Association of *COMT* and *MAO-B* Gene Polymorphic Variants with Sensitivity to Dopaminergic Therapy in Patients with Parkinson's Disease

Yulia I. Khabarova[1], Alexey A. Tappakhov[1,2], Tatiana E. Popova[3], Nadezhda E. Maksimova[4], Aleksandra S. Asekritova[2,4], Olga V. Tatarinova[1,4]

[1]Yakut Scientific Center for Complex Medical Problems, Yakutsk, Russia;

[2]M.K. Ammosov North-Eastern Federal University, Yakutsk, Russia;

[3]Lotus Medical Clinic, Yakutsk, Russia;

[4]Republican Clinical Hospital No. 3, Yakutsk, Russia

Abstract

Introduction. *Levodopa and other dopaminergic agents remain the cornerstone of pharmacotherapy for Parkinson's disease (PD). Two enzymes play key roles in dopamine metabolism: catechol-O-methyltransferase and monoamine oxidase type B, encoded by the COMT and MAO-B genes respectively.*

This study aimed at *analyzing potential association between dopaminergic therapy response and carrier status of COMT (rs4680) and MAO-B (rs1799836) polymorphisms in patients with PD.*

Materials and methods. *The study included 96 PD patients at stages 2–3 on the modified Hoehn and Yahr scale. Most patients (n=64; 66.7%) received levodopa/carbidopa, with 40.6% on combined dopaminergic therapy. All patients underwent assessment of dopaminergic therapy effictiveness using the difference in motor deficit (calculated from part III of the Unified Parkinson's Disease Rating Scale) between the worst and best states (%). COMT and MAO-B polymorhisms were detected by real-time polymerase chain reaction.*

Results. *Allelic analysis demonstrated that carriers of the COMT gene rs4680 G allele responded better to dopaminergic therapy than A allele carriers (p = 0.038) (43.78 ± 18.15% vs 38.53 ± 16.58%; p = 0.038). Among men, we found no significant differences in therapy sensitivity related to MAO-B (rs1799836) variants, while female CC genotype carriers demonstrated better treatment response than TC heterozygotes (35.45 ± 17.78% vs 55.16 ± 11.22%; p=0.019).*

Conclusion. *Our data suggest that in patients with PD, not only drug-induced dyskinesias and motor fluctuations, but also overall sensitivity to dopaminergic therapy may be associated with specific COMT and MAO-B polymorphisms.*

Keywords: *Parkinson's disease; polymorphism; levodopa; dopamine; MAO-B; COMT*

Ethical approval. The study was conducted with the voluntary informed written consent of the patients. The study protocol was approved by the Local committee on biomedical ethics of the Yakut Scientific Center for Complex Medical Problems (protocol No. 51, December 17, 2020).

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For correspondence: 6 Kulakovskogo st., Yakutsk, Russia, 677018. Yakut Scientific Center for Complex Medical Problems. E-mail: september062007@mail.ru. Khabarova Yu.I.

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Ассоциация полиморфных вариантов генов *COMT* и *MAO-B* с чувствительностью к дофаминергической терапии у пациентов с болезнью Паркинсона

Ю.И. Хабарова[1], А.А. Таппахов[1,2], Т.Е. Попова[3], Н.Е. Максимова[4], А.С. Асекритова[2,4], О.В. Татаринова[1,4]

[1]Якутский научный центр комплексных медицинских проблем, Якутск, Россия;

[2]Северо-Восточный федеральный университет имени М.К. Аммосова, Якутск, Россия;

[3]Медицинская клиника «Лотос», Якутск, Россия;

[4]Республиканская клиническая больница № 3, Якутск, Россия

Аннотация

Введение. *Препараты леводопы и другие дофаминергические препараты остаются основой фармакотерапии болезни Паркинсона (БП). В метаболизме дофамина ключевую роль играют два фермента: катехол-О-метилтрансфераза и моноаминоксидаза типа Б, которые кодируются генами COMT и MAO-B соответственно.*

Целью *настоящего исследования явилось изучение возможной взаимосвязи между выраженностью ответа на дофаминергическую терапию и носительством полиморфных вариантов генов COMT (rs4680) и MAO-B (rs1799836) у пациентов с БП.*

Материалы и методы. *В исследовании приняли участие 96 пациентов с БП 2–3-й стадии по модифицированной шкале Hoehn–Yahr. Большинство пациентов (n = 64; 66,7%) принимали препараты леводопы/карбидопы, 40,6% пациентов – комбинированную дофаминергическую терапию. Всем включённым в исследование пациентам проводили тест эффективности принимаемой дофаминергической терапии с расчётом разности двигательного дефицита, оценённого по 3-й части Унифицированной рейтинговой шкалы БП, в фазах наихудшего и наилучшего самочувствия (в %). Определение полиморфных вариантов генов COMT и MAO-B проведено методом полимеразной цепной реакции в реальном времени.*

Результаты. *Аллельный анализ показал, что носители аллеля G гена COMT (rs4680) лучше отвечают на дофаминергическую терапию, чем носители аллеля A (43,78 ± 18,15% против 38,53 ± 16,58%; p = 0,038). Среди мужчин мы не обнаружили значимых различий по чувствительности к дофаминергической терапии в зависимости от носительства полиморфных вариантов гена MAO-B (rs1799836), а женщины – носители генотипа CC характеризовались лучшим ответом на дофаминергическую терапию, чем гетерозиготы TC (35,45 ± 17,78% против 55,16 ± 11,22%; p = 0,019).*

Заключение. *Основываясь на полученных данных, можно предположить, что не только развитие лекарственных дискинезий и моторных флуктуаций, но и чувствительность к дофаминергической терапии в целом у пациентов с БП может быть обусловлена носительством определённых полиморфных вариантов генов COMT и MAO-B.*

Ключевые слова: *болезнь Паркинсона; полиморфные варианты; леводопа; дофамин; MAO-B; COMT*

Этическое утверждение. Исследование проводилось при добровольном информированном письменном согласии пациентов. Протокол исследования одобрен локальным комитетом по биомедицинской этике Якутского научного центра комплексных медицинских проблем (протокол № 51 от 17.12.2020).

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Конфликт интересов. Авторы заявляют об отсутствии явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

Адрес для корреспонденции: 677018, Россия, Якутск, ул. Кулаковского, д. 6. Якутский научный центр комплексных медицинских проблем. E-mail: september062007@mail.ru. Хабарова Ю.И.

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Introduction

Parkinson's disease (PD) is one of the most common neurodegenerative disorders, characterized by progressive degeneration primarily of dopaminergic neurons in the substantia nigra of the brain, leading to severe dopamine deficiency and the emergence of symptoms such as bradykinesia, muscle rigidity, and resting tremor [1, 2]. The prevalence of PD continues to rise annually, which is attributed not only to population aging but also to complex interactions between genetic, epigenetic, and environmental factors that require further investigation [3–5].

The cornerstone of PD pharmacotherapy includes levodopa and other dopaminergic agents [6]. Levodopa, as a dopamine precursor capable of crossing the blood-brain barrier, is converted into dopamine and compensates for the neurotransmitter deficit. Other medications such as dopamine receptor agonists, monoamine oxidase B (MAO-B) inhibitors, and amantadine directly stimulate dopamine receptors or enhance/prolong the effects of levodopa [7, 8].

Individual genetic characteristics may serve as key determinants of therapeutic response to dopaminergic treatment. Dopamine is metabolized by two enzymes: catechol-O-methyltransferase (COMT) and monoamine oxidase type B (MAO-B), encoded by the *COMT* and *MAO-B* genes located on 22q11.21 and Xp11.3 chromosomes, respectively [9].

The *Val158Met* (rs4680) polymorphic variant of the *COMT* gene significantly alters enzyme activity. The G allele (encoding valine) is associated with higher COMT enzyme activity and consequently faster dopamine depletion in the synapse, while the A allele (encoding methionine) is linked to slower COMT activity and prolonged synaptic dopamine retention [10]. The *A644G* (rs1799836) polymorphic variant of the *MAO-B* gene may modify MAO-B enzyme activity. Specifically, *TT (AA)*, *TC* (AG), and *CC* (GG) genotypes correspond to high, intermediate, and low enzyme activity levels, respectively [11].

Most studies have focused on associations between *COMT* and *MAO-B* gene polymorphisms with levodopa-induced dyskinesias and motor fluctuations in PD patients [12–16], but none have investigated the relationship between dopaminergic therapy response intensity and polymorphic variant carrier status. This rationale guided the selection of specific genes and polymorphic variants included in the current study.

Study aim: to analyze the relationship between dopaminergic therapy response and carrier status of *COMT* (rs4680) and *MAO-B* (rs1799836) polymorphisms in patients with PD.

Materials and methods

The study was conducted at the Center for Neurodegenerative Diseases of the Clinic of Yakut Scientific Center for Complex Medical Problems included 96 patients (43 men and 53 women) with PD stages 2–3 according to the modified Hoehn and Yahr scale between January 2021 and December 2022.

Inclusion criteria:
- clinically established diagnosis of PD according to the 2013 criteria of the International Parkinson and Movement Disorder Society;
- continuous use of levodopa or other antiparkinsonian agents for at least the preceding year;
- age 18 years and older.

The non-inclusion criteria:
- patients with secondary parkinsonism or parkinsonism within multisystem neurodegeneration;
- patients with severe medical conditions;
- patients who took anticholinergics, anti-dementia drugs, or antidepressants within the previous 6 months;
- refusal to participate in the study.

All patients provided written informed consent to participate in the study. The study protocol was approved by the Local Biomedical Ethics Committee of Yakut Scientific Center for Complex Medical Problems (Protocol No. 51 dated December 17, 2020).

The mean patient age was 66.58 ± 9.37 years (95% CI 64.68–68.48), with average disease duration of 5.71 ± 3.59 years (95% CI 4.98–6.44). Most patients (66.7%) received levodopa/carbidopa, with a median daily dose of 500.0 [375.0; 750.0] mg. 40.6% of patients received combination dopaminergic therapy. Table 1 shows the complete characteristics of the study participants.

All patients included in the study underwent an efficacy assessment of their dopaminergic therapy. After obtaining consent, all anti-Parkinsonian medications were discontinued until the patient reached their self-assessed worst clinical state (Phase 1), during which motor impairments were evaluated using Part III of the Unified Parkinson's Disease Rating Scale (UPDRS). Following administration of a single dose of their prescribed dopaminergic agents and achievement of the optimal therapeutic effect (Phase 2), motor impairments were reassessed. Scores obtained in the worst clinical state were considered baseline, with percentage change calculated for the best clinical state following dopaminergic agent administration.

The molecular genetic study was conducted at the Laboratory of Molecular Genetics of the Center for Predictive Medicine and Bioinformatics at Republican Clinical Hospital No. 3. Blood samples were collected from patients' cubital veins into Improvacuter vacuum tubes (Guangzhou Improve Medical Instruments, China) containing 0.5 M EDTA solution. Genomic DNA extraction was performed using the AmliSens RIBO-PREP DNA/RNA isolation kit (Central Research Institute of Epidemiology, Rospotrebnadzor, Russia) according to the manufacturer's protocol. The isolated DNA was stored at –20°C. Polymorphic variants of the *COMT* (rs4680) and *MAO-B* (rs1799836) genes were analyzed using real-time polymerase chain reaction on a CFX 96 nucleic acid amplifier (Bio-Rad, USA) with commercial reagent kits (rs4680: Syntol, Russia; rs1799836: TestGen, Russia). For genotyping the *COMT* rs4680 polymorphism, 5'-TCGTGGACGCCGTGATTCAGG-3' and 5'-AGGTCTGACAACGGGTCAGGC-3' primers were used. For genotyping the *MAO-B* rs1799836 polymorphism, 5'-GGAACCTCTTATACCACAGG-3 and 5'-GACTGC-

Table 1. Characteristics of patients

Parameter	Value
Total No. of patients	96
Male, *n* (%)	43 (44.8%)
Mean age, years	66.58 (9.37)
Mean disease duration, years	5.71 (3.59)
Disease subtype, *n* (%):	
complex	65 (67.7%)
akinetic-rigid	18 (18.8%)
tremor-dominant	13 (13.5%)
Use of levodopa/carbidopa, *n* (%)	64 (66.7%)
Median levodopa daily dose, mg	500.0 [375.0; 750.0]
Combined dopaminergic therapy, *n* (%)	39 (40.6%)
Use of dopamine receptor agonists, *n* (%)	45 (46.9%)
Use of amantadine, *n* (%)	31 (32.3%)
Median equivalent levodopa daily dose, mg	500.0 [300.0; 750.0]
Mean Unified Parkinson's Disease Rating Scale (UPDRS) Part III score:	
Phase 1	54.25 (16.57)
Phase 2	32.53 (15.69)
Mean Montreal Cognitive Assessment (MoCA) score:	
Phase 1	19.6 (4.97)
Phase 2	23.43 (4.97)

CAGATTTCATCCTC-3' primers were used. Genotyping results were analyzed using TaqMan allelic discrimination technology with fluorescent probes.

Statistical analysis was performed using SPSS Statistics v. 25.0 software. Quantitative data normality was assessed using Kolmogorov–Smirnov and Shapiro–Wilk tests. For normally distributed data, mean ± standard deviation (M ± SD) with 95% confidence interval (CI) was presented. Non-normally distributed data are shown as median and interquartile range (IQR) (Me [Q_1; Q_3]). One-way ANOVA was used to compare three groups of independent quantitative variables with normal distribution, followed by post-hoc analysis when significant differences were detected. Independent samples t-test was applied for comparing two groups of normally distributed variables. Categorical data are presented as frequencies (%). The level of statistical significance was set at $p \leqslant 0.05$.

Genotype distribution was tested for Hardy–Weinberg equilibrium. Figure 1 shows the frequency distribution of genotypes for the studied gene polymorphisms.

Results

Table 2 compares motor deficit differences in PD patients between the two study phases broken down by the carriage of the *COMT* gene rs4680 polymorphisms. Carriers of the *GG* genotype showed a more pronounced reduction in motor deficit in response to antiparkinsonian therapy compared to *AA* genotype carriers, though the differences were not statistically significant. Allelic analysis demonstrated that carriers of the *COMT* gene rs4680 *G* allele responded better to dopaminergic therapy than *A* allele carriers ($p = 0.038$).

Since the *MAO-B* gene is located on the X chromosome, the analysis was performed both in the overall sample and stratified by gender. In the overall sample, we found no statistically significant difference in the response to antiparkinsonian therapy depending on genotype distribution, though heterozygotes showed a smaller reduction in motor deficit ($p = 0.093$). Among men, no statistically significant differences were observed based on *T* or *C* allele carriage ($p = 0.941$). In women, one-way ANOVA revealed a significant difference ($p = 0.043$) in motor deficit changes depending on

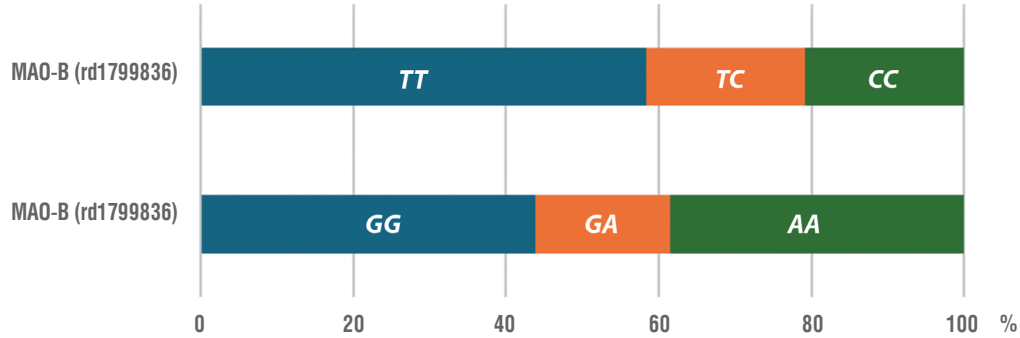

Fig. 1. Distribution of genotype frequencies in the *MAO-B* and *COMT* genes.

Table 2. Association of the *COMT* gene rs4680 polymorphic variant with response to dopaminergic therapy

Genotype/allele	*n*	Difference in UPDRS Part III scores (%)		*p*
		M ± SD	95% CI	
GG	42	45.3 ± 17.8	39.77–50.87	
GA	17	36.15 ± 18.90	26.39–45.91	0.12
AA	37	39.07 ± 16.17	33.68–44.46	
G	101	43.78 ± 18.15	40.2–47.36	**0.038**
A	91	38.53 ± 16.58	35.07–41.97	

rs1799836 polymorphic variant genotypes. Post-hoc testing demonstrated that the difference stemmed from variations between *TC* heterozygotes and *CC* mutant allele homozygotes (35.45 ± 17.78 vs. 55.16 ± 11.22; $p = 0.019$). Consequently, the *CC* genotype in women was associated with a better response to dopaminergic therapy. Meanwhile, allele frequency analysis in both the overall group and gender-stratified subgroups showed no significant differences (Table 3).

Discussion

The polymorphic variants of the *COMT* and *MAO-B* genes included in this study have been extensively investigated across various populations to assess both PD risk and treatment response associations. A meta-analysis of 20 case-control studies involving 2,846 cases and 3,508 controls demonstrated that the *AA* genotype of the *MAO-B A644G* polymorphism is associated with increased PD risk compared to *AG* + *GG* genotypes (OR = 1.32; 95% CI 1.18–1.47) [17]. Conversely, *AG* and *GG* genotypes were linked to earlier onset and higher frequency of drug-induced dyskinesias in patients with PD, potentially due to reduced MAO-B enzyme activity and elevated synaptic dopamine levels [12, 18]. The influence of *COMT* haplotypes (rs6269:*A>G*; rs4633*C>T*; rs4818:*C>G*; rs4680:*A>G*) on levodopa dosing was investigated, revealing that carriers of the *G_C_G_G* haplotype (associated with high COMT enzyme activity) required significantly higher levodopa doses compared to other haplotypes (604.2 ± 261.9 mg vs. 512.2 ± 133.5 mg, $p < 0.05$) [19]. Investigation of *MAO-B* and *COMT* gene effects on PD in the Yakut population remains pending, with planned emphasis on ethnic-specific associations.

Our study assessed whether carrying specific genotypes or alleles of *COMT* and *MAO-B* gene polymorphisms could influence the sensitivity to dopaminergic therapy in patients with PD. By dopaminergic therapy, we meant any treatment capable of enhancing dopaminergic transmission, including levodopa, dopamine receptor agonists, MAO-B inhibitors, and amantadine. We excluded patients taking any other medications that could alter the response to anti-parkinsonian therapy, either by enhancing or suppressing its effects. Our results showed that carriers of the *G* allele of the *COMT* rs4680 polymorphism exhibited more pronounced reduction in motor deficits when receiving anti-parkinsonian medications. However, the *GG* genotype and *G* allele are associated with high COMT enzyme activity and consequent rapid dopamine depletion [15]. Our findings appear partially inconsistent with these data, suggesting the involvement of additional mechanisms modulating treatment response intensity.

According to our data, female carriers of the *CC* genotype of the *MAO-B* gene (rs1799836) demonstrated better response to anti-parkinsonian therapy [17]. The *CC* genotype (designated as *GG* in most studies) is linked to low MAO-B enzyme activity [17]. Consequently, carriers of this genotype may require lower doses of anti-parkinsonian medications or show better response to equivalent drug doses. Conversely, T. Sampaio *et al.* found that male carriers of the *MAO-B G* allele (rs1799836) had a higher relative chance of requiring high-dose levodopa therapy (> 600 mg/day; $p = 0.04$), while no significant differences in genotype/allele frequency or levodopa dosing were observed in women [12].

Table 3. Association of the *MAO-B* gene rs1799836 polymorphic variant with response to dopaminergic therapy

Genotype/allele	*n*	Difference in UPDRS Part III scores, %		*p*
		M ± SD	95% CI	
Overall sample				
TT	56	42.02 ± 18.23	37.13–46.90	0.093
TC	20	35.27 ± 17.3	27.16–43.38	
CC	20	45.26 ± 15.29	38.10–52.42	
T	132	40.99 ± 18.13	37.87–44.12	0.724
C	60	41.93 ± 16.42	37.69–46.17	
Men				
T	30	40.22 ± 17.74	35.71–44.74	0.941
C	13	39.93 ± 14.51	34.07–45.79	
Women				
TT	26	44.09 ± 19.05	36.39–51.78	**0.043** $p_{TT,TC} = 0.1$* $p_{TT,CC} = 0.344$* **$p_{TC,CC} = 0.019$***
TC	20	35.45 ± 17.78	26.89–44.02	
CC	7	55.16 ± 11.22	44.78–65.53	
T	72	41.78 ± 18.86	37.32–46.24	0.604
C	34	43.82 ± 17.97	37.44–50.18	

Our study has several significant limitations. The primary limitation is the lack of stratification of patients by groups of antiparkinsonian medications used. It is likely that carriers of different genotypes will respond differently to levodopa preparations, dopamine receptor agonists, and other agents. Nevertheless, we demonstrated that sensitivity to dopaminergic therapy depends on polymorphic variants of genes whose products are involved in levodopa metabolism. Second, patients received antiparkinsonian agents in varying doses. Therefore, we decided to calculate between-phase differences in the study not in absolute values (points) but in percentage terms. During the study, we did not adjust doses of previously prescribed medications. We temporarily discontinued nighttime antiparkinsonian medications, but most patients did not reach their worst clinical condition by the next morning, necessitating prolongation of the withdrawal period. The third major limitation is the small sample size and lack of ethnic stratification. We hypothesize that representatives of different ethnic groups may also have specific features in sensitivity to antiparkinsonian therapy.

Conclusion

Our data suggest that in patients with PD, not only drug-induced dyskinesias and motor fluctuations, but also overall sensitivity to dopaminergic therapy may be associated with specific *COMT* and *MAO-B* polymorphisms. Larger-scale studies with stratification by antiparkinsonian medications and ethnicity are undoubtedly needed.

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Information about the authors

Yuliya I. Khabarova – junior researcher, neurologist, Head, Neurological department, Center for neurodegenerative diseases, Clinic of the Yakut Scientific Center for Complex Medical Problems, Yakutsk, Russia, https://orcid.org/0000-0002-5674-4426
Alexey A. Tappakhov – Cand. Sci. (Med.), Assoc. Prof., Department of neurology and psychiatry, M.K. Ammosov North-Eastern Federal University, Yakutsk, Russia; senior researcher, Neurodegenerative disorders center, Yakut Scientific Center for Complex Medical Problems, Yakutsk, Russia, https://orcid.org/0000-0002-4159-500X
Tatiana E. Popova – Dr. Sci. (Med.), neurologist, LLC "Lotus Medical Clinic", Yakutsk, Russia, https://orcid.org/0000-0003-1062-1540
Nadezhda E. Maksimova – biologist, Center for predictive medicine and bioinformatics, Republican Clinical Hospital No. 3, Yakutsk, Russia, https://orcid.org/0009-0003-9677-7526
Aleksandra S. Asekritova – Cand. Sci. (Med.), Assoc. Prof., Department of internal medicine and general practice (family medicine), M.K. Ammosov North-Eastern Federal University, Yakutsk, Russia; Head, Center for predictive medicine and bioinformatics, Republican Clinical Hospital No. 3, Yakutsk, Russia, https://orcid.org/0000-0002-5378-2128
Olga V. Tatarinova – Dr. Sci. (Med.), Chief doctor, Republican Clinical Hospital No. 3, Yakutsk, Russia; senior researcher, Yakut Scientific Center for Complex Medical Problems, Yakutsk, Russia, https://orcid.org/0000-0001-5499-9524

Contribution of the authors: *Khabarova Yu.I.* – data collection and research implementation, article design development, data interpretation and analysis, manuscript writing; *Tappakhov A.A.* – conceptualization and article design, coordination of development, manuscript editing and final revision, supervision of the research project, and approval of the final manuscript version; *Popova T.E.* – study design development, final text revision, and manuscript approval; *Asekritova A.S.* – coordination of the study; *Maksimova N.E.* – research implementation; *Tatarinova O.V.* – organization of the study. All authors made significant contributions to the study's conceptualization, execution, and manuscript preparation, and have read and approved the final version for publication.

Информация об авторах

Хабарова Юлия Ильинична – м. н. с., врач-невролог, зав. неврологическим отделением Центра нейродегенеративных заболеваний Клиники Якутского научного центра комплексных медицинских проблем, Якутск, Россия, https://orcid.org/0000-0002-5674-4426
Таппахов Алексей Алексеевич – канд. мед. наук, доцент каф. «Неврология и психиатрия» Медицинского института Северо-Восточного федерального университета им. М.К. Аммосова, Якутск, Россия; с. н. с. Центра нейродегенеративных заболеваний Якутского научного центра комплексных медицинских проблем, Якутск, Россия, https://orcid.org/0000-0002-4159-500X
Попова Татьяна Егоровна – д-р мед. наук, врач-невролог ООО «Медицинская клиника Лотос», Якутск, Россия, https://orcid.org/0000-0003-1062-1540
Максимова Надежда Евгеньевна – биолог Центра предиктивной медицины и биоинформатики Республиканской клинической больницы № 3, Якутск, Россия, https://orcid.org/0009-0003-9677-7526
Асекритова Александра Степановна – канд. мед. наук, доцент каф. «Внутренние болезни и общеврачебная практика (семейная медицина)» Медицинского института Северо-Восточного федерального университета им. М.К. Аммосова, Якутск, Россия; зав. Центром предиктивной медицины и биоинформатики Республиканской клинической больницы № 3, Якутск, Россия, https://orcid.org/0000-0002-5378-2128
Татаринова Ольга Викторовна – д-р мед. наук, главный врач Республиканской клинической больницы № 3, Якутск, Россия; с. н. с. Якутского научного центра комплексных медицинских проблем, Якутск, Россия, https://orcid.org/0000-0001-5499-9524

Вклад авторов: *Хабарова Ю.И.* – сбор и проведение исследования, разработка дизайна статьи, интерпретация данных, анализ данных, написание текста статьи; *Таппахов А.А.* – разработка концепции и дизайна статьи, координация разработки, редактирование и финальная корректировка текста статьи, курирование научно-исследовательской работы, утверждение окончательного варианта текста; *Попова Т.Е.* – разработка проекта исследования, финальная корректировка текста, утверждение окончательного варианта текста; *Асекритова А.С.* – координация разработки исследования; *Максимова Н.Е.* – проведение молекулярно-генетического исследования; *Татаринова О.В.* – организация исследования. Все авторы внесли существенный вклад в разработку концепции, проведение исследования и подготовку статьи, прочли и одобрили финальную версию перед публикацией.