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Original Article

SNCA Variants and Expression Levels of α-synuclein Transcripts in Multiple System Atrophy: A Retrospective Case–control Study

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Abstract

Background and objectives: Synucleinopathies, including Parkinson's disease (PD), dementia with Lewy bodies, and multiple system atrophy (MSA), are a group of neurodegenerative diseases characterized by the oligomerization of α-synuclein protein in neurons or glial cells. Various splicing isoforms of α-synuclein have been described, each with different aggregation properties. The α-synuclein gene (*SNCA*) has been identified as a highly significant genetic risk locus associated with various synucleinopathies across populations. This study aimed to assess the association of *SNCA* genetic variants with MSA and the levels of *SNCA* transcripts in peripheral blood mononuclear cells (PBMCs) from MSA and PD patients.

Methods: In this retrospective case–control study, 96 MSA patients, 1086 PD patients, and 485 healthy volunteers were included. PCR followed by restriction endonuclease analysis was used to detect four *SNCA* single-nucleotide polymorphisms (rs356219, rs3756063, rs11931074, and rs356168) in these individuals. In addition, RT-qPCR was performed to detect the levels of α-synuclein transcripts (*SNCA* mRNA isoforms -140, -126, and -112) in PBMCs of 24 MSA patients (including parkinsonian (MSA-P) and cerebellar (MSA-C) variants), 31 PD patients, and 32 healthy volunteers.

Results: The frequency of the 'T' allele (of rs11931074) was significantly higher in MSA patients than in the healthy controls. The level of *SNCA*-140 mRNA was significantly decreased in MSA and PD patients compared with the controls, while the level of *SNCA*-112 mRNA was significantly increased in MSA-P patients than in PD patients and the controls. *SNCA*-112 mRNA/*SNCA*-140 mRNA and *SNCA*-112 mRNA/*SNCA*-126 mRNA ratios were significantly increased in MSA patients than in the controls.

Conclusions: The *SNCA* rs11931074 polymorphism is associated with MSA. There is a pronounced alteration in the expression of *SNCA* transcripts in PBMCs of MSA and PD patients.

Keywords: Parkinson's disease; Multiple system atrophy; α-synuclein; *SNCA* single-nucleotide polymorphisms; *SNCA* expression; *SNCA* transcripts.

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Introduction

Synucleinopathies represent a heterogeneous class of age-related neurodegenerative disorders unified by the abnormal misfolding and aggregation of the α-synuclein protein encoded by the *SNCA* gene. α-synuclein aggregates take the form of intraneuronal inclusions—such as Lewy bodies and Lewy neurites—in disorders like Parkinson's disease (PD) and dementia with Lewy bodies (DLB), or of glial cytoplasmic inclusions in multiple system atrophy (MSA). Prevalence estimates for these disorders vary substantially with age, sex, and geographic factors, with PD affecting approximately 0.3% of the general population, a figure that rises to 1% in

individuals over 60 years old and reaches 3–4% in those over 80.[1] In contrast, DLB tends to affect up to 5% of the general population and up to 30.5% of all dementia cases,[2] while MSA is estimated to affect roughly 0.5–17 per 100,000 individuals in the global population.[3] Despite overlapping motor symptoms with PD, MSA is distinguished by its poor response to levodopa and a much more aggressive disease course with difficult early diagnosis.[4] MSA is characterized by neuronal loss and gliosis in multiple areas of the central nervous system and has a much more aggressive and severe disease course compared to other synucleinopathies.[5] In MSA, α-synuclein aggregates in oligodendrocytes[5]; however, the mechanisms leading to the formation of insoluble α-synuclein aggregates in these cells are not fully understood. Based on the predominant motor phenotype, two main variants of MSA can be identified: the parkinsonian (MSA-P) and the cerebellar (MSA-C).[5] MSA-P is characterized by nigrostriatal and striatonigral degeneration, and MSA-C is characterized by olivopontocerebellar atrophy.[5]

PD is the second most common neurodegenerative disease after Alzheimer's disease and the most common of all synucleinopathies. It is characterized by the progressive loss of dopaminergic neurons in the substantia nigra pars compacta and the formation of Lewy bodies in the affected brain areas.[6]

SNCA mutations are a rare cause of familial PD; meanwhile, the *SNCA* locus has been identified as a highly significant genetic risk factor for the sporadic form of PD and MSA across populations in genome-wide association studies (GWAS).[7,8] Single-nucleotide polymorphisms (SNPs) in both *SNCA* promoter and 3′-untranslated regions (3′-UTR) were associated with a risk of sporadic PD and MSA in various populations in replicative studies.[8–14]

The *SNCA* gene undergoes alternative splicing, including 5′- and 3′-UTR splicing and exon skipping.[15] The skipping of either exon 3 or 5 produces various splice variants (*SNCA*-140, -126, -112, -98), which vary in their coding sequence. The full-length (*SNCA*-140) sequence, comprising 6 exons, encodes a 140 amino acid protein. Exon 3 and 5 skipping variants encode the 126- and 112-amino acid α-synuclein, respectively.[16] *SNCA*-98 is a brain-specific splice variant that lacks both exons 3 and 5. Overexpression of the main α-synuclein isoforms (*SNCA*-112, -126, -98) was observed in the brain in synucleinopathies.[17–20] Specific α-synuclein isoforms have been associated with intracellular aggregation and are differentially expressed in various tissues.[18,21,22] It was shown that splice isoforms of α-synuclein have different membrane-binding properties and may thereafter have different toxicities, forming aggregates of various conformations.[23,24]

The level of expression of α-synuclein isoforms in PD has been studied more thoroughly than in other synucleinopathies. While multiple studies have robustly documented changes in *SNCA* alternative splicing in MSA brain tissue, none have extended these analyses to peripheral blood samples from MSA patients.[15,20,25]

This study aimed to assess the association of *SNCA* genetic variants (rs356219, rs3756063, rs11931074, and rs356168) with MSA and *SNCA*-140, -126, and -112 mRNA levels in PBMCs from MSA and PD patients. Additionally, we assessed the impact of *SNCA* genetic variants on *SNCA* transcript levels in PBMCs from MSA and PD patients.

Materials and methods

Subjects

This research was a retrospective case–control study (Fig. 1) conducted between 2018 and 2023. Inclusion criteria for the study were self-declared Russian descent and residence in the North-Western region of Russia. To assess the expression of *SNCA* transcript variants in PBMCs, the following criteria were applied:

- *Inclusion criteria:* participants aged 50–75 years; L-DOPA-naive PD patients; sporadic PD patients.
- *Exclusion criteria:* individuals with endocrine, autoimmune, or oncological diseases; and carriers of common *GBA1* (N370S, L444P) or *LRRK2* (G2019S) mutations.

Control subjects were excluded if they had any diagnosed neurological disorders.

The study included 96 unrelated MSA patients (age 62.4 ± 6.2 years, age of disease onset 58.4 ± 6.1 years, 39% males) and 1086 PD patients (age 65.0 ± 10.9 years, age of disease onset 58.2 ± 12.7 years, 44% males) with no other neurodegenerative diseases (Table 1). The diagnosis of PD was established according to the MDS criteria.[26] MSA was diagnosed according to the consensus criteria.[27] The patients were examined at the Pavlov First Saint-Petersburg State Medical University and the N.P. Bechtereva Institute of the Human Brain of the Russian Academy of Sciences.

The control group comprised 485 healthy individuals (age 61.4 ± 9.3 years, 37% males) enrolled at the Pavlov First Saint-Petersburg State Medical University (Table 1). The study groups did not differ in age and sex ($P > 0.05$).

The study was conducted according to the guidelines of the Declaration of Helsinki (as revised in 2024) and was approved by the Ethics Committee of Pavlov First Saint-Petersburg State Medical University (Approval Number: 204, Approval Date: 26 February 2018) and the Institute of the Human Brain of the Russian Academy of Sciences (Approval Number: 1, Approval Date: 26 November 2020). Signed informed consent was obtained from all studied individuals. Laboratory technicians performing genotyping and RT-qPCR assays were blinded to the clinical diagnosis (case/control status) of all individuals in the studied groups.

Genotyping

Genomic DNA was extracted from whole blood using the phenol–chloroform method.[28] Screening for rs356219, rs11931074, rs3756063, and rs356168 in the *SNCA* gene was performed using PCR followed by restriction endonuclease analysis. The restriction endonucleases used for screening these SNPs were HpySE526I (E583, SibEnzyme, Russia), Bse1I (E035, SibEnzyme, Russia), MspI (E091T, SibEnzyme, Russia), and FspBI (BfaI) (ER1761, Thermo Fisher Scientific, USA), respectively, as described previously.[29] DNA fragments were separated electrophoretically in 8% PAAG, stained with ethidium bromide, and visualized with UV light.

SNCA transcript variants (SNCA-140, -126, -112) expression in PBMCs

mRNA levels of the *SNCA* gene were assessed in PBMCs obtained by density gradient centrifugation (GE17-1440-03, Ficoll-Paque PLUS, GE Healthcare, USA) from 31 L-DOPA-naive PD patients (age 62.8 ± 9.4 years, 42% males), 24 MSA patients (age 63.6 ± 7.3 years, 42% males), and 32 controls (age 64.9 ± 6.7 years, 50% males) (Table 1). Total RNA was extracted from PBMCs using the RNA Solo kit (BC034S, Evrogen, Russia), and cDNA was synthesized using the RevertAid First cDNA Synthesis kit (K1622, Thermo Fisher Scientific, USA) according to the manufacturer's instructions. For reverse transcription, 1 μg of total RNA was used. RT-qPCR was performed on a CFX96 Touch Real-Time PCR Detection System (Bio-Rad, USA) using SsoAdvanced Universal SYBR Green Supermix (1725271, Bio-Rad, USA) with an initialization step at 95 °C for 30 s, followed by 45 cycles of 95

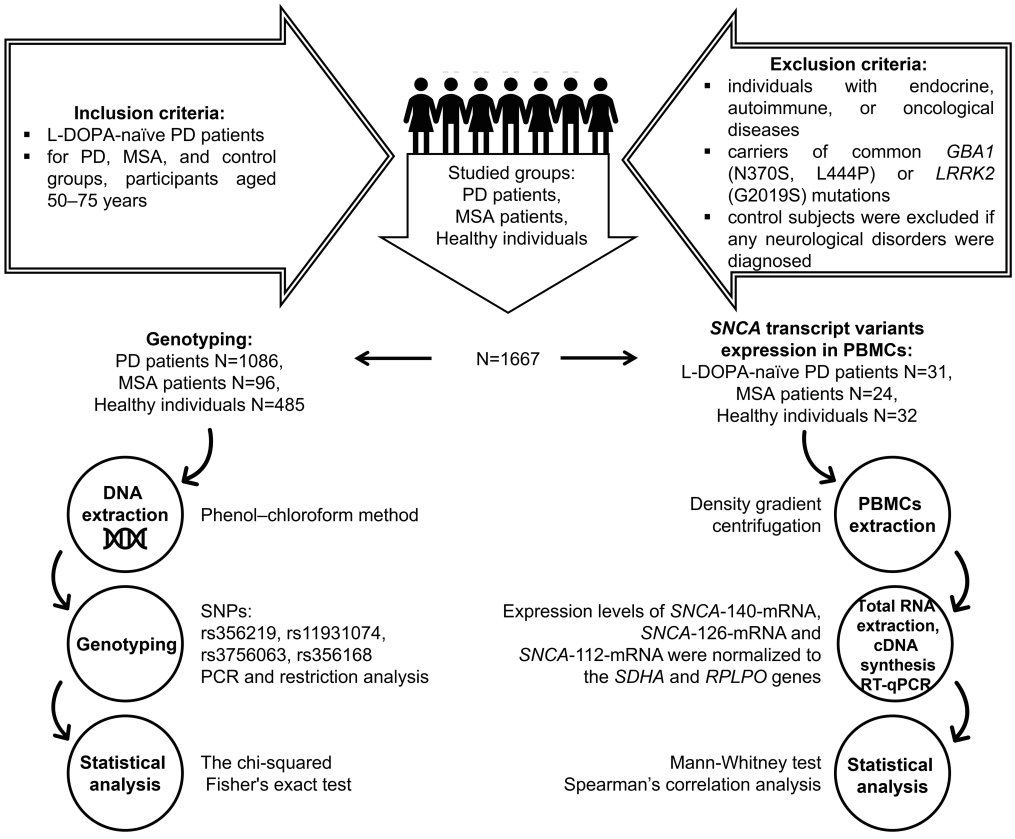

Fig. 1. Study design. STROBE-compliant flow diagram of the participant selection algorithm and methodological workflow, documenting inclusion/exclusion criteria and final analytical sample composition. cDNA, complementary DNA; DNA, deoxyribonucleic acid; MSA, multiple system atrophy; PBMCs, peripheral blood mononuclear cells; PD, Parkinson's disease; RNA, ribonucleic acid; RT-qPCR, quantitative real-time polymerase chain reaction, SNPs, single-nucleotide polymorphisms.

°C for 10 s and 60 °C or 63 °C for 15 s (60 °C for *SNCA*-140 and *SNCA*-126 and 63 °C for *SNCA*-112) using previously published primers.[30] The levels of *SNCA*-140 mRNA, *SNCA*-126 mRNA, and *SNCA*-112 mRNA were normalized to the *SDHA* and *RPLPO* genes. Relative transcript variant expression data were calculated using the $2^{-\Delta\Delta Cq}$ method.[31] All PCR reactions were performed for each sample in triplicate. In all assays, the control and experimental groups did not differ in age or sex ($P > 0.05$).

Table 1. Clinical characteristics of MSA patients, PD patients, and controls

General characteristics	Genotyping assay			mRNA α-synuclein level assay						
	MSA patients N = 96	PD patients N = 1086	Controls N = 485	MSA patients, N = 24	MSA-P patients, N = 15	MSA-C patients, N = 9	MSA duration ≤3 years, N = 13	MSA duration >3 years, N = 11	PD patients, N = 31	Controls, N = 32
Sex, male (%)	37 (39)	477 (44)	179 (37)	10 (42)	6 (40)	4 (44)	5 (38)	5 (45)	13 (42)	16 (50)
Age (years), mean ± SD	62.4 ± 6.2	65.0 ± 10.9	61.4 ± 9.3	63.6 ± 7.3	62.0 ± 6.5	63.0 ± 5.6	61.4 ± 6.4	63.2 ± 5.9	62.8 ± 9.4	64.9 ± 6.7
Age at disease onset (years), mean ± SD	58.4 ± 6.1	58.2 ± 12.7	NA	60.1 ± 7.5	57.8 ± 6.1	59.5 ± 6.0	58.9 ± 6.3	58.0 ± 5.9	60.8 ± 10.3	NA
Disease duration, mean ± SD	3.6 ± 1.9	5.7 ± 5.5	NA	3.6 ± 1.4	4.1 ± 2.0	4.2 ± 2.1	2.5 ± 0.6	5.6 ± 1.7	2.0 ± 2.1	NA
Hoehn-Yahr stage	NA	2.0 ± 0.6	NA	NA	NA	NA	NA	NA	1.9 ± 0.5	NA

MSA, multiple system atrophy; MSA-C, cerebellar variant of MSA; MSA-P, parkinsonian variant of MSA; NA, not applicable; PD, Parkinson's disease; SD, standard deviation.

Statistical analysis

The chi-squared test and Fisher's exact test were used to test for Hardy-Weinberg equilibrium (HWE) and to compare genotype distributions between groups and by sex. To measure the strength of genetic association, odds ratios with 95% confidence intervals were calculated. The Shapiro-Wilk test was used to assess the normality of the data. Comparisons between groups were performed using the Mann–Whitney test. The level of significance was set at $P < 0.05$. Correlations were evaluated using Spearman's correlation coefficient. Statistical analysis was performed using R software (version 4.5.1). Clinical and experimental data are expressed as the mean ± standard deviation or the median (min–max), correspondingly.

Results

Genotyping of SNCA rs356219, rs11931074, rs3756063, and rs356168

In this study, we assessed the frequency of the *SNCA* variants rs356219, rs3756063, rs11931074, and rs356168 in MSA patients and controls from the North-Western region of Russia. We also refined the frequencies of the rs356219, rs11931074, and rs356168 *SNCA* variants in the extended group of PD patients compared to our previously published data.[29] The genotype distribution of the studied SNPs in patients and controls is shown in Table 2. No deviation from HWE was observed for any of the studied SNPs in MSA patients, PD patients, or controls ($P > 0.05$) (Table 2). We showed an association of the GG genotype (rs356219, G allele is minor) and the GG genotype (rs356168, G allele is major) in the *SNCA* gene with PD ($P = 0.011$; $P = 0.0002$, respectively). The 'T' allele of rs11931074 had a significantly higher frequency in MSA and PD patients compared to controls ($P = 0.012$; $P = 0.0001$, respectively). Notably, the 'T' allele of rs11931074 had a significantly higher frequency in MSA-P patients compared to controls ($P = 0.017$).

In this study, we also assessed the influence of the *SNCA* variants rs356219, rs3756063, rs11931074, and rs356168 on *SNCA*-140, -126, and -112 mRNA levels in PBMCs from MSA and PD patients in the studied groups (Supplementary Fig. 1).

Relative expression of SNCA splice variants in PBMCs of MSA and PD patients

In the present study, the expression levels of *SNCA* splicing variants (*SNCA*-140, *SNCA*-126, and *SNCA*-112) in PBMCs from MSA and PD patients, as well as controls, were assessed (Fig. 2).

The *SNCA*-140 mRNA level was significantly decreased in MSA (P = 0.041) and PD ($P = 0.025$) patients compared to controls (Fig. 3a). A decreased level of *SNCA*-140 mRNA was also found in the combined group of MSA and PD patients compared to controls ($P = 0.01$) (Fig. 3e).

We also assessed the *SNCA*-112 mRNA/*SNCA*-140 mRNA, *SNCA*-126 mRNA/*SNCA*-140 mRNA, and *SNCA*-112 mRNA/*SNCA*-126 mRNA ratios in the PBMCs of the investigated groups. The *SNCA*-112 mRNA/*SNCA*-140 mRNA and *SNCA*-112 mRNA/*SNCA*-126 mRNA ratios were increased in MSA patients compared to controls ($P = 0.000311$ and $P = 0.001$, respectively) (Fig. 3c and d).

Relative expression of SNCA splice variants in PBMCs of MSA-P and MSA-C patients

We also assessed the transcript levels and *SNCA* transcript ratios in PBMCs from MSA-P and MSA-C patients. The *SNCA*-112 mRNA level was significantly increased in MSA-P patients compared to PD patients ($P = 0.04$) and controls ($P = 0.02$) (Fig. 3b). The *SNCA*-112 mRNA/*SNCA*-140 mRNA and *SNCA*-112 mRNA/*SNCA*-126 mRNA ratios were increased in MSA-P patients compared to controls ($P = 0.0003$ and $P = 0.0004$, respectively) (Fig. 3c and d). We found no differences in *SNCA*-140, -126, or -112 mRNA expression levels when comparing the two MSA forms with each other or with controls.

Relative expression of SNCA splice variants in PBMCs of MSA patients depending on disease duration

Since this study included a group of MSA patients with a mean disease duration of more than 3 years, we assessed transcript levels and their ratios in the group of MSA patients with a disease duration of up to and including 3 years (≤ 3 years) and greater than 3 years (>3 years). A decrease in the *SNCA*-140 mRNA level was found in MSA patients (≤ 3 years) compared to controls ($P = 0.03$) (Fig. 4a). An increase in the *SNCA*-112 mRNA level was also found in MSA patients (>3 years) compared to controls ($P = 0.02$) (Fig. 4b). The *SNCA*-112 mRNA/*SNCA*-140 mRNA and *SNCA*-112 mRNA/*SNCA*-126 mRNA ratios were elevated in both MSA groups compared to controls ($P = 0.01$ and $P = 0.02$ for MSA (≤ 3 years) and $P = 0.0001$ and $P = 0.001$ for MSA (>3 years), respectively) (Fig. 4c and d).

Correlations between *SNCA*-112, -126, and -140 mRNA levels, as well as their ratios, and clinical parameters (age, age at disease onset, disease duration) in MSA and PD patients were also assessed in this study. These results are presented in the supplementary materials (Supplementary Fig. 2).

Discussion

In this study, we assessed the association of *SNCA* genetic variants (rs356219, rs3756063, rs11931074, rs356168) with MSA and *SNCA* transcript levels in PBMCs from MSA and PD patients and controls. There is growing evidence that specific isoforms of alpha-synuclein encoded by distinct *SNCA* transcripts are associated with intracellular aggregation and are differentially expressed in human synucleinopathies.[17–22] A recent post-mortem brain study revealed substantially greater transcript complexity at the *SNCA* locus than was previously known.[32]

To date, the assessment of *SNCA* isoform expression in synucleinopathies has been mainly carried out in the brain, whereas data on the expression of α-synuclein isoforms in PBMCs are limited.

Only a few publications have addressed the expression of the different *SNCA* transcripts in PBMCs in PD and DLB.[33–35] This is the first study to assess the mRNA levels of splicing isoforms in PBMCs from patients with MSA. The influence of the most common SNPs in the 3′ UTR of the *SNCA* gene on the mRNA levels of splicing isoforms in MSA and PD patients was also estimated.

We found that the *SNCA*-112 mRNA level in PBMCs was significantly increased in MSA-P patients compared to PD patients and controls. Moreover, the *SNCA*-112 mRNA/*SNCA*-140 mRNA and *SNCA*-112 mRNA/*SNCA*-126 mRNA ratios were increased in MSA (MSA-P + MSA-C types) and MSA-P patients compared to controls. These data indicate that evaluating *SNCA* transcript ratios is also important in assessing the contribution of transcript expression to the pathogenesis of synucleinopathies. Previously, *SNCA*-112 has been shown to be overexpressed in the brain in various synucleinopathies, including MSA,[18,20] and several studies have indicated that the *SNCA*-112 protein isoform is susceptible to increased aggregation.[22,36] Notably, the expression of *SNCA*-

Table 2. Association between *SNCA* SNPs and synucleinopathies

SNP	Genotype	MSA, n (%)	MSA-P, n (%)	MSA-C, n (%)	PD, n (%)	Controls, n (%)	HWE (*P*-value)
rs3756063	Total	96	60	36	1086	485	0.218
	GG	25 (26.04)	18 (30.00)	7 (19.44)	308 (28.36)	150 (30.93)	
	GC	46 (47.92)	29 (48.33)	17 (47.22)	545 (50.18)	224 (46.18)	
	CC	25 (26.04)	13 (21.67)	12 (33.34)	233 (21.46)	111 (22.89)	
	G allele	96 (50.00)	65 (54.17)	31 (43.06)	1161 (53.45)	524 (54.02)	
	C allele	96 (50.00)	55 (45.83)	41 (56.94)	1011 (46.55)	446 (45.98)	
OR (95% CI), *P*		(GC+CC vs. GG) = 1.27 [95% CI: 0.78–2.09], *P* = 0.341 (CC vs. GC+GG) = 1.19 [95% CI: 0.72–1.96], *P* = 0.505 (C vs. G) = 1.17 [95% CI: 0.86–1.60], *P* = 0.308	(GC+CC vs. GG) = 1.045 [95% CI: 0.58–1.88], *P* = 0.883 (CC vs. GC+GG) = 0.93 [95% CI: 0.49–1.78], *P* = 0.832 (C vs. G) = 0.99 [95% CI: 0.68–1.45], *P* = 0.976	(GC+CC vs. GG) = 1.86 [95% CI: 0.79–4.33], *P* = 0.153 (CC vs. GC+GG) = 1.68 [95% CI: 0.82–3.48], *P* = 0.158 (C vs. G) = 1.55 [95% CI: 0.96–2.52], *P* = 0.074	(GC+CC vs. GG) = 1.13 [95% CI: 0.90–1.43], *P* = 0.301 (CC vs. GC+GG) = 0.92 [95% CI: 0.71–1.19], *P* = 0.526 (C vs. G) = 1.02 [95% CI: 0.87–1.19], *P* = 0.768	NA	
rs11931074	Total	96	60	36	474	383	0.192
	GG	76 (79.17)	47 (78.33)	29 (80.56)	378 (79.75)	339 (88.51)	
	GT	19 (19.79)	12 (20.00)	7 (19.44)	86 (18.14)	44 (11.49)	
	TT	1 (1.04)	1 (1.67)	0 (0.00)	10 (2.11)	0 (0)	
	G allele	171 (89.06)	106 (88.33)	65 (90.28)	842 (88.82)	722 (94.26)	
	T allele	21 (10.94)	14 (11.67)	7 (9.72)	106 (11.18)	44 (5.74)	
OR (95% CI), *P*		(GT+TT vs. GG) = 2.03 [95% CI: 1.13–3.64], *P* = 0.018 (T vs. G) = 2.02 [95% CI: 1.17–3.48], *P* = 0.012	(GT+TT vs. GG) = 2.13 [95% CI: 1.07–4.25], *P* = 0.032 (T vs. G) = 2.17 [95% CI: 1.15–4.09], *P* = 0.017	(GT+TT vs. GG) = 1.86 [95% CI: 0.77–4.50], *P* = 0.169 (T vs. G) = 1.77 [95% CI: 0.77–4.08], *P* = 0.182	(GT+TT vs. GG) = 1.96 [95% CI: 1.33–2.88], *P* = 0.0006 (T vs. G) = 2.07 [95% CI:1.43–2.98], *P* = 0.0001	NA	
rs356219	Total	96	60	36	489	383	0.731
	AA	37 (38.54)	19 (31.67)	18 (50.00)	184 (37.63)	162 (42.30)	
	AG	50 (52.08)	34 (56.66)	16 (44.44)	223 (45.60)	180 (47.00)	
	GG	9 (9.38)	7 (11.67)	2 (5.56)	82 (16.77)	41 (10.70)	
	A allele	124 (64.58)	72 (60.00)	52 (72.22)	591 (60.43)	504 (65.80)	
	G allele	68 (35.42)	48 (40.00)	20 (27.78)	387 (39.57)	262 (34.20)	
OR (95% CI), *P*		(GG vs. AG+AA) = 0.86 [95% CI: 0.40–1.84], *P* = 0.703 (GG+AG vs. AA) = 1.17 [95% CI:0.74–1.85], *P* = 0.505 (G vs. A) = 1.05 [95% CI: 0.76–1.47], *P* = 0.752	(GG vs. AG+AA) = 1.10 [95% CI: 0.47–2.58], *P* = 0.824 (GG+AG vs. AA) = 1.58 [95% CI: 0.89–2.83], *P* = 0.122 (G vs. A) = 1.28 [95% CI: 0.86–1.90], *P* = 0.217	(GG vs. AG+AA) = 0.49 [95% CI: 0.11–2.12], *P* = 0.340 (GG+AG vs. AA) = 0.73 [95% CI: 0.37–1.45], *P* = 0.374 (G vs. A) = 0.74 [95% CI: 0.43–1.27], *P* = 0.271	(GG vs. AG+AA) = 1.68 [95% CI:1.12–2.51], *P* = 0.011 (GG+AG vs. AA) = 1.22 [95% CI: 0.92–1.60], *P* = 0.162 (G vs. A) = 1.26 [95% CI: 1.03–1.53], *P* = 0.022	NA	

(continued)

Table 2. *(continued)*

SNP	Genotype	MSA, n (%)	MSA-P, n (%)	MSA-C, n (%)	PD, n (%)	Controls, n (%)	HWE (*P*-value)
rs356168	Total	96	60	36	489	383	0.961
	AA	24 (25.00)	10 (16.66)	14 (38.89)	91 (18.61)	89 (23.24)	
	AG	47 (48.96)	31 (51.67)	16 (44.44)	232 (47.44)	209 (54.57)	
	GG	25 (26.04)	19 (31.67)	6 (16.67)	166 (33.95)	85 (22.19)	
	A allele	95 (49.48)	51 (42.50)	44 (61.11)	414 (42.33)	387 (50.52)	
	G allele	97 (50.52)	69 (57.50)	28 (38.89)	564 (57.67)	379 (49.48)	
OR (95% CI), *P*		(GG vs. AG+AA) = 1.23 [95% CI: 0.74–2.07], *P* = 0.423 (GG+AG vs. AA) = 0.91 [95% CI: 0.54–1.53], *P* = 0.716 (G vs. A) = 1.04 [95% CI: 0.76–1.43], *P* = 0.796	(GG vs. AG+AA) = 1.62 [95% CI: 0.90–2.95], *P* = 0.110 (GG+AG vs. AA) = 1.51 [95% CI: 0.74–3.11], *P* = 0.259 (G vs. A) = 1.38 [95% CI: 0.94–2.04], *P* = 0.103	(GG vs. AG+AA) = 0.70 [95% CI: 0.28–1.74], *P* = 0.444 (GG+AG vs. AA) = 0.48 [95% CI: 0.23–0.97], *P* = 0.041 (G vs. A) = 0.65 [95% CI: 0.40–1.07], *P* = 0.088	(GG vs. AG+AA) = 1.80 [95% CI: 1.33–2.44], *P* = 0.0002 (GG+AG vs. AA) = 1.32 [95% CI: 0.95–1.84], *P* = 0.094 (G vs. A) = 1.39 [95% CI: 1.15–1.68], *P* = 0.0007	NA	

*Genotyping call rates differed by SNP; therefore, denominators (sample sizes) vary across variants due to missing data. CI, confidence interval; HWE, Hardy-Weinberg equilibrium; MSA, multiple system atrophy; MSA-C, cerebellar variant of MSA; MSA-P, parkinsonian variant of MSA; NA, not applicable; OR, odds ratio; PD, Parkinson's disease; SNP, single-nucleotide polymorphism.

112 is also upregulated by some parkinsonism mimetics (MPP+, rotenone) and related oxidants.[37] We did not find any changes in the expression of *SNCA* isoforms in PD patients compared to controls. In contrast to our findings, Locasij and colleagues showed a decreased level of *SNCA*-112 expression in the blood in PD.[33] Interestingly, in PBMCs as well as in the brain, the *SNCA*-112 transcript had the lowest expression compared to all the transcripts we evaluated. Thus, it suggests that even small effects on expression caused by disease progression may lead to significant changes in *SNCA*-112 transcript levels and its subsequent aggregation.[34]

Thus, we detected altered expression of α-synuclein transcripts in the PBMCs of MSA and PD patients. It is currently believed that the formation of α-synuclein aggregates with different conformations in the brain may contribute to the development of various synucleinopathies.[38] Therefore, we hypothesize that altered α-synuclein transcript expression may contribute to the formation of α-synuclein aggregates with different conformations.

The present study is the first to reveal a decrease in the mRNA level of the *SNCA*-140 splicing isoform in PBMCs of MSA and PD patients. It is noteworthy that previous studies have detected reduced expression of *SNCA* transcripts, including the most common isoforms, in PBMCs of patients with rapid eye movement sleep behavior disorder and DLB.[34,39] However, Marsal-García and colleagues did not find any differences in the expression levels of various *SNCA* transcripts in the peripheral blood of PD patients compared to controls.[34]

We demonstrated that the expression levels of *SNCA*-112 and *SNCA*-140 in MSA are influenced by disease duration. We showed that in the early stages of MSA (with a disease duration of less than 3 years), a decreased level of *SNCA*-140 mRNA is observed, while in later stages, an increase in the *SNCA*-112 mRNA level occurs. Previously, a relationship between the duration of synucleinopathies (PD and DLB) and the expression of transcripts, including the most common and 126 isoforms, was shown in the blood.[34]

Here, we found no changes in the *SNCA*-126 mRNA level in PBMCs in either PD or MSA. Previously, the same results were obtained for *SNCA* transcripts in the peripheral blood of PD patients.[34] Interestingly, both an increase and a decrease in the level of *SNCA*-126 transcript expression in peripheral blood have been previously shown in DLB.[34,35]

Taken together, each synucleinopathy may be characterized by a distinct pattern of *SNCA* isoform expression.

Notably, our study included PD patients at early stages of the disease who were not taking L-DOPA. Previous studies have shown the influence of L-DOPA on the methylation of the regulatory region of the *SNCA* gene and its expression.[40,41] However, it remains unknown which specific α-synuclein transcript levels are regulated by the methylation of the *SNCA* gene's regulatory region.

It is currently unclear what may influence the expression of *SNCA* transcripts. The interplay between miRNA differential expression and alternative splicing modification in PD has been recently investigated.[42] Furthermore, it has been shown that the expression of the *SNCA* gene and its transcripts can be influenced by miRNAs, which, via neuron-specific extracellular vesicles capable of crossing the blood-brain barrier, can enter the bloodstream.[43,44] For example, the poly-T variant in intron 2 of the *SNCA* gene comprises three alleles (5T, 7T, and 12T), and the length of the poly-T stretch is directly associated with *SNCA*-126 expression levels in the normal brain, influencing the splicing efficiency of *SNCA* exon 3.[45]

Moreover, SNPs in the *SNCA* 3′-UTR show significant effects on the relative levels of *SNCA*-112 mRNA (the exon 5 in-frame skipping isoform) from total *SNCA* transcript levels in human

brain tissues.[46]

In the present study, we have specified the frequencies of the most common *SNCA* SNP variants (rs356219, rs11931074, rs3756063, and rs356168) in MSA and PD and have assessed their influence on *SNCA*-140, -126, and -112 mRNA levels in PBMCs. All variants chosen for the present study had been repeatedly reported to confer an increased risk for developing synucleinopathies.[8,47,48] Notably, rs356219 and rs11931074 are located in the *SNCA* 3′ UTR. It has previously been shown that the use of an alternative 3′-UTR outside the open reading frame affects mRNA stability and localization in neurons,[49] and the extended *SNCA* 3′-UTR may play a key role in regulating α-synuclein expression levels and localization.[50–52] These features may be critical in PD pathogenesis, given that small fluctuations in α-synuclein concentration, or isoform usage, may alter its propensity to aggregate.[22,53] This may be explained by the cis-regulatory effect of genetic variants in the *SNCA* 3′-UTR on the splicing mechanism.[46] The rs3756063 was associated with an increased risk of PD only in the Chinese population,[54] but influenced the degree of *SNCA* gene methylation in different populations.[40,54,55]

In this study, we showed an association between rs11931074 and MSA. When stratifying by MSA subtypes, an association between rs11931074 and the risk of developing MSA-P was identified. The association of this polymorphism with MSA has been previously reported in both GWAS and replication studies.[8,11,56–58] We also confirmed the association of rs11931074, rs356219, and rs356168 with PD reported by us earlier.[29] The 3′-UTR of human *SNCA* as a whole, and rs17016074 in particular, are loci of potential importance for disease development, possibly via post-transcriptional effects on *SNCA* expression levels.[59] We show the influence of the studied SNPs on *SNCA* splicing variant expression (see Supplementary Fig. 1). Notably, the results of our study suggest an association between specific variants in untranslated regions of *SNCA* and the expression of *SNCA* splicing isoforms that warrants further investigation in follow-up functional studies.

Limitations

Our study has some limitations. The main limitation is the relatively small sample size of the studied groups. Therefore, the reported *P*-values should be interpreted with caution. Accordingly, our results need to be verified in additional independent, larger groups, as well as using other expression assessment methods.

Conclusions

This study confirmed the association of the *SNCA* rs11931074 polymorphism with MSA as well as the significance of the *SNCA* locus in MSA development. The pronounced alteration in the expression of *SNCA* transcripts in PBMCs of MSA patients found in this study highlights the importance of analyzing different *SNCA* transcript variants, rather than total *SNCA*, in biomarker research and may contribute to understanding the specific role of α-synuclein transcripts in the pathogenesis of MSA and PD. Our results also provide unique insights into the complexity of *SNCA* transcription and strengthen the relevance of *SNCA* splicing isoforms to MSA pathology.

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Conflict of interest

The authors have no conflicts of interest related to this publication.

Author contributions

Study design (AZ, AL, HF, AE), performance of experiments (AE, AZ, AL, VP, ED, HF, AT, IM), analysis and interpretation of data (AE, AZ, AL, VP), statistical analysis (AZ, AL, VP), manuscript writing (AZ, AL, AE), critical revision (HF, SP, AE), administrative, technical, and material support, and study supervision (SP, AE). All authors have made significant contributions to this study and have approved the final manuscript.

Ethical statement

The study was conducted according to the guidelines of the Declaration of Helsinki (as revised in 2024) and was approved by the Ethics Committee of Pavlov First Saint-Petersburg State Medical University (Approval Number: 204, Approval Date: 26 February 2018) and the Institute of the Human Brain of the Russian Academy of Sciences (Approval Number: 1, Approval Date: 26 November 2020). Signed informed consent was obtained from all studied individuals.

Data sharing statement

The data generated in the present study may be requested from the corresponding author.

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