Polymorphisms in the *SNCA* Gene and the Risk of Synucleopathy

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Abstract

Introduction. *Synucleinopathies are mostly sporadic and multifactorial neurodegenerative disorders, which determines the involvement of various risk factors in their development. The polymorphic variants of the SNCA gene are considered as one of the predisposing genetic factors.*

Study aim*: to evaluate the effect of the 16 single nucleotide polymorphisms (SNP) located in various regulatory regions of the SNCA gene on the risk of developing three main forms of synucleinopathy – PD, DBL, and MSA – in Russian cohort of patients.*

Materials and methods. *The study included 73 PD patients, 46 MSA patients, 10 DLB patients, and 62 healthy volunteers. Genotyping of 16 SNPs of the SNCA gene was performed by direct Sanger sequencing on a capillary genetic analyzer. The Benjamini–Hochberg procedure was applied for multiple pairwise comparisons.*

Results. *A comparative case-control study showed that only one (rs11931074) of the 16 SNP analyzed was associated with PD: the minor T allele, located in the 3'-UTR region of the SNCA gene, increased the risk of PD (OR = 5.19; $p < 0.05$ (Benjamini–Hochberg adjusted $p = 0.6$)). An association with MSA was found for 11 of 16 SNP. The minor allele of 5 SNP (rs2619364, rs2619363, rs2619362, rs2619361, rs181489) reduced the risk of the disease, while for 6 SNP (rs7687945, rs2301134, rs2301135, rs3756063, rs2736990, rs11931074) increased the risk. The Benjamini–Hochberg procedure neutralized the significance of only one of these associations (rs181489).*

Conclusion. *This study is the first to genotype a large group of polymorphisms located in various regulatory regions of the SNCA gene and to establish significant associations with the risk of developing one of the forms of synucleinopathies, MSA, in the Russian population.*

Keywords: *synucleinopathies; SNCA gene single nucleotide polymorphisms; SNP*

Ethics approval. The study was conducted with the voluntary informed consent of the patients. The study protocol was approved by the Ethics Committee of the Research Center of Neurology (Protocol No. 2-8/24, 18 March, 2024).

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Полиморфные варианты гена *SNCA* и риск развития синуклеинопатий

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Аннотация

Введение. *Большинство форм синуклеинопатий являются спорадическими и имеют многофакторную природу, что определяет участие различных факторов риска в их развитии. Как один из таких предрасполагающих генетических факторов рассматривается участие различных полиморфных вариантов гена SNCA.*

Цель *исследования: изучение влияния 16 однонуклеотидных полиморфных вариантов, локализованных в различных регуляторных областях гена SNCA, на риск развития в когорте пациентов российской популяции трёх основных форм синуклеинопатий: болезни Паркинсона (БП), деменции с тельцами Леви (ДТЛ) и мультисистемной атрофии (МСА).*

Материалы и методы. *В исследование были включены 73 пациента с БП, 46 с МСА, 10 с ДТЛ и 62 неврологически здоровых добровольца. Генотипирование 16 однонуклеотидных полиморфных вариантов (SNP) гена SNCA проводили методом прямого секвенирования по Сэнгеру на капиллярном генетическом анализаторе. Для коррекции ошибки при множественном попарном сравнении использовали поправку Беньямини–Хохберга.*

Результаты. *По результатам сравнительного анализа «диагноз–контроль» только 1 из 16 протестированных SNP (rs11931074), локализованный в области 3'-UTR гена SNCA, продемонстрировал связь с БП: минорный аллель T проявил тенденцию к увеличению риска развития БП (ОШ = 5,19; p < 0,05 (с поправкой Беньямини–Хохберга p = 0,6)). Для 11 из 16 SNP выявлена ассоциация с МСА. Минорный аллель 5 SNP из них (rs2619364, rs2619363, rs2619362, rs2619361, rs181489) снижал риск заболевания, а для 6 SNP (rs7687945, rs2301134, rs2301135, rs3756063, rs2736990, rs11931074) – повышал. Применение поправки Беньямини–Хохберга нивелировало значимость только одной из этих ассоциаций (rs181489).*

Заключение. *В результате проведённого исследования впервые генотипирована большая группа полиморфных вариантов, расположенных в различных регуляторных областях гена SNCA, и установлены значимые ассоциации с риском развития одной из форм синуклеинопатий – МСА – в российской популяции.*

Ключевые слова: *синуклеинопатии; однонуклеотидные полиморфные варианты; ген SNCA*

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Introduction

Synucleinopathies are a group of neurodegenerative disorders characterized by the aberrant accumulation of α-synuclein aggregates in neurons, nerve fibers, or glial cells. It is estimated that α-synucleinopathies affect over 10 million people worldwide [1].

Alpha-synuclein is a small, 140 amino acid protein [2, 3], widely represented in the human brain, primarily in presynaptic terminals. Normally, α-synuclein, found in the cell as a tetramer, presumably regulates vesicular transport processes and dopamine neurotransmission [4], and is crucial for normal brain functioning [5]. α-Synuclein is a type of protein that lacks a stable secondary structure in solution and tends to aggregate. Increased accumulation of α-synuclein in solution leads to the formation of insoluble fibrils and discrete spherical structures causing cell death [6].

Parkinson's disease (PD) is the most common phenotype form of synucleinopathies, with a prevalence of 100–200 cases per 100,000 people [7]. Less frequent is multiple system atrophy (MSA), with 2–5 cases per 100,000 people [8], and dementia with Lewy bodies (DLB), accounting for 4.2–5.0% of

all dementias [9]. Historically, the distinction of PD, MSA, and DLB was based on clinical manifestations and neuropathological signs. Subsequently, an active study of molecular-genetic mechanisms underlying neurodegenerative processes in this group revealed structural features of protein aggregates for different forms of synucleinopathy. Such filaments from patients with MSA are straight or twisted compared with the mostly straight filaments from PD patients [10]. MSA is associated with predominantly oligodendroglial α-synuclein insertions, whereas α-synuclein aggregates predominantly accumulate in neurons of PD patients [11].

Many questions regarding the pathogenesis of this disease remain unanswered. The mechanisms that trigger α-synuclein aggregation and subsequent neurodegeneration remain to be elucidated. These include genetic variants, epigenetic, and transcriptional processes. Most forms of synucleinopathy are sporadic and multifactorial in origin, and only 10% of cases have an aggravated family history. Several recent genome-wide association studies (GWAS) in PD have identified an association of the disease with single nucleotide polymorphisms (SNP) located in different regulatory regions of the *SNCA* gene encoding α-synuclein [12–14]. However, the contribution of most of these SNPs in the regulation of *SNCA* gene expression has not been studied. Two PD associated significant linkage disequilibrium blocks were identified: one covers the promoter region, while the other affects the 4th intron and the 3'-UTR regulatory region of the *SNCA* gene [15, 16]. Polymorphisms located in the 5'-region of the *SNCA* gene may affect the gene's transcriptional activity. For example, specific SNP (rs3756063) has been shown to be associated with hypomethylation in PD patients [17]. Polymorphisms located in the regulatory 3'-region may, in turn, play a role in the stability of mRNA translation by affecting its binding to the corresponding microRNA, as well as in alternative splicing [12, 13, 18].

Individual SNPs may have varying effects on the regulation of *SNCA* gene expression, leading to both down-regulation and up-regulation. In particular, a "protective" function of 2 SNPs genotypic combination was shown to be strongly correlated with low levels of mRNA [19]. In contrast, another study demonstrated a significant association of the SNP rs356168 minor allele with an increased *SNCA* gene expression due to enhancer activation and subsequently increased gene transcription [20, 21].

The impact of the *SNCA* gene polymorphisms on the synucleinopathy pathogenesis has not yet been sufficiently studied. A number of SNP for some forms of synucleinopathy has not been studied in the Russian population. Other populations have been studied to a limited extent. Hence, **the aim** of the study was to assess the effect of 16 SNP in the *SNCA* gene on the risk of synucleinopathy (PD, DLB, and MSA) developing in a cohort of Russian patients.

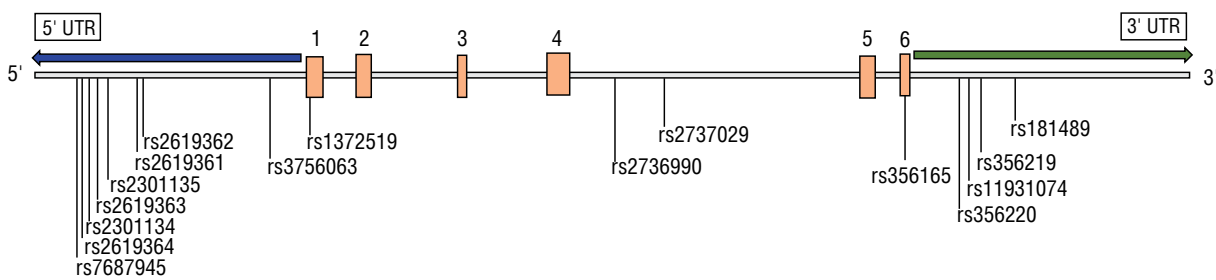
Materials and methods

The study was conducted at the Research Center of Neurology and included 73 PD patients diagnosed according to the MDS UPDRS criteria [22]; 46 patients with MSA: 17 patients with cerebellar type (MSA-C) and 29 patients with Parkinsonian type (MSA-P) [23]; and 10 patients with DLB diagnosed according to the relevant diagnostic criteria [9]. The Montreal Cognitive Assessment Scale (MoCA) was used to assess the cognitive status. The control group included 62 volunteers with no neurological disorders. The groups were mainly represented by people of Slavic ethnicity living in the European part of the Russian Federation. All participants were familiarized with the upcoming procedures and signed an informed consent before the study. The study protocol was approved by the Ethics Committee of the Research Center of Neurology (Protocol No. 2-8/24 dated 18 March, 2024).

Based on a meta-analysis of several available PD GWAS datasets for different populations [24], we selected 16 SNP identified as significantly associated with PD progression and localized in different regions of the *SNCA* gene: 9 in the 5'-UTR and promoter region; 2 in the 4th intron region; and 5 in the 3'-UTR region (Figure).

Genomic DNA samples were extracted from whole blood using the DNA-extran-1 reagent kit (Syntol, Moscow, Russia). 16 SNP of the *SNCA* gene were genotyped by direct Sanger sequencing on the Nanofor 05 capillary genetic analyzer (Institute for Analytical Instrumentation, Russian Academy of Sciences, Moscow, Russia).

The statistical analysis was carried out using the SPSS Statistics, version 26.0. (IBM). We used the Benjamini–Hochberg (BH) procedure for multiple pairwise comparisons. The null hypothesis was rejected at an adjusted significance level of $p_{adj} < 0.05$ based on FDR scores. Mean and standard deviation were used to describe quantitative variables, while absolute and relative frequencies were used to describe categorical variables. Categorical variables in the groups were compared using Pearson's χ^2 test; if there were limitations to its applica-



Structure of the SNCA gene and location of the 16 SNPs analyzed.

tion, Fisher's exact test was used. The odds ratio (OR) and the 95% confidence interval (CI) were calculated to quantify the relationship between the disease development and specific genotypes or alleles.

Results

The study groups were characterized according to clinical and demographic parameters (Table 1). The mixed form of PD was observed in 60 (82.2%) patients, while the akinetic-rigid form was observed in 13 (17.8%) patients. Patients were divided into groups according to the disease stage, as determined by the Hoehn–Yahr scale. Thus, 41 (56.2%) patients were diagnosed with stage 3, 23 (31.4%) with stage 2, 8 (11.0%) with stage 1, and 1 (1.4%) with stage 4. Late onset was found in 57 (78.1%) patients (⩾ 45 years), and 16 (21.9%) patients had early onset (21–44 years) of disease.

Table 2 summarizes the results of minor allele frequencies for the 3 phenotype groups of the synucleinopathy. Genetic screening showed variations in individual SNP minor allele frequencies in our sample compared to the European population in the international Genome Aggregation Database (GnomAD). According to the population databases, the prevalence of minor alleles for rs7687945, rs2301134, rs2301135 and rs2736990 was higher in our control group than in the European population. Accordingly, a comparative analysis of the incidence was conducted for the risk allele identified in our sample.

A comparative case-control study showed that only one (rs11931074) of 16 SNPs analyzed was associated with PD: the minor allele increased the risk of the disease. However, the BH correction leveled the significance of this correlation.

Eleven out of 16 SNPs showed correlation with MSA. For 5 of them (rs2619364, rs2619363, rs2619363, rs2619362, rs2619361, and rs181489), the minor allele reduced the risk of disease, while for 6 others (rs7687945, rs2301134, rs2301135, rs3756063, rs2736990, and rs11931074) it increased the risk. The BH correction leveled the significance of only one of these associations (rs181489).

Five out of 16 SNPs showed correlation with DLB. For 4 of them (rs2619364, rs2619363, rs2619362, rs2619361) the minor allele reduced the risk of disease, while for rs1372519 the risk was increased. However, the BH correction leveled the significance of all of these associations.

Quantification of the association between disease presence and genotype status was performed for the 11 SNPs that showed a significant association with MSA. For this purpose, we calculated the ORs for 2 genetic models: dominant and recessive (Table 3). Analyses were performed for both the total MSA group and for the 2 major subtypes: MSA-C and MSA-P.

Five SNPs (rs7687945, rs2301134, rs2301135, rs3756063, rs11931074) significantly increased disease risk for MSA patients for the minor allele in homozygous and heterozygous genotypes in the dominant model. Five other SNPs (rs2619364, rs2619363, rs2619363, rs2619362, rs2619361, rs181489) reduced disease risk for the minor allele in homozygous and heterozygous genotypes in the dominant model. For 4 of these SNPs (rs2619364, rs2619363, rs2619362, rs2619361), the recessive model was significantly less represented of homozygotes for the minor allele among patients with MSA (namely the absence of such).

During the MSA-P analysis, the risk of disease was significantly higher for minor allele of 5 SNPs (rs7687945, rs2301134, rs2301135, rs3756063, rs11931074) for homozygotes and heterozygotes compared to homozygotes for the more common allele in the dominant model. Moreover, the risk was significantly reduced only for minor allele of 2 SNPs (rs2619362, rs2619361) in homozygotes and heterozygotes compared to homozygotes for the more common allele in the dominant model. The recessive model did not show significant differences in the representation of homozygotes for the minor allele between the groups for any of the SNPs.

The MSA-C analysis did not show significant associations between genotypes and the disease in any of the models. This may be attributed to the low power of analysis, as the volume of the study group is small (n = 17).

Discussion

Disease-associated polymorphic genes are considered risk factors for multifactorial diseases. We performed genetic screening of 16 polymorphisms of the *SNCA* gene across three groups with different forms of synucleinopathy, where we relied on a large meta-analysis of the association between *SNCA* polymorphisms and the risk of PD, focusing on the most significant SNPs [24].

A number of studies have shown the greatest association with the risk of idiopathic PD for rs11931074 located in the

Table 1. Clinical and demographic characteristics of patients and control subjects, *M* ± *SD*

Parameter	PD (n = 73)	MSA (n = 46)		DLB (n = 10)	Control (n = 62)
		MSA-P (n = 29)	MSA-C (n = 17)		
Sex (M/F)	38/35	11/18	8/9	9/1	44/18
Age, years	59.0 ± 11.6	64.1 ± 8.4	56.1 ± 6.6	70.2 ± 4.1	53.4 ± 9.8
Onset age, years	54.0 ± 11.4	59.7 ± 8.4	53.2 ± 7.2	66.0 ± 5.0	–
MoCA score	23.9 ± 3.7	24.4 ± 3.6	24.3 ± 1.8	15.4 ± 3.8	–

Table 2. Association analysis of minor SNP alleles of the *SNCA* gene with the presence of SP

SNP	Allele	Group	Allele frequency	OR (95% CI)	*p*	p_{adj}
		GnomAD	0.52			
		Control	0.41			
rs7687945	*T*	PD	0.47	1.296 (0.795–2.115)	0.321	1.000
		MSA	0.60*	2.194 (1.252–3.845)	0.008	0.020
		DLB	0.31	0.659 (0.215–2.015)	0.590	1.000
		GnomAD	0.24			
		Control	0.41			
rs2619364	*G*	PD	0.38	0.891 (0.546–1.452)	0.708	1.000
		MSA	0.18*	0.311 (0.160–0.604)	< 0.001	0.005
		DLB	0.10*	0.159 (0.035–0.716)	0.011	0.258
		GnomAD	0.24			
		Control	0.40			
rs2619363	*T*	PD	0.36	0.872 (0.533–1.429)	0.616	1.000
		MSA	0.18*	0.331 (0.173–0.634)	0.001	0.006
		DLB	0.15*	0.270 (0.075–0.971)	0.044	0.301
		GnomAD	0.52			
		Control	0.39			
rs2301134	*G*	PD	0.48	1.458 (0.897–2.370)	0.141	1.000
		MSA	0.58*	2.167 (1.247–3.766)	0.008	0.021
		DLB	0.40	1.056 (0.402–2.770)	1.000	1.000
		GnomAD	0.52			
		Control	0.40			
rs2301135	*C*	PD	0.48	1.360 (0.836–2.213)	0.219	1.000
		MSA	0.60*	2.241 (1.283–3.914)	0.005	0.016
		DLB	0.45	1.211 (0.468–3.135)	0.807	1.000
		GnomAD	0.23			
		Control	0.40			
rs2619362	*T*	PD	0.40	1.026 (0.627–1.679)	1.000	1.000
		MSA	0.17*	0.322 (0.169–0.616)	0.001	0.005
		DLB	0.15*	0.270 (0.075–0.971)	0.044	0.263
		GnomAD	0.27			
		Control	0.40			
rs2619361	*A*	PD	0.40	1.026 (0.627–1.679)	1.000	1.000
		MSA	0.17*	0.322 (0.169–0.616)	0.001	0.004
		DLB	0.15*	0.270 (0.075–0.971)	0.044	0.234
		GnomAD	0.40			
		Control	0.40			
rs3756063	*C*	PD	0.44	1.190 (0.731–1.939)	0.535	1.000
		MSA	0.62*	2.493 (1.433–4.337)	0.002	0.007
		DLB	0.40	1.020 (0.389–2.677)	1.000	1.000

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SNP	Allele	Group	Allele frequency	OR (95% CI)	*p*	p_{adj}
		GnomAD	0.21			
		Control	0.21			
rs1372519	*A*	PD	0.17	0.738 (0.399–1.368)	0.349	1.000
		MSA	0.21	0.961 (0.494–1.869)	1.000	1.000
		DLB	0.45*	3.021 (1.132–8.063)	0.046	0.221
		GnomAD	0.40			
		Control	0.47			
rs2737029	*C*	PD	0.48	1.051 (0.647–1.708)	0.902	1.000
		MSA	0.37	0.670 (0.385–1.167)	0.164	0.225
		DLB	0.28	0.440 (0.147–1.310)	0.203	0.648
		GnomAD	0.54			
		Control	0.42			
rs2736990	*A*	PD	0.44	1.064 (0.640–1.769)	0.897	1.000
		MSA	0.60*	2.045 (1.152–3.630)	0.015	0.034
		DLB	0.61	2.143 (0.769–5.969)	0.199	0.683
		GnomAD	0.36			
		Control	0.46			
rs356165	*G*	PD	0.54	1.393 (0.858–2.263)	0.218	1.000
		MSA	0.39	0.765 (0.434–1.347)	0.390	0.468
		DLB	0.40	0.788 (0.300–2.066)	0.809	1.000
		GnomAD	0.36			
		Control	0.45			
rs356220	*T*	PD	0.52	1.327 (0.817–2.154)	0.269	1.000
		MSA	0.38	0.743 (0.419–1.318)	0.315	0.388
		DLB	0.40	0.815 (0.311–2.137)	0.809	1.000
		GnomAD	0.07			
		Control	0.02			
rs11931074	*T*	PD	0.08*	5.194 (1.139–23.688)	0.025	0.595
		MSA	0.16*	10.973 (2.424–49.672)	< 0.001	0.008
		DLB	0.05	3.053 (0.264–35.339)	0.377	0.953
		GnomAD	0.36			
		Control	0.47			
rs356219	*G*	PD	0.53	1.285 (0.786–2.100)	0.381	
		MSA	0.37	0.672 (0.369–1.225)	0.228	1.000
		DLB	0.40	0.759 (0.290–1.985)	0.635	0.296
		GnomAD	0.29			
		Control	0.37			
rs181489	*T*	PD	0.40	1.135 (0.681–1.890)	0.697	1.000
		MSA	0.23*	0.495 (0.263–0.930)	0.031	0.059
		DLB	0.39	1.071 (0.385–2.980)	1.000	1.000

Note. *Significant differences from the control.

Table 3. SNP genotype association analysis for SNCA gene with the presence of MSA (n = 46), MSA-P (n = 29), and MSA-C (n = 17) compared with healthy volunteers (n = 62)

SNP	MSA type	The dominant model		The recessive model	
		OR (95% CI)	p_{adj}	OR (95% CI)	p_{adj}
rs7687945	MSA	6.833* (1.882–24.807)	0.007	2.125 (0.805–5.610)	0.215
	MSA-P	13.500* (1.709–106.648)	0.029	1.545 (0.491–4.869)	0.727
	MSA-C	3.500 (0.724–16.922)	0.207	3.400 (0.988–11.697)	0.166
rs2619364	MSA	0.265* (0.116–0.604)	0.008	NA	0.025
	MSA-P	0.298 (0.115–0.772)	0.054	NA	0.111
	MSA-C	0.216 (0.066–0.707)	0.128	NA	0.235
rs2619363	MSA	0.283* (0.126–0.633)	0.010	NA	0.043
	MSA-P	0.313 (0.125–0.782)	0.054	NA	0.124
	MSA-C	0.233 (0.071–0.758)	0.083	NA	0.234
rs2301134	MSA	6.045* (1.916–19.067)	0.008	1.905 (0.715–5.079)	0.289
	MSA-P	7.962* (1.731–36.619)	0.038	1.536 (0.490–4.818)	0.710
	MSA-C	4.128 (0.860–19.816)	0.164	2.677 (0.751–9.546)	0.209
rs2301135	MSA	7.000* (1.937–25.299)	0.006	2.208 (0.838–5.821)	0.215
	MSA-P	13.317* (1.688–105.050)	0.024	1.683 (0.533–5.314)	0.618
	MSA-C	3.841 (0.802–18.397)	0.201	3.212 (0.948–10.882)	0.157
rs2619362	MSA	0.273* (0.122–0.610)	0.007	NA	0.041
	MSA-P	0.313* (0.125–0.782)	0.050	NA	0.118
	MSA-C	0.213 (0.066–0.686)	0.108	NA	0.247
rs2619361	MSA	0.273* (0.122–0.610)	0.006	NA	0.040
	MSA-P	0.313* (0.125–0.782)	0.047	NA	0.112
	MSA-C	0.213 (0.066–0.686)	0.090	NA	0.241
rs3756063	MSA	7.883* (2.190–28.376)	0.007	2.576 (1.001–6.631)	0.104
	MSA-P	15.400* (1.960–120.995)	0.022	1.874 (0.620–5.662)	0.600
	MSA-C	4.125 (0.863–19.718)	0.160	4.122 (1.246–13.642)	0.100
rs2736990	MSA	2.449 (0.943–6.358)	0.116	2.550 (1.020–6.372)	0.117
	MSA-P	1.664 (0.597–4.635)	0.658	2.567 (0.927–7.110)	0.213
	MSA-C	7.941 (0.969–65.065)	0.093	2.520 (0.740–8.576)	0.238
rs11931074	MSA	11.952* (2.533–56.401)	0.006	NA	0.500
	MSA-P	13.500* (2.678–68.064)	0.022	NA	NA
	MSA-C	9.500 (1.558–57.929)	0.081	NA	0.250
rs181489	MSA	0.313* (0.135–0.723)	0.021	NA	1.000
	MSA-P	0.348 (0.133–0.910)	0.121	NA	1.000
	MSA-C	0.263 (0.084–0.816)	0.082	NA	1.000

Note. NA: OR estimate is impossible (one variant of compared genotypes / their combinations is missing in at least one of the groups) or significance level estimate is impossible (one variant of compared genotypes / their combinations is missing in both groups).

* Significant differences compared to the control.

3'-UTR region of the *SNCA* gene [12–14, 25]. It was predicted that rs11931074 would affect mRNA stability and translation efficiency [12, 13, 18, 25, 26]. The results of our study also showed that the rs11931074 minor allele (*T*) tended to increase the risk of PD (OR = 5.19; $p < 0.05$ ($p_{adj} = 0.6$).

Our sample demonstrated no associations with PD risk for the other 15 SNPs. It is likely explained by the heterogeneity of the PD group (both the clinical picture and the rate of disease progression), which precluded observing significant associations with specific disease forms. To assess the association of *SNCA* polymorphisms with PD, the PD groups should be specified by clinical, temporal, and demographic characteristics, as well as by the age at disease onset. Furthermore, the role of individual SNPs in the regulation of *SNCA* gene expression is population-dependent. For example, in the East Asian group, rs11931074, rs2736990, and rs356219 are associated with an increased risk of PD, while in the European group, rs11931074, rs356219, rs181489, rs2737029, and rs356165 are associated with an increased risk of PD [24, 27–30]. There are only rarely studies about the role of individual polymorphisms in *SNCA* contributing to the risk of PD in the Russian population. Thus, one study demonstrated an increase in α-synuclein levels in $CD45^+$ blood cells in the Russian PD group, which was significantly associated with rs356168 and rs356219 [31].

In the MSA group, 11 out of 16 analyzed *SNCA* polymorphisms were statistically significant ($p < 0.05$) for the risk. Our study focused on polymorphisms located in the promoter and 5'-UTR regions of the *SNCA* gene that affect the gene's transcriptional activity. Eight out of 9 SNPs in this region were associated with the risk of MSA in our patient cohort. Of these, an increased risk of MSA was observed for 4 SNPs (rs7687945, rs2301134, rs2301135, and rs3756063), which was confirmed only for patients with P-MSA in a dominant inheritance model, where a minor allele in both homozygous and heterozygous states influences the development of the disease. According to Y. Wei et al., a *G>C* nucleotide substitution in the rs3756063 polymorphism results in a CpG site in the promoter region, and affecting the DNA methylation status of *SNCA* may increase the risk of PD [32]. Another multi-center study found an association between rs7687945 and the age of PD onset [33]. In our study, another 4 SNPs (rs2619361, rs2619362, rs2619363, rs2619364), for which the significance of association with an increased PD risk has been confirmed in several studies [24, 34], showed a protective role of the minor allele of these SNPs against MSA ($p < 0.05$).

Of the two analyzed SNPs located in intron 4 (rs2737029, rs2736990), only the rs2736990 minor *A* allele showed a significant association ($p = 0.034$) with an increased risk of MSA. In the Asian population, rs2736990 is associated with PD risk but not with MSA risk [35]. In the literature, this SNP is linked with the enrichment of one of the *SNCA* splicing variants, called *SNCA-112*, which lacks exon 5 [36–39].

In our study, 5 SNPs (rs356165, rs356220, rs11931074, rs356219, rs181489) are located in the 3'-UTR region of the *SNCA* gene, of which only rs11931074 was statistically significant for MSA: the minor *T* allele was a risk factor for the disease progression (OR = 10.973; 95% CI 2.424–49.672; $p < 0.001$). Genotype analysis for this SNP showed an increased risk only for the P-MSA in the dominant inheritance model (OR = 13.5; 95% CI 2.678–68.064; $p = 0.022$). In multi-center studies in a European population, this SNP also showed a high risk of MSA: OR (recessive model) = 6.2 (95% CI 3.4–11.2; $p = 5.5 \times 10^{-12}$) [40] and OR (recessive model) = 9.32 (95% CI 4.03–21.55; $p < 0.00001$) [41]. However, it should be noted that in one GWAS study including 1,030 European patients with MSA, the risk of rs11931074 was not confirmed [42]. The authors attribute it to potential intrapopulation differences in the European group. No association between MSA and rs11931074 was found in the Asian population [27]. In addition, we found a trend toward a decreased risk of MSA with rs181489 (OR = 0.495; 95% CI 0.263–0.930; $p = 0.031$).

Despite the limited DLB sample in our study, we found a trend towards a decreased risk for 4 SNPs (rs2619364, rs2619363, rs2619362, rs2619361) and an association of rs1372519 with an increased risk of the disease.

Thus, we were the first to analyze a large group of polymorphisms in various regulatory regions of the *SNCA* gene for their association with the risk of developing three forms (PD, MSA, and DLB) in the Russian population. Our study had several limitations. First, the small sample size and individual groups may have reduced the power of the analysis, increasing the likelihood of missing significant associations. Second, some significant associations may have been diminished by strict adjustment for multiple comparisons. The results of risk assessment and its significance also depended on the population characteristics of the control group [40–42].

Considering the above-mentioned limitations, we established significant associations between *SNCA* polymorphisms and different forms of synucleinopathy based on the study findings. This study should be continued in larger, carefully defined cohorts in comprehensive research examining the role of genetic and epigenetic factors in the regulation of *SNCA* gene expression, taking into account population-specific features.

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