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Personalized Psychiatry and Neurology

Article

Screening for mutations in the *GBA1* and *LRRK2* genes in schizophrenia in the Northwestern region of Russia

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Citation: Syryeva O.V., Lavrinova A.O., Demidova E.A., Pidyurchina V.N., Usenko T.S., Krapova A.K., Moshkovskaya A.O., Zalutskaya N.M., Nasyrova R.F., Neznanov N.G., Pchelina S.N., Emelyanov A.K. Screening for mutations in the *GBA1* and *LRRK2* genes in schizophrenia in the Northwestern region of Russia. *Personalized Psychiatry and Neurology* **2026;** 6 (2): 56-60. https://doi.org/10.52667/2712-9179-2026-6-2-56-60

Chief Editor: Nikolaj G. Neznanov, D Med Sci, Professor

Received: 19 March 2026
Accepted: 10 June 2026
Published: 15 June 2026

Publisher's Note: V.M. Bekhterev NMRC PN stays neutral with regard to jurisdictional claims in published maps and institutional affiliations.

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Abstract: Schizophrenia (SCZ) is a severe mental disorder which exact pathogenesis remains unknown. The disorder has been linked to disturbances in lipid metabolism and lysosomal function. A link between this disorder and Parkinson's disease (PD) is suggested. Pathogenic mutations in the *GBA1* gene, which lead to dysfunction of the lysosomal enzyme glucocerebrosidase, are a high-risk factor of PD. Meanwhile, mutations in the *LRRK2* gene are the most common cause of hereditary forms of PD and may indirectly affect the activity of this enzyme. *GBA1*- and *LRRK2*-related PD are the most prevalent forms of the disease known today. **Materials and Methods:** In this study, we used PCR followed by the restriction analysis and real-time PCR allelic discrimination to assess the frequency of mutations in the *LRRK2* (G2019S) and *GBA1* (N370S, L444P, E326K) genes among 161 SCZ patients and 434 control individuals residing in the Northwestern region of Russia. **Results:** The study found no association between the investigated mutations and the risk of SCZ. Among SCZ patients, no carriers of the N370S mutation in the *GBA1* gene or the G2019S mutation in the *LRRK2* gene were identified. The frequency of *GBA1* mutations (L444P+N370S+E326K) among SCZ patients was found to be 3.2%. **Conclusions:** Thus, this study demonstrated that mutations in the *GBA1* gene are not associated with the risk of SCZ.

Keywords: *Schizophrenia, Parkinson's disease, mutations in the GBA1 and LRRK2 genes.*

1. INTRODUCTION

Schizophrenia (SCZ) is a severe multifactorial mental disorder characterized by negative and positive symptoms, as well as cognitive impairments. Heredity accounts for up to 80% of the risk of this disorder. Currently, a relationship has been identified between Parkinson's disease (PD), a common neurodegenerative disorder, and SCZ [1, 2]. It has been shown that SCZ patients may develop PD during antipsychotic therapy, while treatment for PD may also lead to the manifestation of schizophrenic symptoms [3]. Moreover, cases of comorbid idiopathic PD and SCZ have been described [2]. It should be noted that in clinical practice, there are difficulties in diagnosing of PD in SCZ patients, as true parkinsonian symptoms can be mistakenly interpreted as manifestations of drug-induced parkinsonism caused by antipsychotic medication [4]. However, the precise molecular mechanisms underlying the development of SCZ, as well as the comorbid course of this disorder with PD, remain unknown. In recent years, a growing body of evidence has linked SCZ to disruptions in lipid metabolism, particularly involving lysosphingolipids, and to lysosomal dysfunction [5, 6].

A key player in lysosphingolipid metabolism is the enzyme glucocerebrosidase (GCase), encoded by the *GBA1* gene. Mutations in this gene lead to enzyme dysfunction and the development of the most common lysosomal storage disease (LSD), Gaucher disease (GD) [7], and are also a well-established risk factor for developing PD. Epidemiological data indicate that patients with both GD and other LSD have an increased risk of developing psychotic disorders, including SCZ [8].

Furthermore, PD patients who carrying *GBA1* gene mutations (GBA1-PD) also exhibit an increased frequency of psychiatric symptoms, which tend to manifest at an earlier age compared to other forms of PD [9].

Other genetic factors contributing to hereditary forms of PD include mutations in the gene encoding leucine-rich repeat kinase 2 (*LRRK2*). Evidence suggests a functional link between LRRK2- and GCase-mediated pathways in the context of lysosomal-lipid metabolism [10-12]; however, the nature and mechanisms of this interaction remain under active investigation. Additionally, experimental and bioinformatic data indicate that mutations in the *LRRK2* gene may be accompanied by mitochondrial dysfunction [13]. Such impairments are considered one of the potential pathophysiological mechanisms involved in the development of SCZ [14].

The aim of the present study was to evaluate the association of mutations in the *GBA1* (N370S, L444P, E326K) and *LRRK2* (G2019S) genes with the risk of SCZ in the Northwestern region of Russia.

2. MATERIAL AND METHODS

The study included 161 SCZ patients (age 35.0±17.2 years; 129 males, 32 females). All participants underwent a standard neurological clinical examination. Patient evaluations were conducted at two clinical centers of Saint Petersburg, St. Petersburg Psychiatric Hospital No. 1, named after P. P. Kashchenko, and the V.M. Bekhterev National Medical Research Center for Psychiatry and Neurology. The diagnosis of SCZ was established according to ICD-10 criteria. The control group consisted of 434 healthy unrelated individuals (age 63.0±14.6 years; 162 males, 272 females) with no family history of neurological or psychiatric disorders. This group was formed at the Pavlov First Saint Petersburg State Medical University. Identification of the *GBA1* gene mutations (L444P, E326K) was performed using PCR followed by the restriction analysis [15]. The allelic discrimination method with real-time PCR was employed to detect mutations (G2019S) in the *LRRK2* gene and (N370S) in the *GBA1* gene using a CFX96 instrument (Bio-Rad, USA) [15]. The detected mutations in the *GBA1* and *LRRK2* genes were confirmed by Sanger sequencing performed on the Nanophor-05 system (Syntol, Russia). The study was approved by the ethics committees of the aforementioned medical institutions and was conducted with the informed consent of all participants from the study groups.

To assess the association of the studied variants in the *GBA1* and *LRRK2* genes with the risk of SCZ, odds ratios (OR) along with 95% confidence intervals (CI) were calculated. Statistical processing of the obtained data was performed using the MedCalc service (https://www.medcalc.org/calc/odds_ratio.php). The level of significance was set at $p<0.05$.

3. RESULTS

The screening identified one carrier of *GBA1* L444P mutation (1/157; 0.6%) and four carriers of the *GBA1* E326K mutation (4/161; 2.5%) in the group of SCZ patients. *GBA1* N370S and *LRRK2* G2019S mutations in this group were not detected. In the control group, 1 carrier of the *GBA1* L444P mutation (1/400; 0.3%), 13 carriers of the *GBA1* E326K mutation (13/434; 3.0%), and two carriers of the *LRRK2* G2019S mutation (2/400; 0.5%) were identified. The *GBA1* N370S mutation was not detected in the control group. The combined frequency of *GBA1* gene mutations (L444P and E326K) was 3.2% (5/157) in the SCZ patient group and 3.5% (14/400) in the control group. A comparative analysis of the frequencies of the studied genetic variants between the groups revealed no statistically significant differences. Detailed data on the distribution of *GBA1* and *LRRK2* gene mutations are presented in **Table 1**.

4. DISCUSSION

In this study, we performed the first screening for the most common mutations (L444P, N370S, and E326K) in *GBA1* gene associated with an increased risk of PD among SCZ patients and control individuals residing in the Northwestern region of Russia. It should be noted that the L444P and N370S mutations in *GBA1* gene are the most common causes of GD and increase the risk of developing PD up to 10-fold [16]. *GBA1* L444P mutation in a homozygous state has been shown to lead to the development of a severe neuronopathic form of GD and significant GCase dysfunction, with residual activity of approximately 5% [17].

Table 1. Distribution of *GBA1* and *LRRK2* gene mutations in SCZ patients and controls

Groups	SCZ patients	Control
	The *GBA1* gene	
n (%) E326K /N OR (95% CI) *p*-value	4 (2.5) /161 0.83 (95%CI: 0.27–2.57), *0.74*	13 (3.0) /434
n (%) L444P /N OR (95% CI) *p*-value	1 (0.6) /157 2.55 (95%CI: 0.16–41.15), *0.51*	1 (0.3) /400
n (%) N370S /N OR (95%CI) *p*-value	0 /157	0 /400
n (%) (L444P+ E326K)/ N OR (95% CI) *p*-value	5 (3.2) /157 0.91 (95%CI: 0.32–2.56), *0.85*	14 (3.5) /400
	The *LRRK2* gene	
n (%) G2019S /N OR (95% CI) *p*-value	0 /157	2 (0.5) /400

The "mild" *GBA1* N370S mutation in a homozygous state leads to the development of type 1 GD and decreased enzyme activity, with residual activity of approximately 20% [17]. Meanwhile, the *GBA1* E326K mutation does not lead to the development of GD but increases the risk of PD up to 2-fold [18, 19]. It has also been demonstrated that patients with GBA1-PD exhibit a higher frequency of cognitive impairment compared to patients with the idiopathic form of the disease [20–23]. Our findings revealed no statistically significant differences in the frequencies of the investigated *GBA1* gene mutations between the patient and control groups. Previously, a meta-analysis of exome data from SCZ patients and controls representing various populations suggested an association between SCZ and mutations in genes causing LSD, excluding GD [24]. However, it is important to note that this study employed next-generation sequencing, which, due to technical limitations, is unable to detect genetic variants in coding regions of genes for which pseudogenes have been described. Since *GBA1* has a highly homologous pseudogene, *GBA1P*, the authors were unable to assess the association of *GBA1* genetic variants with the risk of SCZ. This would require direct Sanger sequencing of the *GBA1* coding region, which, according to our data, has not yet been performed for a group of SCZ patients.

In the present study, we also screened for the G2019S mutation in the *LRRK2* gene among SCZ patients and controls. It is noteworthy that mutations in the *LRRK2* gene are not only a major cause of hereditary forms of PD [25] but also contribute to genetic predisposition to the most common neurodegenerative disorder, Alzheimer's disease [26], as well as to other diseases such as Crohn's disease [27] and certain cancers [28].

The G2019S mutation in the *LRRK2* gene, which encodes leucine-rich repeat kinase 2, has been shown to enhance its kinase activity and impair mitochondrial functions, including fission/fusion dynamics, depolarization, and mitophagy, as demonstrated in cellular and animal models [29].

These findings provided the rationale for hypothesizing that mutations in the *LRRK2* gene might confer susceptibility to a broad spectrum of neuropsychiatric disorders, including SCZ. However, our screening did not identify any carriers of the *LRRK2* G2019S mutation among patients with SCZ. Similarly, this mutation was previously not detected in patients with this pathology in a Chinese population [30].

5. CONCLUSION

The N370S, L444P, and E326K mutations in the *GBA1* gene, as well as the G2019S mutation in the *LRRK2* gene, are not associated with the risk of SCZ among residents of the Northwestern region of Russia.

Author Contributions: Conceptualization, A.E. and S.N.; methodology, A.E.; formal analysis, O.S.; investigation, O.S., A.L., E.D., V.P., T.U., A.K., A.M., N.Z., R.P., and N.N.; resources, A.M., N.Z., R.P., and N.N.; writing—original draft preparation, O.S., A.L., A.K., and A.E.; writing—review and editing, A.E. and S.N.; visualization, O.S.; supervision, A.E. and S.N.; project administration, A.E. and S.N. All authors have read and agreed to the published version of the manuscript.

Funding: The research was carried out within the state assignment of Ministry of Science and Higher Education of the Russian Federation (theme №1024011100004-4-1.6.8;1.6.4;1.6.7;1.6.1).

Institutional Review Board Statement: The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the ethics committee of the Center for Personalized Psychiatry and Neurology of the N.N., V.M. Bekhtereva (Saint Petersburg, Russia) (Approval Code: 2; Approval Date: 27 February 2023).

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Conflicts of Interest: The authors declare no conflict of interest.

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