Can serine Hydroxy Methyl Transferase-1 gene Polymorphism (rs1979277) predict the Risk and Severity of Parkinson's disease? A case-control study

Abeer A. Tony[a], Sara A. Atta[b*], Effat AE. Tony[c], Emad F. Kholeef[d], Mariam E. Abdallah[e]

[a]Department of Neuropsychiatry, Faculty of Medicine, Aswan University, Aswan, Egypt.
[b]Department of Medical Biochemistry, Faculty of Medicine, Assiut University, Assiut, Egypt.
[c]Department of Internal Medicine, Faculty of Medicine, Assiut University, Assiut, Egypt.
[d]Department of Clinical Pathology, Faculty of Medicine, Aswan University,Aswan, Egypt.
[e]Department of Clinical Pathology, Faculty of Medicine, Assiut University, Assiut, Egypt.

Abstract

Background: Serine hydroxymethyl transferase (SHMT1) is an enzyme with a particular role in the interconversion of serine and glycine. SHMT1 may contribute to Parkinson's disease pathogenesis and progression through its role in neuronal function.

Objectives: This study aims to assess the role of SHMT1 polymorphism (rs1979277) A/G in predicting the risk and severity of Parkinson's disease in addition to its correlation with vitamin B12 and folic acid serum levels.

Patients and methods: A descriptive case-control study involved 192 participants divided into two groups: (group A) included 96 patients diagnosed as Parkinson's disease and (group B) 96 healthy, age- and sex-matched subjects as controls. SHMT1-SNP genotyping A/G (rs1979277) detection was done. Moreover, the serum levels of folic acid and vitamin B12 were estimated for all patients genotypes.

Results: The GA+AA versus GG genotype were significantly susceptible to Parkinson's disease: OR 95% CI= 2.14 (1.16-3.96) and p-value =0.014. The G allele was protective, and the A allele was a predisposing genetic factor for Parkinson's disease (p-value <0.011 and OR, 95% CI=2.04 (1.36-3.07). Patients with the GA+AA genotype had a statistically significant lower median MMSE total score than those with the GG genotype (16.0 vs. 21.5 years, respectively; p-value = 0.021). However, there was no statistically significant difference between GA+AA vs GG and mean vit-B12 and folate.

Conclusion: Parkinson's disease along with the severity of depression was substantially more likely to develop in people with the genotype GA+AA than GG. Consequently, for Parkinson's disease, the G allele may be protective while the A allele was a genetic risk factor.

Keywords: Parkinson`s disease; SHMT1; Folic Acid; Vitamin B12.
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Introduction

Parkinson's disease (PD) is a progressive incapacitating neurological disorder. It follows Alzheimer's disease in prevalence among world's population regarding neurological disorders. PD could also considered as misfolding disorder characterized by loss of dopaminergic neurons in the substantia nigra and the development of "Lewy bodies" **(Kouli et al., 2018).** Given a worldwide load that has more than doubled since the earlier generation **(GBD, 2016).** This number of Parkinson's sufferers is predicted to have doubled by 2030 **(Elbaz et al., 2016).**

Parkinson's disease manifests as a variety of symptoms affecting the motor system, such as sluggishness, tremors, and rigidity, as well as other cognitive symptoms, such as depression, dementia, and other symptoms that affect the patient`s daily life **(Ayano, 2016; Nicoletti et al., 2017)**

It has been recognized that the complex nature of PD results from the combination of hereditary and environmental factors, even if the etiology is still unknown in most cases. There have been many monogenic variants of PD postulated over the past 20 years **(Wang et al., 2021)**. Genetic types of Parkinson's disease, which account for 3–5% of all cases of the condition, are brought on by mutations in several single nuclear genes **(Klein and Westenberger, 2012; Ryan et al., 2015).**

The key enzyme serine hydroxymethyl transferase (SHMT) is essential for properly functioning the central nervous system (CNS). SHMT1 performs an exceptional role in the interconversion of serine and glycine and the generation of 1-carbon units for folate metabolic processes. This single-carbon unit is used in the synthesis of active methyl groups of methionine via homocysteine remethylation **(Nonaka et al., 2019).**

Previous studies assumed that the defect in the association between SHMT and folate cycle; either genetic mutation of SHMT or deficiency of folate and B12 could be a possible causation for various neurological disorders as neuronal tube defects, depressive disorders, or dementia (**Reynolds, 2014).**

Hein, our study aims to discover the correlation between serum vitamin B12 and folic acid levels and the cytoplasmic SHMT1 variant rs1979277 in predicting the severity and risk of Parkinson's disease.

Patients and methods

Participants and design

The study designed as descriptive case-control study involving 192 participants divided into two groups: (group A) included 96 patients with PD who were chosen from the Neuropsychiatric department of the Aswan University Hospital's inpatient and outpatient clinics, and (group B) of 96 healthy controls who were chosen to be age- and sex-matched with patients, had no known family or personal history of Parkinsonism, other neuropsychiatric, cerebrovascular, or other chronic disease. The study procedures were conducted in both Medical Biochemistry and Clinical Pathology departments of the Faculty of Medicine, Assiut and Aswan Universities, Egypt.

The Declaration of Helsinki's guidelines were followed when recruiting patients and controls for this study. The study was conducted in the period from June 2021 to April 2023 and the protocol was approved by the Ethics Committee of the Faculty of Medicine, Aswan University, Egypt (code number: asw.u./578/11/21).

All participants provided written informed permission after being briefed on the study's goal and methodology. Patients with parkinsonian plus syndrome, secondary parkinsonism, Past and/or present history of epilepsy, disturbed consciousness level,

malignancies, chronic medical conditions, and other neurological illnesses, were all disqualified from the study.

The sample size was determined using the G*Power 3 with P-value 0.05 and 80% power, an estimated 96 participants (controls and cases) were needed for a one-tailed test (type I error).

Clinical assessments and data collection

The onset of PD was estimated by the period of first appearance of clinical symptoms of PD. The extent or severity of PD was evaluated using "the Unified Parkinson's Disease Rating Scale (UPDRS)" especially motor symptoms. In addition to assessing the cognitive functions and depression through using the Arabic versions of the Mini-mental state examination (MMSE) and the Beck Inventory Depression Score (BIDS) respectively.

Estimation of serum vitamin B12 and folic acid levels

Three millimeters of blood was collected through venipuncture into sterile plain vacutainer tubes, which were subsequently centrifuged at 10,000 RPM to separate the serum into sterile epindorph tubes. Estimation of serum levels of vitamin B12 and folic acid was done using a colorimetric technique (ABC Diagnostic, Egypt. Catalog number: BC-2022).

Detection of SHMT1 polymorphism by TaqMan SNPs genotyping assays

Three millimeters of venous blood collected in EDTA tubes was obtained from all patients and controls. DNA was extracted from whole blood using Thermo Fisher Scientific genomic DNA purification, catalog no. K0512 (supplied by Thermo Fisher Scientific Inc., USA), following guidelines of the manufacturer, the purity and quality of the extracted DNA were tested by nanodrop. Purified DNA samples were genotyped on Applied Biosystems (Foster, CA, USA) by a TaqMan assay designed to distinct the variants of both SHMT1 A/G (rs 1979277) polymorphism catalog no. 4351379 using fluorescent-labeled probes (VIC/FAM) TCAGGCAGGCCAGGCAGAGGGAAGA[A/G]AGAGGCGAAGCTCTCAACCTCCTCC respectively, manufactured in Waltham, Massachusetts, by Thermo Fisher Scientific. DNA was genotyped in accordance with the manufacturer's instructions. The following components were added to each reaction: To make 10 µL, combine 10 ng of pure DNA, 5 µL of Master Mix, 0.5 µL of assay mix, and water. Every PCR cycle included "non-template negative controls" (NTCs) to verify the free reaction **(Taximaimaiti and Li, 2019)**. Samples were replicated across plates to verify the genotyping's correctness. The allele distribution and amplification plots of rs928553 and rs12782374 were demonstrated in (**Fig.1A ,B**).

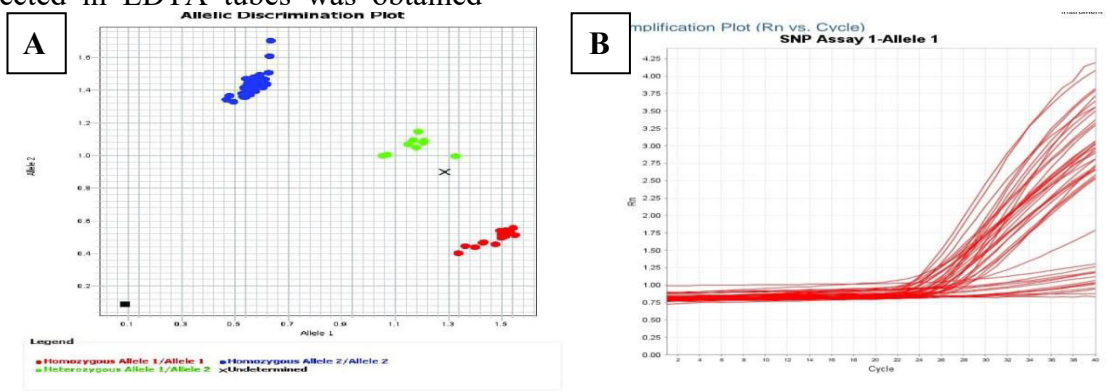

Fig. 1. **TaqMan SNPs genotyping of SHMT1 variants (A)** Allelic discrimination plots, **(B)** Amplification plots

Statistical analysis

IBM-SPSS Software version 26.0 was used to analyze the data. Frequencies and percentages will be used to display categorical data. Once the Shapiro-Wilk test has confirmed that the data is normal, the mean ± SD or median and range are employed for numerical variables. The proportion between groups was compared using the Chi-square ($\chi 2$) test. The odds ratio (OR) and 95% confidence intervals (95% CI) were used to determine the risk ratio and association between Parkinson's disease, SHMT1 A>G genotypes, and its alleles. Independent Sample Mann-Whitney/T-test The U test analyzes the mean and median of various genotypes. A P value of less than 0.05 was deemed to be significant.

Results

Demographic Data of the Study Groups

Among a total sample of 96 cases and 96 controls, as shown in (**Table.1**) no statistically significant difference was determined between subjects regarding age, gender, P value >0.05.

Table (1): Demographic data of different studied groups

Variables	Group A (N=96)	Group B (n=96)	P-value*
Age (years) Mean ± SD	64.06±9.23	63.65±9.82	0.762
Gender Male: Female	48:48 (50:50%)	48:48 (50:50%)	0.999

Data is expressed as Mean ± SD (range), or frequency (%); * The Chi-square test compares the proportion between different groups and the Independent Sample T-test compares the mean difference between groups.

Regarding clinical data and examination of patients: family history of Parkinson's was detected in 8.3% of patients and 27.1% were in consanguineous marriage. Regarding UPDRS; the median for mentation, behavior, and mood sub score was 3, the activities of daily living score was 10, the motor examination score was 29, and the median total UPDRS was 49.50. Regarding MMSE, the total median score was 17, 16.7% were normal, 16.6% had minimal longitudinal impairment and 66.7% had dementia. Regarding the Beck depression inventory, 18.8% had mild depression, 20.8% had moderate depression, 37.5% had severe depression and 22.9% had extreme depression as presented in **(Table.2).**

Table 2. Clinical data and examination of patients with Parkinson's disease

Clinical data	N=96
• Family History of a similar case	8(8.3%)
• Consanguinity	26 (27.1%)
• Disease duration (years): median (range)	9.0 (3-20)
UPDRS	**Median (range)**
• Mentation, Behavior, and Mood	3.00 (1-23)
• Activities of daily living	10.00 (3-27)
• Motor Examination	29.00 (7-67)
Total UPDRS score	49.50 (12-104)
MMSE 30: Median (range)	**Median (range)**
• Normal (>24)	16 (16.7%)
• Minimal cognitive impairment (MCI) (21-24)	16 (16.7%)
• Dementia (<21)	64 (66.7%)

MMSE score	17.0 (10-29)
BDI	N (%)
• Mild	18 (18.8%)
• Moderate	20 (20.8%)
• Severe	36 (37.5%)
• Extreme	22 (22.9%)

*UPDRS: Unified Parkinson's Disease Rating Scale, MMSE: Mini-mental state examination, BDI: Beck Depression Inventory

Distribution of SHMT1 A>G genotypes and its alleles among the subjects

It was observed that there was a higher risk of Parkinson's disease among individuals with genotype GA, AA. Moreover, AA and GG genotypes had the most positive and negative correlation with Parkinson's disease respectively. GG genotype was 25.0% among cases compared to 41.7% among controls, GA was 31.3% among cases compared to 33.3% among controls, OR 95% CI= 1.56 (0.76-3.17), AA was 43.8% among cases compared to 25.0% among controls and OR, 95%CI= 2.92 (1.43-5.94), p-value =0.011.

Moreover, individuals with AA versus GG+GA genotype were significantly susceptible to Parkinson's disease: OR 95% CI= 2.33 (1.26-4.31), p value=0.006 and individuals with GA+AA versus GG genotype were significantly susceptible to Parkinson's disease: OR 95%CI= 2.14 (1.16-3.96) and p-value =0.014. The allele frequency in the SNP shows a significant difference between patients and healthy subjects, the G allele was protective, and the A allele was a predisposing genetic factor for Parkinson's disease (p-value <0.011 and OR, 95% CI=2.04 (1.36-3.07), G allele was 59.3% among cases versus 41.7 % among controls **(Table. 3).**

Table 3. Comparison of SHMT1 A>G genotypes and their alleles among subjects

Variables	Group A (N=96)	Group B (n=96)	OR (95% CI)	Test value (χ^2)	P-Value*
Genotypes					
• GG	24 (25.0%)	40 (41.7%)	Reference	8.97	**0.011**
• GA	30 (31.3%)	32 (33.3%)	56 (0.76-3.17)		
• AA	42 (43.7%)	24 (25.0%)	92 (1.43-5.94)		
Dominant model					
• GG+GA	54 (56.3%)	72 (75.0%)	Reference	7.48	**0.006**
• AA	42 (43.7%)	24 (25.0%)	33 (1.26-4.31)		
Recessive model					
• GG	24 (25.0%)	40 (41.7%)	Reference	6.00	**0.014**
• GA+AA	72 (75.0%)	56 (58.3%)	14 (1.16-3.96)		
Alleles					
• G (wild)	78 (40.6%)	112 (58.3%)	Reference	12.04	**<0.001**
• A (mutant)	114 (59.4%)	80 (41.7%)	04 (1.36-3.07)		

Data is expressed as frequency (%),* Chi-square test compares between the proportion of different groups. P value significant if <0.05

Factors associated with SHMT1 A>G genotypes among subjects

As presented in (**Table.4**) there was a higher mean age among patients with GA+AA genotype compared to GG genotype (65.92±8.93 vs 58.50±7.90 respectively), P value <0.001. Male gender had a higher statistically significant percentage of GA+AA genotype (58.3%) compared to 25.0% of males who were found to have GG genotype, p-value =0.005. Moreover, there was a higher statistically significant median duration of disease among

patients with GA+AA genotype compared to GG genotype (10.0 vs 6.5 years respectively), p-value =0.004, lower statistically significant median MMSE total score among patients with GA+AA genotype compared to GG genotype (16.0 vs 21.5 years respectively), p-value =0.021 and patients with severe/extreme depression had higher statistically significant of percent of GA+AA genotype (72.2%) compared to 25.0% of patients with severe/extreme depression had GG genotype, p-value <0.001. However, no statistically significant difference between GG+AA vs GG regarding family history, consanguinity, total UPDRS score, mean vit-B12, and folate.

Table 4. Factors associated with SHMT1 A>G genotypes among patients

Variables	GG (N=24)	GA+AA (n=72)	P-Value*
Age: Mean ± SD	58.50±7.90	65.92±8.93	**<0.001**
Gender			
• Male	6 (25.0%)	42 (58.3%)	**0.005**
• Female	18 (75.0%)	30 (41.7%)	
Family History of a similar case	4 (16.7%)	4 (5.6%)	0.104
Consanguinity	8 (33.3%)	18 (25.0%)	0.426
Disease duration: median (range)	6.50 (4-15)	10.00 (3-20)	**0.004**
Total UPDRS: median (range)	50.00 (12-104)	48.50 (18-104)	0.150
MMSE 30 score: median (range)	21.50 (11-27)	16.00 (10-29)	**0.021**
Beck Depression Inventory (BDI)			
• Mild/Moderate	18 (75.0%)	20 (27.8%)	**<0.001**
• Severe/Extreme	6 (25.0%)	52 (72.2%)	
Vit-B12 (pg/ml)	580.83±16.00	620.11±19.72	0.799
Folate (ng/ml)	36.3±1.09	35.5±1.7	0.946

*UPDRS: Unified Parkinson's Disease Rating Scale, MMSE: Mini-mental state examination, BDI: Beck Depression Inventory; * The Chi-square test compares the proportion between different groups and the Independent Sample T-test/Mann Whitney U test compares the mean/median difference between groups.

Discussion

Parkinson's disease as a prevalent neurodegenerative condition characterized by particular loss of dopaminergic neurons in the substantia nigra **(Dunnett and Björklund, 1999)**. The cause of Parkinson's disease (PD) remains largely unclear in most cases because of the variety of etiologies resulting from the interplay of inherited and environmental variables **(Wang et al., 2021)**.

Noticeably, it was shown that cytoplasmic SHMT activity is decreased in schizophrenic-psychotic people **(de Bartolomeis et al., 2020).** These findings motivated us to investigate how SHMT1 polymorphisms affect the risk of Parkinson's disease development. We also studied the association between folic acid and B12 levels and other patient characteristics with the SHMT1 polymorphism for a better understanding.

Our study observed that the allele frequency in the SNP exhibited a significant difference between patients and healthy subjects: the G allele was protective, and the A allele was a predisposing genetic factor for Parkinson's disease (p-value <0.011 and OR, 95% CI = 2.04 (1.36-3.07), and the G allele was 59.4% among cases versus 41.7% among controls.

Skibola et al. (2002) found that SHMT 1420 C>T serves a protective effect in several diseases, including acute lymphocytic leukemia, coronary artery disease, and breast cancer, however, their

findings are contradictory **(Skibola et al., 2002).**

In a prior investigation, **dos Santos et al. (2009)** found that the plasma folate levels of PD patients were diminished compared those of control subjects. Additionally, in PD patients, plasma folate levels are inversely linked with plasma homocysteine (Hcy) levels, indicating that plasma folate levels are key modulators for Hcy levels **(dos Santos et al., 2009).** According to **McCarter et al. (2019)**, both levodopa-treated and untreated participants had higher homocysteine levels in patients with PD **(McCarter et al., 2019; Triantafyllou et al., 2008).**

Similarly, our study's findings indicated that patients' serum levels of folate and vitamin B12 were negligibly lower than those in the control group. This suggests that the SHM1 polymorphism can lead to a reduction in active folate hence, a rise in blood Hcy levels that was proved as oxidative and toxic agent for the nervous system.

Our study is the first to disclose the association between the length of the disease duration and the SHMT1 polymorphism, revealed that patients with the GA+AA genotype had significantly longer median disease durations than those with the GG genotype. We concluded that polymorphisms might contribute to increased PD duration.

Another added strength point to our research is that we revealed a strong correlation between the GA+AA genotype and MMSE and BDI scores (that are used as measures of disease severity), the p-value was (0.021, <0.001) respectively. This indicated that PD severity may be predicted by the A>G genotype ratio. Therefore, our study is the first to assess and identify the significance of SHMT1 in predicting both PD duration and severity.

Conclusion

Multiple genetic and environmental variables interact to cause the pathophysiology of Parkinson's disease. In this research, we assessed the impact of the SHMT1 A/G rs 1979277 Polymorphism in predicting the risk and severity of PD and its association with serum folate and B12 levels. We discovered that the presence of the A allele considerably increases the risk, but the G allele has a protective role.

Based on the previously identified relationship between plasma homocysteine (Hcy) level and plasma folate level, we recommend further studies correlating the assayed biomarkers with homocysteine level.

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References

- **Ayano G. (2016).** Parkinson's Disease: A Concise Overview of Etiology, Epidemiology, Diagnosis,

Comorbidity and Management. J Neurol Disord, 4: 298.

- **de Bartolomeis A, Manchia M, Marmo F, Vellucci L, Iasevoli F, Barone A. (2020).** Glycine Signaling in the Framework of Dopamine-Glutamate Interaction and Postsynaptic Density. Implications for Treatment-Resistant Schizophrenia. Front Psychiatry, 14(11):369.
- **dos Santos E, Busanello E, Miglioranza A, Zanatta Â, Barchak A, Vargas C, et al. (2009).** Evidence that folic acid deficiency is a major determinant of hyperhomocysteinemia in Parkinson´s disease. Metabolic Brain Disease, 24(2): 257-269.
- **Dunnett S, Björklund A. (1999).** Prospects for new restorative and neuroprotective treatments in Parkinson's disease. Nature, 399(6738): A32-A39.
- **Elbaz A, Carcaillon L, Kab S, Moisan F. (2016).** Epidemiology of Parkinson's disease. Revue Neurologique, 172(1): 14-26.
- **GBD 2016 Parkinson's Disease Collaborators. Global, regional, and national burden of Parkinson's disease. (1990-2016).** a systematic analysis for the Global Burden of Disease Study 2016. Lancet Neurol. 2018 Nov;17(11): 939-953.
- **Klein C, Westenberger A. (2012).** Genetics of Parkinson's disease. Cold Spring Harb Perspect Med, 2(1): a008888.
- **Kouli A, Torsney KM, Kuan WL. (2018).** Parkinson's Disease: Etiology, Neuropathology, and Pathogenesis.Parkinson's Disease: Pathogenesis and Clinical Aspects, [Internet]
- **McCarter S, Teigen L, McCarter A, enarroch E, St. Louis E, Savica R. (2019).** Low Vitamin B12 and Parkinson Disease: Potential Link to Reduced Cholinergic Transmission and Severity of Disease. Mayo Clinic Proceedings, 94(5): 757-762.
- **Nonaka H, Nakanishi Y, Kuno S, Ota T, Mochidome K, Saito Y, et al. (2019).** Design strategy for serine hydroxymethyltransferase probes based on retro-aldol-type reaction. Nat Commun, 10(1):876.
- **Nazari Mehrabani S, Shushizadeh M, Abazari M, Nouri Aleagha M, Ardalan A, Abdollahzadeh R, et al. (2019).** Association of SHMT1, MAZ, ERG, and L3MBTL3 Gene Polymorphisms with Susceptibility to Multiple Sclerosis. Biochem Genet, 57(3): 355-370.
- **Nicoletti A, Mostile G, Stocchi F, Abbruzzese G, Ceravolo R, Cortelli P, et al. (2017).** Factors influencing psychological well-being in patients with Parkinson's disease. PLoS One, 12(12): e0189682.
- **Reynolds EH. (2014).** The neurology of folic acid deficiency. Handb Clin Neurol. ,120:927-43.
- **Ryan B, Hoek S, Fon E, Wade-Martins R. (2015).** Mitochondrial dysfunction and mitophagy in Parkinson's: from familial to sporadic disease. Trends Biochem Sci, 40(4): 200-210.
- **Skibola C, Smith M, Hubbard A, Shane B, Roberts A, Law G, et al. (2002).** Polymorphisms in the thymidylate synthase and serine hydroxymethyltransferase genes and risk of adult acute lymphocytic leukemia. Blood, 99(10): 3786-3791.
- **Taximaimaiti R, Li H. (2019).** MUL1 gene polymorphisms and Parkinson's disease risk. Acta Neurol Scand, 139(5): 483-487.
- **Triantafyllou N, Nikolaou C, Boufidou F, Angelopoulos E, Rentzos M, Kararizou E, et al. (2008).** Folate and vitamin B12 levels in levodopa-treated Parkinson's disease patients: Their relationship to clinical

manifestations, mood and cognition. Parkinsonism & Related Disorders, 14(4): 321-325.

- **Wang Q, Zhang B, Yue Z. (2021).** Disentangling the Molecular Pathways of Parkinson's Disease using Multiscale Network Modeling. Trends in Neurosciences, 44(3): 182-188.