Study of cognitive impairment and genetic polymorphism of SLC41A1 (rs11240569 allele) in Parkinson’s disease in Upper Egypt: case-control study

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Abstract

Background: Parkinson’s disease is one of the neurodegenerative disorders that is caused by genetic and environmental factors or interaction between them. Solute carrier family 41 member 1 within the PARK16 locus has been reported to be associated with Parkinson’s disease. Cognitive impairment is one of the non-motor symptoms that is considered a challenge in Parkinson’s disease patients. This study aimed to investigate the association of rs11240569 polymorphism; a synonymous coding variant in SLC41A1 in Parkinson’s disease patients in addition to the assessment of cognitive impairment in those patients.

Results: In a case-control study, rs11240569 single nucleotide polymorphisms in SLC41A1, genes were genotyped in 48 Parkinson’s disease patients and 48 controls. Motor and non-motor performance in Parkinson’s disease patients were assessed by using the Movement Disorder Society-Sponsored Revision of the Unified Parkinson’s Disease Rating Scale (MDS-UPDRS). The genotype and allele frequencies were compared between the two groups and revealed no significant differences between case and control groups for rs11240569 in SLC41A1 gene with P value .523 and .54, respectively. Cognition was evaluated and showed the mean ± standard deviation (SD) of WAIS score of PD patients 80.4 ± 9.13 and the range was from 61 to 105, in addition to MMSE that showed mean ± SD 21.96 ± 3.8.

Conclusion: Genetic testing of the present study showed that rs11240569 polymorphism of SLC41A1 gene has no significant differences in distributions of alleles and genotypes between cases and control group, in addition to cognitive impairment that is present in a large proportion of PD patients and in addition to the strong correlation between cognitive impairment and motor and non-motor symptoms progression.

Keywords: Parkinson’s disease, SLC41A1, rs11240569, Dementia, Cognitive Impairment

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1. Background
Parkinson’s disease (PD) is the second most frequent neurodegenerative disease after Alzheimer disease affecting near to 1–2% of people over the age of 65 [1]. PD is clinically characterized by resting tremor, bradykinesia, postural instability and rigidity. Pathologically, characterized by the loss of pars-compacta nigral-cell and an accumulation of aggregated α-synuclein in the specific brain stem, spinal cord, and cortical regions [2].

PD is caused by both genetic and environmental factors, but its exact etiology is still unknown [3, 4]. Most of the PD patients are idiopathic, but there is some mutations have been detected in some Mendelian forms [5]. The patients with PD may be sporadic, familial, and monogenic cases with a frequency of 85%, 10–15%, and 5% of all cases, respectively [6].

There are some genes found to be direct causative factors for PD, including SNCA, PINK1, and PARKIN [7]. SNCA and LRRK2 loci have shown susceptibility for idiopathic PD [8].

SLC41A1 is one of the several genes located in PARK16 locus, a well-established susceptibility locus for PD [11, 12]. SLC41A1 encodes a cytoplasmic integral protein involved in the regulation and homeostasis of intracellular magnesium [13–15].

Cognitive impairment is an important non-motor feature that affects 50% of PD patients with disease symptoms for more than 10 years [16]. Cognitive impairment in PD patients reduces the quality of life, increases mortality, and intensifies caregiver burden [17]. Cognitive impairment in Parkinson’s disease, characterized by predominant executive deficits, visuospatial dysfunction, and relatively unaffected memory, ranges from mild cognitive impairment to severe PD dementia [18].

This study aims to investigate the association of rs11240569 polymorphism, a synonymous coding variant in SLC41A1 in Upper Egypt PD patients in addition to the assessment of cognitive impairment in those patients and correlate it with motor and non-motor symptoms.

2. Methods
A total of 48 patients diagnosed as PD who attending in-patients and outpatient clinics, according to diagnostic criteria of United Kingdom PD Brain Bank [19] in addition to 48 normal healthy control group were recruited. Motor, non-motor, and functional performance were assessed using the Movement Disorder Society-Sponsored Revision of the Unified Parkinson’s Disease Rating Scale (MDS-UPDRS) [20].

MDS-UPDRS has 4 parts. Part I is concerned with non-motor experiences of daily living, part II is concerned with motor experiences of daily living, part III is concerned with motor examination, and part IV is concerned with motor complications. Based on MDS-UPDRS scores, cut-off points to subclassify PD patients are as the following (cut-off points between mild/moderate and moderate/severe levels as follows: part 1: 10/11 and 21/22; part 2: 12/13 and 29/30; part 3: 32/33 and 58/59; and part 4: 4/5 and 12/13) [21].

Assessment of cognitive functions using an Arabic form of Mini-mental state examination (MMSE), the test was carried out as described in the original version [22], the highest possible result was 30 points, also, an Arabic [23] of the Wechsler Adult Intelligence Scale–Revised (WAIS–R) [24].

Ethical consideration
The study protocol was approved by the ethics committee of our Faculty of Medicine. Written informed consent was obtained from all participants after being informed that the confidentiality of their results will be kept along with the whole study, and thereafter.

Blood samples were taken on EDTA (in a sterile tube) and subjected to genetic testing and analysis of mutations (deoxyribonucleic acid (DNA) extraction and polymerase chain reaction (PCR)) and detection of SLC41A1 polymorphism in rs11240569 allele in PD patients and comparing the 48 patients with another 48 control group. There were also no familial relationships between the cases.

Table 1 Total score of different parts of Movement Disorder Society-Sponsored Revision of the Unified Parkinson’s Disease Rating Scale (MDS-UPDRS)

| MDS-UPDRS parts grading | Part I MDS-UPDRS | Part II MDS-UPDRS | Part III MDS-UPDRS | Part IV MDS-UPDRS |
|--------------------------|-----------------|-----------------|-----------------|-----------------|
| Mild n (%)               | 14 (29.2)       | 6 (12.5)        | 6 (12.5)        | 19 (39.9)       |
| Moderate n (%)           | 17 (35.4)       | 27 (56.3)       | 15 (31.3)       | 22(45.8)        |
| Severe n (%)             | 17 (35.4)       | 15 (31.3)       | 27 (56.3)       | 7(14.6)         |
The genetic analysis was conducted at the Molecular Biology Research Centre in our Faculty of Medicine. Genomic DNA was extracted from venous blood using a pure linked kit and the procedure recommended by the manufacturer (vivantis) extracted DNA was quantified using nanodrop analyzer model (ND-1000) Spectrophotometer (BMG Spectrostarnanodrop Technologies Inc., Ortenberg, Germany).

Polymorphism was examined using allelic discrimination Taqman assay according to manufacturer protocol (Applied Bio-system Step one plus) genotyping were performed using real time PCR with a thermal profile (60 °C for 30 s, 95 °C for 10 min, 95 °C for 15 s, 60 °C for 90 s).

Analysis of data allelic discrimination of rs11240569 (c/t) (vic/fam) (allele 1/allele 2) using 48 samples and 48 control, data interpretation show that 15 cases are homozygous for allele 1, 79 cases are homozygous for allele 2, and 2 cases are heterogenous or carrier.

Data were analyzed using Statistical Package for the Social Sciences (IBM-SPSS) version 18 (Publisher: Wiley; 1st Edition, 2011 country of origin of the software is the USA). Categorical variables were described using frequency and percentage. Means and standard deviations were computed for quantitative variables. Significance was assessed using the chi square test for categorical variables and t tests and analysis of variance (ANOVA) for quantitative variables. P value < 0.05 was regarded as statistically significant and P < 0.001 was considered highly significant.

3. Results

The mean ± standard deviation (SD) of age in this study is 61.31 ± 9.18, 36 (75%) were males and 12 (25%) were females. The mean ± SD of disease duration in this study was 4.97 ± 2.53, and 24 (50%) patients had disease duration less than 5 years, 23 (47.9%) patients between 5 and < 10 years, and only 1 patient (2.1%) had disease duration more than 10 years. Using MMSE and WAIS, cognition was evaluated and showed the mean ± SD of WAIS score of PD patients 80.4 ± 9.13, and the range was from 61 to 105. They were classified in to 50% of patients were below average and 31.3% of patients were in the borderline category. The mean ± SD of performance and verbal domain was 79.73 ± 9.4 and 85.48 ± 10.21 with range 62–105 and 66–105, respectively.

The total score of different parts of MDS-UPDRS in PD patients with different severity are summarized in Table 1.

In addition to MMSE that showed mean ± SD 21.96 ± 3.8, classified into 60.4% of patients show cognitive impairment in MMSE graded from mild to severe dementia as illustrated in Tables 2 and 3.

The results show an inverse correlation between MMSE and MDS-UPDRS part III with P value .006 which means more deterioration in cognition with more progression of motor symptoms in PD patients (Table 4).

Analysis of genotype and allele frequency distribution revealed the following frequency that is showed in Table 5. TT is the most frequent genotype in PD patients followed by CC and only one carrier CT with the following percentages respectively 85.4%, 12.5%, and 2.1%. The same also was detected in the control group with the highest genotype frequency of TT genotype followed by CC and there were no carriers with percentages of 83.3 and 16.7%, respectively. Analysis of genotype and allele frequency distribution revealed no significant differences between case and control groups for rs11240569 in SLC41A1 gene with P value .523 and .54, respectively (Table 5).

4. Discussion

This study aims to investigate the role of rs11240569 allele in PD disease SLC41A1 gene and the determination of cognitive impairment among PD patients. This study showed no significant differences in the distribution of alleles and genotypes between cases and controls, and

| Total | Verbal function | Performance |
|-------|----------------|-------------|
| Very superior (> 130) n(%) | 0 (0) | 0 (0) | 0 (0) |
| Superior(120–129) n(%) | 0 (0) | 0 (0) | 0 (0) |
| High average (110–119) n(%) | 0 (0) | 0 (0) | 0 (0) |
| Average (100–109) n (%) | 5 (10.4) | 18 (37.5) | 5(10.4) |
| Below average (80–89) N (%) | 24(50) | 17 (35.4) | 23(47.9) |
| Borderline (70–79) n (%) | 15 (31.3) | 11(22.9) | 14 (29.2) |
| Extremely low (69 and below) n(%) | 4 (8.3) | 2(4.2) | 6(12.5) |

**Table 2** Wechsler Adult Intelligence Scale among Parkinson disease patients (WAIS)
this is in agreement with previous studies in England, China, and Slovenia [25, 26].

This was in disagreement with other studies, as Callele and CC genotype of the rs11240569 polymorphism were found to be significantly associated with decreased risk of PD and this was reported in studies in Iran and China [10, 27]. Many factors may account for the variant findings between different studies. As differences in sample size and methodology must be considered, in addition to genetic heterogeneity between different populations and population stratification differences between cases and controls. Also, gene–environment and gene–gene interactions may be attributed to the varied findings across different studies, such as the rs11240569 variant may be in linkage disequilibrium with other causative variants or interact with unidentified variants of other genes.

Studies that used WAIS in PD are few. Cognitive assessment in this study showed that 50% of the patients were below average category, 31.3% of patients were borderline category, and 8.3% were extremely low by WAIS; those percentages were higher than a study in the USA which showed 10% were in below average category, 12% were in borderline category, and only 2% were in extremely low category [28–30]. This discrepancy may be due to the differences in the study design that depend on comparison with the control group and high illiteracy in the present study that had its effect on cognitive impairment.

In this study, 60% of PD patients were suffering from mild to severe dementia according to MMSE which is higher than other international studies that show about one-third of the patients suffering from mild to moderate dementia in the USA [31]. Also, it affects 40% of another study in the USA [32]. Dementia was recorded in 22.3% of PD patients in another Egyptian study, and most of them have a mild degree of dementia according to MMSE [33]. In addition to MMSE that showed mean ± SD 21.96 ± 3.8 which was lower than a study in Japan with mean ± SD 27.4 ± 2.4 [34].

Another study showed that the mean MMSE score of patients with PD was 27.4 and 17% of patients had a score below 23/30 [35]. However, MMSE may be inadequate to evaluate these cognitive dysfunctions in patients with PD.

Many factors affect cognition as age, disease duration, severity, and also level of education. It seems that the high education level can postpone the progression of the disease [36].

There was an inverse correlation between motor symptoms assessed by UPDRS part III on one side and cognitive impairment assessed by MMSE, and this was in agreement with many previous studies in England, Iran, and Morocco [37–39] which show. Thus, patients with more severe PD who have worse non-motor symptoms and motor symptoms have a less cognitive reserve; this may be explained due to depletion of more dopaminergic neurons with progression of the disease [37].

There was a negative correlation between WAIS (Verbal domain) and UPDRS Part III and this may be due to mild cognitive impairment that affects the patients, and this was noticed in another study in Italy [40] which showed typical features of cognitive impairment.

The limitation of this study is the small number of the patients and high cost of genetic analysis.
5. Conclusion
Genetic testing of the present study showed that rs11240569 polymorphism of SLC41A1 gene has no significant differences in distributions of alleles and genotypes between cases and control group. In addition to cognitive impairment that is present in a large proportion of PD patients, PD severity and disease duration are strong predictors for cognitive impairment in PD patients using MMSE. There is strong correlation between cognitive impairment and motor and non-motor symptoms progression.

Abbreviations
DNA: Deoxynucleobasic acid; MMSE: Mini-mental state examination; MDS-UPDRS: Movement Disorder Society-Sponsored Revision of the Unified Parkinson’s Disease Rating Scale; PD: Parkinson’s disease; PCR: Polymerase chain reaction; SLC41A1: Solute carrier family 41 member 1; SD: Standard deviation; WAIS: Wechsler Adult Intelligence Scale-Revised

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Authors’ contributions
HE designed the study and aim of the study and revision of the total work. TS and HS perform most of genotyping. AH, WF, and HE were responsible for collection of clinical data, scale performance, and share in results formations. AK and SS share in writing methodology and discussion. HE, AH, and WF wrote the manuscript and all authors critically reviewed the manuscript and checked the final version. All authors read and approved the final manuscript.

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All data are available within the paper.

Declarations
Ethics approval and consent to participate
The research was approved by Sohag Faculty of Medicine Ethics Committee (April 2016), and we had written informed consent from all patients (reference number is not available).

Consent for publication
Not applicable

Competing interests
The authors declare that they have no competing interests.

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