5 points - severe AP-induced akathisia [**27**]. If a schizophrenic patient developed AP-induced akathisia (> 1 point by BARS), he was excluded from this study.

The AIMS was used by us for the differential diagnosis of AIP and AP-induced dyskinesia at the randomization stage and two subsequent visits (visit 1 and visit 2). This is a 12-item scale for assessing dyskinesias. The first 7 items pertain to abnormal movements in three specific anatomical sites: facial and oral movements (4 items); extremity movements (2 items); and trunk movements (1 item) [**28**]. The remaining items are global assessments (3 items, including global severity, incapacitation, and patient awareness), and 2 items specific to dentition. Except for items related to dentition, items are scored on a 5-point scale: none, normal (1 point), minimal (2 points), mild (3 points), moderate (4 points), or severe (5 points). If a schizophrenic patient developed AP-induced dyskinesia (> 2 point by AIMS), he was excluded from this study.

2.4. Genetic Analysis

Blood was collected in a volume of 10 ml from the cubital vein under aseptic conditions into vacuum tubes "IMPROVACUTER" (Guangzhou Improve Medical Instruments, China) containing a 0.5 M solution of ethylenediaminetetraacetic acid (EDTA). Isolation of genomic DNA was carried out by the sorption method from 0.1 ml of

leukocyte suspension using the DNA-Sorb-B kit (103-20, AmpliPrime, Russia) according to the manufacturer's instructions. Reagents of the single nucleotide variant (SNV) rs167771 of the *DRD3* gene were developed specifically for this study at the Central Research Institute of Epidemiology (Moscow, Russia). The alleles and genotypes determination using RT-PCR was performed with locked nucleic acid oligonucleotides and protocol designed analogously for TLR SNVs [**29**]. Determination of carriage of SNV rs167771 (NG_008842.2:g.46980C>T, NG_008842.2:g.46980C>G, NG_008842.2:g.46980C>A) of the *DRD3* gene was carried out using RT-PCR on the Rotor-Gene 6000 device (Corbett Life Science, Australia) using TaqMan allelic discrimination technology and commercially available fluorescent probes (Applied Biosystems, USA).

2.5. Statistical Analysis

Database analysis was carried out using ISB SPSS version 22.0 (SPSS Inc, USA). To assess clinical and genetic biomarkers of AIP, the odds ratio (OR) was calculated (OR 95% confidence interval (CI). Intergroup differences were significant at p-value < 0.05.

3. RESULTS

3.1. Clinical Results

In the group 1 (SSDs with AIP), the severity of AIP at the second visit was predominantly mild and moderate (p-value = 0.006). When assessing the form of AIP at the second visit, AIP was recorded predominantly as an akinetic-rigid or mixed form (p-value = 0.034). According to the study, no AIP was registered in the comparable group 2 (SSDs without AIP) at the second visit (p-value = 0.019).

All patients in the group 1 were assessed for symptoms using the Schwab & England Scale. When assessing the relationship between the severity of AIP and the severity of daily activity at the first visit, mild AIP was predominantly recorded and a decrease in daily activity by 10% was noted (p-value = 0.031). At the second visit, the severity of AIP increased, and the decrease in daily activity reached 20% (p-value = 0.257) (**Tables 2, 3**).

Patients in the group 1 were assessed for the dynamics of extrapyramidal disorders from the first to the second visit. The severity of hypokinesia in the lower extremities increased significantly from the first to the second visit (p-value = 0.004). Also, the severity of fast multidirectional movements in the right (p-value = 0.012) and left (p-value = 0.017) hands increased statistically significantly from none to mild and moderate severity.

According to the results of the study using the H&Y scale, the severity of clinical symptoms corresponded to stage 2 of parkinsonism on the H&Y scale, which is explained by the more rapid development of akinetic-rigid syndrome in patients with AIP compared with Parkinson's disease [**30**] (**Fig. 4**).

Table 2. Correlation between the severity of antipsychotic-induced parkinsonism and the severity of daily activity in the main group (visit 1)

Severity of daily activities according (Schwab & England scale)	Degree of AIP severity			
	Normal, n (%)	Mild, n (%)	Moderate, n (%)	Severe, n (%)
100%	5 (17.85%)	0 (0%)	2 (3.5%)	0 (0%)
90%	1 (3.5%)	10 (35.71%)	1 (3.5%)	0 (0%)
80%	2 (7.14%)	3 (3.5%)	0 (0%)	2 (7.14%)
70%	0 (0%)	1 (0%)	0 (0%)	0 (0%)
60%	0 (0%)	1 (0%)	0 (0%)	0 (0%)

Note: AIP - antipsychotic-induced parkinsonism.

Table 3. Correlation between the severity of antipsychotic-induced parkinsonism and the severity of daily activity in the main group (visit 2)

Severity of daily activities according (Schwab & England scale)	Degree of AIP severity			
	Normal, n (%)	Mild, n (%)	Moderate, n (%)	Severe, n (%)
100%	0 (0%)	0 (0%)	0 (0%)	0 (0%)
90%	1 (3.5%)	6 (21.42%)	7 (25%)	0 (0%)
80%	0 (0%)	3 (10.7%)	6 (21.42%)	0 (0%)
70%	1 (3.5%)	1 (3.5%)	1 (3.5%)	1 (3.5%)
60%	0 (0%)	1 (3.5%)	0 (0%)	0 (0%)

Note: AIP - antipsychotic-induced parkinsonism.

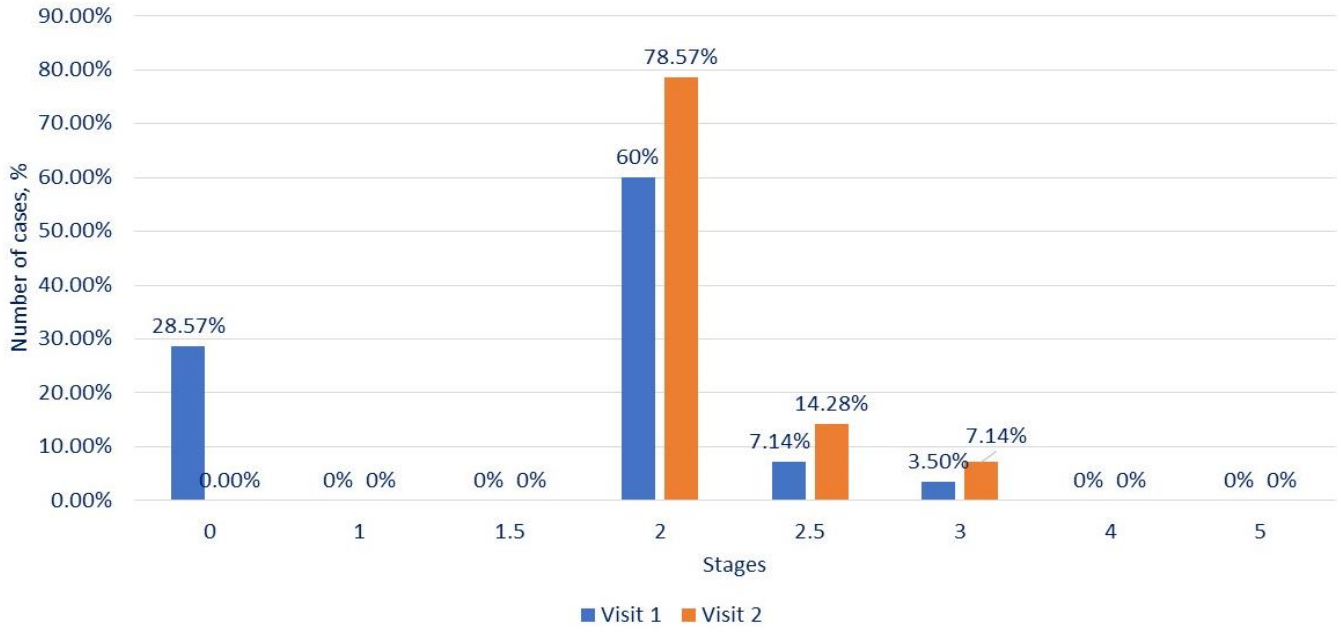

Figure 4. The severity of antipsychotic-induced parkinsonism on the Hoehn and Yahr scale at visits 1 and 2

At the same time, during the neurological examination, the development of mild action tremor and/or postural tremor in the extremities in patients with AIP was recorded by the second visit predominantly in the hemitype on the left at visit 2 (**Table 4).**

Table 4. Characteristics of limb tremor in patients with antipsychotic-induced parkinsonism

Characteristics of action tremor	Right hand, n (%)		Left hand, n (%)		Right leg, n (%)		Left leg, n (%)	
	Visit							
	1st	2nd	1st	2nd	1st	2nd	1st	2nd
None	18 (64.28%)	15 (53.57%)	17 (60.71%)	13 (46.4%)	20 (71.42%)	18 (64.28%)	20 (71.42%)	18 (64.28%)
Mild action tremor	7 (25%)	10 (35.71%)	8 (28.57%)	12 (42.85%)	5 (17.85%)	8 (28.57%)	6 (21.42%)	9 (32.14%)
Medium amplitude action tremor	1 (3.5%)	1 (3.5%)	2 (7.14%)	1 (3.5%)	0 (0%)	1 (3.5%)	0 (0%)	0 (0%)
Combination of action tremor and postural tremor of medium amplitude	2 (7.14%)	2 (7.14%)	1 (3.5%)	2 (7.14%)	3 (10.7%)	1 (3.5%)	2 (7.14%)	1 (3.5%)

Almost large amplitude, interferes with food intake	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Statistical analysis	p-value = 0.849 X^2 = 0.802		p-value = 0.572 X^2 = 2.0		p-value = 0.424 X^2 = 2.8		p-value = 0.595 X^2 = 1.04	

The results obtained explain the importance of early diagnosis of AIP at an earlier stage. It is important not to miss the therapeutic opportunities for neuroprotection of the development of this neurological adverse drug reaction to psychopharmacotherapy of SSDs.

3.2. Genetic Results

In the control (group 3), the frequency of the minor allele *G* of the studied SNV rs167771 of the *DRD3* gene in healthy Caucasians living in Northwest Russia was comparable to that in the countries of Northern Europe, also in the countries of Southeast Asia and some regions of Northern Europe and South America (**Fig. 5**).

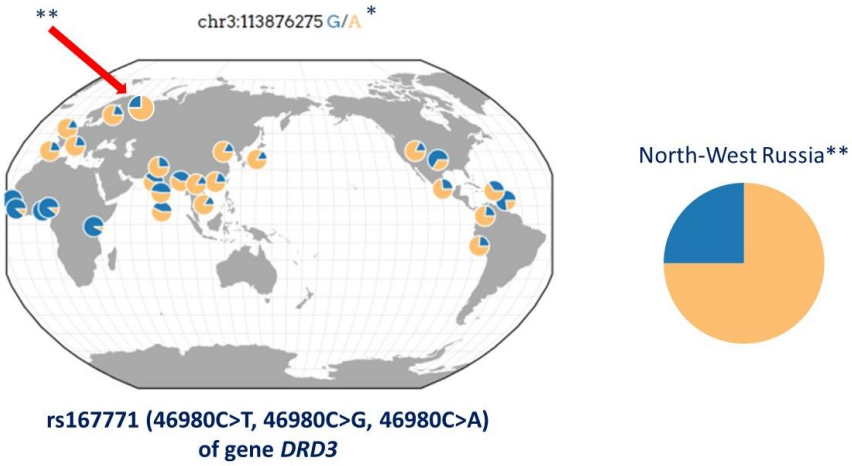

Figure 5. Geography of single nucleotide variant rs167771 of the DRD3 gene.
Note: *according to data Geography of Genetic Variants Browser [31].** according to our research

There are identified statistically significant differences in the frequency of carriage of the major allele *A* (p-value = 0.004), heterozygous genotype *AG* (p-value = 0.012) rs167771 (NG_008842.2:g.46980C>T, NG_008842.2:g.46980C>G, NG_008842.2:g.46980C>A) of the *DRD3* gene in the groups 1 and 2 compared to the group 3 (**Table 5**).

Table 5. Frequency of alleles and genotypes of the single nucleotide variant rs167771 of the DRD3 gene in the study groups

Allele/genotype	Group 1 (SSDs with AIP)	Group 2 (SSDs without AIP)	Group 3 (control)	p-value
A	51 (85%)	56 (96.5%)	48 (75%)	p = 0.004 X^2 = 11.2
G	9 (15%)	2 (3.5%)	16 (25%)	
A/A	21 (23.1%)	27 (29.7%)	17 (18.7%)	p = 0.012 X^2 = 12.9
A/G	9 (9.9%)	2 (2.2%)	14 (15.4%)	
G/G	0 (0%)	0 (0%)	1 (1.1%)	

Note: AIP - antipsychotic-induced parkinsonism; SSDs – schizophrenia spectrum disorders.

An assessment of ORs depending on the studied alleles and genotypes of the SNV rs167771 of the *DRD3* gene demonstrated that the major allele A is protective against the risk of developing schizophrenia spectrum disorders, but not AIP (OR < 0.001) (**Table 6**).

Table 6. Comparison of alleles and genotypes of rs167771 of the DRD3 gene in the study groups

Allele/genotype	χ2	p-value	OR	95% CI
Group 1 (SSDs with AIP) vs. Group 2 (SSDs without AIP)				
A	4.656	0.031	0.805	0.042 – 0.981
G	5.656	0.031	0.805	1.019 – 2.,95
A/A	5.189	0.023	0.834	0.034 – 0.886
A/G	5.189	0.023	0.834	1.128 – 29.67
G/G	-	-	-	-
Group 1 (SSDs with AIP) vs. Group 3 (control)				
A	1.924	0.166	0.463	0.763 – 4.678
G	1.924	0.166	0.463	0.214 – 1.311
A/A	1.858	0.173	0.533	0.724 – 5.854
A/G	1.255	0.263	0.535	0.193 – 1.571
G/G	0.953	0.329	Infinity	0
Group 2 (SSDs without AIP) vs. Group 3 (control)				
A	11.236	<0.001	0.775	2.042 – 42.662
G	11.236	<0.001	0.775	0.023 – 0.49
A/A	12.096	<0.001	0.814	2.416 – 58.726
A/G	10.678	0.002	0.815	0.019 – 0.470
G/G	0.921	0.338	Infinity	0

Note: AIP - antipsychotic-induced parkinsonism; SSDs – schizophrenia spectrum disorders; OR – odds ratio; CI - confidence interval.

4. DISCUSSION

As we know, this is the first associative genetic study of the role SNV rs167771 of the *DRD3* gene in development of AIP in Caucasian patients with SSDs in the ethnically heterogeneous population of Russia. We were shown, that the allelic frequency of the SNV rs167771 of the *DRD3* gene in Caucasians of North-West Russia complements the results of previous studies in other regions of the world [**31**].

Our study showed that AIP is characterized by bradykinesia with a decrease in the amplitude of multidirectional movements and hypokinetic gait, but without postural instability and resting tremor.

Mild and moderate asymmetry in the severity of action tremor by hemitype on the left is characteristic of the early stages of AIP development and is missed in more than 80% of cases by the 8th week from the start of AP intake.

The obtained results explain the importance of early diagnosis of AIP at an early stage according to the H&Y scale, in order not to miss the therapeutic possibilities of neuroprotection.

The results we obtained indicate that the allele frequency of the studied SNV in residents of St. Petersburg and Leningrad Region of European descent is comparable to that in the countries of Northern Europe. SNV rs1800497 and polymorphism rs1799732 of the *DRD2* gene, SNV rs6280 of the *DRD3* gene are neutral and do not increase the risk of developing AIP in the study population. However, the major allele A of rs167771 of the *DRD3* gene is protective against the risk of developing SSDs, but not AIP.

In general, studies of this SNV in patients with AIP are still isolated. So, in the study of Gassó et al. [**12**], a significant association was registered between carriage of the minor allele G of the SNV rs167771 of the *DRD3* gene with the risk of developing risperidone-induced AIP among Spaniards with SSDs (p-value = 0.0001). Also, there are conflicting reports about the negative association of rs167771 of the *DRD3* gene with the risk of developing AIP (p-value = 0.474), AP-induced tardive dyskinesia (p-value = 0.56) and AP-induced akathisia (p-value = 0.0512) on long-term therapy with AP in patients with SSDs

from the Netherlands [9]. A negative association of rs167771 of the *DRD3* gene with the risk of developing AP-induced tardive dyskinesia was also found among the Russian population (Eastern Russia) [**10, 32**].

Previously, in Russia (Eastern Russia), a statistically significant association of carriage of the GG genotype SNV rs167771 of the *DRD3* gene was registered in patients with Parkinson's disease (p-value = 0.041) [**8**]. However, the results of our study demonstrated the absence of a significant association of this SNV with the risk of developing AIP in the population of North-West Russia, which may be due to genetic drift [**33, 34**] ethnic and racial heterogeneity of the country's population [**35**].

5. LIMITATIONS

This study had limitations, including: duration of the study (no more than 8 weeks); representatives of other ethnic groups living in North-West Russia were not included; sample size.

6. CONCLUSIONS

Our results indicate that the allelic frequency of the SNV rs167771 of the *DRD3* gene in Caucasians of North-West Russia (Saint Petersburg and the Leningrad region) is comparable to that in the countries of Northern Europe, also in the countries of Southeast Asia and some regions of North and South America. Mild and moderate asymmetry in the severity of action tremor according to the hemitype on the left is characteristic of the early stages of the development of AIP. The major allele A of rs167771 of the *DRD3* gene is protective against the risk of developing SSDs, but not AIP in Caucasians from North-West Russia.

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