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The Association of *GSTT1* Deletion, HindIII C>G *PAI-1*, and rs11808092 Polymorphisms with Parkinson's Disease Susceptibility: A Genetic Study in an Egyptian Cohort

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Abstract

Background Parkinson's disease (PD) is a progressive neurodegenerative disorder characterized by a wide spectrum of motor and non-motor symptoms. Although the precise aetiology remains incompletely understood, a cardinal feature of the disease is the dopamine deficiency in the striatum, which is caused by the progressive loss of dopaminergic neurons in the substantia nigra pars compacta. The severity and progression of PD are commonly assessed using the Unified Parkinson's Disease Rating Scale (UPDRS).

Objectives This study aims to investigate the association of PAI-1 HindIII polymorphism (C>G), EVI5 rs11808092, and GSTT1 null genotypes with PD incidence for the first time in Egyptian cases.

Materials and methods DNA extraction of white blood cells of patients and normal controls, followed by 3 duplex PCR processes to detect the GSTT1 gene null and EVI5 rs11808092 SNPs. On the other hand, the polymerase chain reaction-restriction fragment length polymorphism (PCR–RFLP) technique was used to examine the HindIIIPAI-1 C>G locus.

Results The 50 PD patients (29 females and 21 males) had a mean age of 70.3±3.4 years, and the 100 normal controls (52 females and 48 males) had a mean age of 71.1±3.7 years. On comparison of control and PD groups, GSTT1 null polymorphism (P = 0.003), the HindIII C>G PAI-1 GC genotype (P = 0.005), and the C allele (P = 0.046) were significantly more frequent in the PD group. On the other hand, the rs11808092 polymorphism showed no significant correlation with PD susceptibility (p= 0.175).

Conclusion The findings of this study indicated a significant association between the GSTT1 null polymorphism, the HindIII C>G PAI-1 GC genotype, and the C allele, which correlates with an increased incidence of Parkinson's disease (PD) in the Egyptian PD cohort. In contrast, no significant association was found between the EVI5 rs11808092 SNP and susceptibility to Parkinson's disease (PD). This study is the first to identify genetic factors that influence both the diagnosis and progression of Parkinson's disease in the Egyptian population.

Keywords Oxidative stress; Parkinson's Disease; PD; GSTT1 gene, HindIII C>G PAI-1 GC, rs11808092; polymorphisms.

Introduction

Parkinson's disease (PD), which affects over one percent of the elderly population, presents with a wide spectrum of motor and non-motor symptoms and is the second most common neurodegenerative disorder after Alzheimer's disease. Despite extensive research, the precise aetiology of Parkinson's disease remains incompletely understood [1].

The clinical manifestations of Parkinson's disease (PD) include motor symptoms such as bradykinesia, rigidity, resting tremor, and postural instability. In addition to motor symptoms, PD also presents with non-motor symptoms such as anxiety, depression, constipation, and sensory disturbances like olfactory dysfunction [2, 3]. The severity of PD is assessed using the Unified Parkinson's Disease Rating Scale (UPDRS), which classifies the disease into four stages: minimal, mild, moderate, and severe [4]. Several pharmacological treatments for PD have been reviewed by ZhuParris et al. (2023) [4].

The hallmark of Parkinson's disease (PD) is a striatal dopamine deficit caused by the progressive loss of dopaminergic neurons in the substantianigra pars compacta [5, 6]. The depletion of neuromelanin-containing dopaminergic neurons leads to macroscopic depigmentation of the substantianigra. Microscopically, intracellular α-synuclein aggregates and dopaminergic cell damage are defining features for the definitive diagnosis of PD [2, 7]. Both plasmin activity and oxidative stress play

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significant roles in PD pathogenesis [8, 9]. Plasmin is a crucial enzyme involved in the breakdown of fibrin. Polymorphisms in the plasminogen activator inhibitor 1 (PAI-1), such as the HindIII polymorphism C>G, modulate its expression [8]. Patients with Parkinson's disease have significantly higher plasma levels of PAI-1 compared to healthy individuals, and increasing disease severity is associated with further elevations in PAI-1 levels. Several correlational studies have shown that the HindIII C/G PAI-1 polymorphism is linked to increased PAI-1 concentrations [10].

Oxidative stress contributes to both the onset and progression of Parkinson's disease (PD). Degenerating dopaminergic neurons generate reactive oxygen species (ROS) through both mitochondrial and extramitochondrial pathways. These ROS induce intracellular apoptosis and microglia-mediated neuroinflammation, which further increase oxidative stress and exacerbate neuronal damage. Antioxidants are therefore considered valuable therapeutic agents in the management of PD [9].

The human glutathione S-transferases (GSTs) are a family of enzymes that play a crucial role in the detoxification of reactive oxygen species (ROS). The GSTT1 gene is located on 22q11.23. A homozygous deletion of the GSTT1 gene leads to a complete loss of its enzyme activity. The association between this genetic deletion and susceptibility to Parkinson's disease (PD) is a subject of ongoing research. While some studies have reported a positive correlation, others have found no significant correlation, highlighting the need for further investigation to clarify the role of this genetic variation in PD pathogenesis [11].

Central nervous system (CNS) diseases such as Parkinson's disease (PD) and multiple sclerosis (MS) are chronic, progressive disorders characterized by neurodegeneration of brain and spinal cord neurons [12]. While the association between the EVI5 rs11808092 variant and MS susceptibility is well established [13], its potential link to PD—despite the shared pathology of neuronal loss—has not previously been investigated.

This study is the first to investigate the association of the PAI-1 HindIII polymorphism (C>G), EVI5 rs11808092, and GSTT1 null genotypes with Parkinson's disease (PD) susceptibility in the Egyptian population. These findings highlighted the genetic factors of PD and provided future strategies for diagnosis and enhancing our understanding of disease pathogenesis.

Subjects and methods

The study included 50 patients diagnosed with PD and 100 age- and sex-matched healthy controls. Cases have been selected from the outpatient clinic and the neurology department. The National Research Center's Medical Research Ethics Committee granted permission to the study (approval number 02410724). All of the participants provided their informed consent before being enrolled in the study.

Clinical methods

Patients who were diagnosed with PD fulfilled the criteria for diagnosis of idiopathic Parkinson's disease based on British Brain Bank criteria [14]. Exclusion criteria: patients with secondary parkinsonism (drug-induced, posttraumatic, or postinfectious) or atypical parkinsonism from June 2023 until June 2025. All patients in this study were submitted to the following: thorough history taking and neurological examination according to the standardized sheet of the Neurology Department, Kasr Al-Ainy Hospital. All patients were evaluated for Parkinson's disease severity while in their best state using the Unified Parkinson's Disease Rating Scale (UPDRS) [15].

Molecular methods

The Puregene DNA extraction kit (Gentra Systems Inc., Minneapolis, MN) was employed in genomic DNA extraction from the peripheral blood lymphocytes of 50 PD patients and 100 normal individuals. This study investigated three distinct polymorphisms: *EVI5* rs11808092, *GSTT1* gene deletion, *and HindIII* C>G PAI-1.

To detect the homozygous deletion of the GSTT1 gene, a duplex polymerase chain reaction (PCR) assay was performed using two primer pairs targeting specific regions of the GSTT1 gene and the β-globin housekeeping gene, which served as an internal control (Table 1). The presence of both 480 bp (GSTT1) and 268 bp (β-globin) amplification products confirms the presence of the GSTT1 gene. Conversely, amplification of only the 268 bp β-globin fragment indicates a homozygous deletion of GSTT1. Applying the polymerase chain reaction-restriction fragment length polymorphism (PCR–RFLP) technique to examine the Hind III PAI-1 C>G locus starts by designing a pair of primers (Table 1),generating 600 bp amplification fragments. This 600 bp product is digested for one hour at 37°C via the HindIII restriction enzyme (New England Biolabs, Beverly, Mass.). Following digestion, the existence of a 600 bp fragment denotes the presence of the G allele; however, the C allele forms a HindIII restriction site that gives two fragments, spanning 371 bp and 229 bp.

Table (1) represents the primer sequence of *GSTT1*, β-globin and Hind III PAI-1 C>G polymorphisms.

Polymorphism	Sequence of primers	Annealing temperature	Amplification size (bp)
Hind III PAI-1 C>G	F: 5′-CTGGCCCGCTGTTCTTTAG-3′ R:5′-GGTTTCACGCCATTCTCCTG-3′	57.9	600
GSTT1	F:5'-TTCCTTACTGGTCCTCACATCTC-3' R:5'-TCACCGGATCATGGCCAGCA-3'	60.9	480
β-globin	F:5'-CAACTTCATCCACGTTCACC-3' R:5'-GAAGAGCCAAGGACAGGTAC-3'	60.9	268

To investigate the presence of the G allele at the EVI5 rs11808092 locus, two duplex PCR assays were performed. The first assay utilizes non-allele-specific primers (forward outer and reverse outer) to amplify a 589 bp fragment, serving as an internal control to confirm successful amplification. Additionally, a forward inner primer paired with the reverse outer primer yields a 266 bp product if the G allele is present. Therefore, the simultaneous detection of both 266 bp and 589 bp fragments indicates the presence of the G allele, whereas amplification of only the 589 bp fragment signifies its absence.

- Forward outer primer (5' - AATACTAGTAAATGCCAATCCAGGAAA - 3') with 1.5 µM concentration
- Reverse outer primer (5' - TCAGCCTTGAATGACTTGATTTTAA - 3') with 3 µM concentration.
- Forward inner primer (G allele): (5' - CAGAAAGATACTGCACTTTCCCC- 3') with 1.5 µM concentration

The second duplex PCR assay is designed to detect the presence of the T allele. It utilizes two non-allele-specific primers (forward outer and reverse outer) to amplify a 589 bp fragment, serving as an internal control for successful PCR

amplification. In the presence of the T allele, a reverse inner primer in combination with the forward outer primer generates an additional 373 bp product. Therefore, the simultaneous amplification of both 373 bp and 589 bp fragments confirms the presence of the T allele, whereas the presence of only the 589 bp fragment indicates its absence.

- Forward outer primer (5' - AATACTAGTAAATGCCAATCCAGGAAA - 3') with 3 µM concentration
- Reverse outer primer (5' - TCAGCCTTGAATGACTTGATTTTAA - 3') with 1.5 µM concentration.
- Reverse inner primer (T allele): (5'-GCAGAACAAGAGGTGATTAGCCTATAT-3') with 1.5 µM concentration.

The typical PCR method requires a 5-minute primary denaturation stage at 95°C, followed by 40 cycles, including a half-minute denaturation at 95°C, a half-minute annealing step at a suitable annealing temperature, a minute extension step at 72°C, and then ending with an extension for 7 minutes at 72°C. To examine the PCR outcomes, a 2.5% agarose gel stained with ethidium bromide was employed for gel electrophoresis.

Statistical analysis

IBM SPSS Statistics (Statistical Package for the Social Sciences) software version 28.0, IBM Corp., Chicago, USA, 2021, was employed to code, tabulate, and statistically analyze the collected information. ANOVA and the independent t-test were applied to compare the quantitative data, which were interpreted as the mean ± SD (standard deviation) and the range's minimum and maximum. The chi-square and Fisher's exact tests served to compare qualitative data, which was defined as numbers and percentages. For post hoc comparisons, the Bonferroni test was used. The significance level was established at a p-value of less than 0.050.

Results

This study included 100 normal controls (52 females and 48 males) with a mean age of 71.1±3.7 years and 50 PD instances (29 females and 21 males) with a mean age of 70.3±3.4 years. Age and sex were matched between the two cohorts. The p-value went beyond 0.05 (Table 2).

Table (2) represents the age and sex between PD and control groups.

Variables		PD group (Total=50)	Control group (Total=100)	p-value
Age (years)	Mean ±SD	70.3±3.4	71.1±3.7	0.208
	Range	65.0–79.0	63.0–77.0	
Sex (n, %)	Male	29 (58.0%)	52 (52.0%)	0.487
	Female	21 (42.0%)	48 (48.0%)	

There were no statistically significant differences in age or sex between the study groups, as shown in Table 2.

Motor clinical manifestations of PD included tremors (48%), bradykinesia (26%), and rigidity (26%), while non-motor symptoms comprised constipation (62%), insomnia (66%), and anosmia (6%). Hypertension and diabetes mellitus were present in 40% and 22% of cases, respectively. A family history of PD was reported in 14% of patients. The primary treatment regimens included Sinemet (86%) and Parkintreat (40%), with Ramixole (22%) and Stalevo (18%) used less frequently. This therapeutic approach achieved disease control in 52% of cases. The mean age of onset for PD cases was 64.5 ± 3.5 years, and the mean duration of illness was 6.1 ± 3.1 years. The average severity scores for PD, as measured by UPDRS parts 1 through 4, were 17.0 ± 11.5, 20.6 ± 13.5, 35.3 ± 17.4, and 6.8 ± 6.6, respectively (Table 3).

Table (3) represents the clinical characteristics of the PD group.

Variables		n	%
Hypertension		20	40.0%
Diabetes mellitus		11	22.0%
Family history		7	14.0%
First motor symptom	Tremors	24	48.0%
	Bradykinesia	13	26.0%
	Rigidity	13	26.0%
Non-motor symptom	Constipation	31	62.0%
	Insomnia	33	66.0%
	Anosmia	3	6.0%
Treat	Sinemet	43	86.0%

ment	**Parkintreat**	20	40.0%
	Stalevo	9	18.0%
	Ramixole	11	22.0%
Control	**Controlled**	26	52.0%
	Uncontrolled	24	48.0%
		Mean±SD	**Range**
Age of onset (years)		64.5±3.5	58.0–72.0
Duration of illness (years)		6.1±3.1	1.0–15.0
UPDRS 1		17.0±11.5	5.0–42.0
UPDRS 2		20.6±13.5	7.0–50.0
UPDRS 3		35.3±17.4	17.0–70.0
UPDRS 4		6.8±6.6	1.0–20.0
UPDRS total		79.6±41.9	34.0–155.0

Total= 50.

Table 3 shows that more than half of the studied cases (52.0%) achieved disease control following treatment.

The genotypes and allele frequencies of EVI5 rs11808092, HindIII C>G PAI-1, and GSTT1 null SNPs in both PD and control groups are presented in Table 4. Comparison between the control and PD groups revealed that the GSTT1 null polymorphism (P = 0.003), the HindIII C>G PAI-1 GC genotype (P = 0.005), and the C allele (P = 0.046) were significantly more frequent in the PD group. In contrast, the rs11808092 polymorphism showed no significant association with PD cases (P = 0.175).

Table (4) represents the molecular finding between PD and control groups.

Variables		**Parkinsonism group (Total=50)**	**Control group (Total=100)**	**p-value**	**Odds ratio (95% CI)**
GSTT1	**Positive**	26 (52.0%)	76 (76.0%)	**0.003***	0.34 (0.17–0.70)
	Negative	24 (48.0%)	24 (24.0%)		Reference
***HindIII*C>G PAI-1**	**GG**	9 (18.0%)	41 (41.0%)	**0.005***	0.32 (0.14–0.72)
	GC	41 (82.0%)	59 (59.0%)		Reference
rs11808092	**CC**	31 (62.0%)	53 (53.0%)	0.175	0.58 (0.16–2.18)
	CA	14 (28.0%)	42 (42.0%)		0.33 (0.08–1.32)
	AA	5 (10.0%)	5 (5.0%)		Reference
Alleles		**Total=100**	**Total=200**		
***HindIII*C>G PAI-1**	**G**	59 (59.0%)	141 (70.5%)	**0.046***	0.60 (0.37–0.99)
	C	41 (41.0%)	59 (29.5%)		Reference
rs11808092	**C**	76 (76.0%)	148 (74.0%)	0.707	1.11 (0.64–1.94)
	A	24 (24.0%)	52 (26.0%)		Reference

*Significant (p-value <0.050). CI: Confidence Interval.

Table 4 shows that the Parkinsonism group had a significantly higher frequency of the GSTT1 null genotype, as well as greater expression of the HindIII C>G PAI-1 GC genotype and its C allele.

Controlled PD cases demonstrated a highly significant association with the presence of the GSTT1 gene (P=0.011), while no correlation was observed between other SNPs and controlled PD cases (Table 5).

Table (5) represents the genetic studies between control status.

Variables		Controlled (Total=26)	Not controlled (Total=24)	p-value	Odds ratio (95% CI)
GSTT1	Positive	18 (69.2%)	8 (33.3%)	0.011*	4.50 (1.37–14.78)
	Negative	8 (30.8%)	16 (66.7%)		Reference
Pa1	GG	5 (19.2%)	4 (16.7%)	0.99	1.19 (0.28–5.08)
	GC	21 (80.8%)	20 (83.3%)		Reference
rs11808092	CC	18 (69.2%)	13 (54.2%)	0.403	0.92 (0.13–6.34)
	CA	5 (19.2%)	9 (37.5%)		0.37 (0.05–3.01)
	AA	3 (11.5%)	2 (8.3%)		Reference
Alleles		Total=52	Total=48		
Pa1	G	31 (59.6%)	28 (58.3%)	0.896	1.05 (0.47–2.34)
	C	21 (40.4%)	20 (41.7%)		Reference
rs11808092	C	41 (78.8%)	35 (72.9%)	0.488	1.38 (0.55–3.48)
	A	11 (21.2%)	13 (27.1%)		Reference

*Significant (p-value <0.050). CI: Confidence Interval.
Table (5) showed that: Cases with controlledparkinsonism had significant more frequent GSTT1 gene.

Table (6) represents the clinical characteristics according to the studied SNPs among the PD group.

Variables			UPDRS 1	UPDRS 2	UPDRS 3	UPDRS 4	UPDRS total
GSTT1	Positive	6	13.9±11.7	15.9±10.7	31.0±15.6	4.9±5.9	65.7±37.0
	Negative	4	21.1±11.1	26.3±13.7	43.0±16.6	9.6±6.5	100.0±38.1
	p-value		0.029*	0.004*	0.011*	0.010*	0.002*
Pa1	GG		19.0±12.1	26.6±14.2	35.7±20.8	6.6±6.7	87.8±43.3
	GC	1	17.0±11.9	19.6±12.8	37.0±16.4	7.3±6.6	81.0±40.9
	p-value		0.651	0.155	0.832	0.756	0.656
rs11808092	CC	1	17.2±11.5	20.3±13.9	35.6±16.1	6.2±6.0	79.3±40.1
	CA	4	20.6±13.2	20.4±10.8	39.8±18.6	9.5±7.4	90.2±43.4
	AA		9.6±6.8	25.8±16.6	35.4±21.5	6.6±7.2	77.4±45.6
	p-value		0.206	0.687	0.747	0.300	0.694

*Significant (p-value <0.050).
Table 6 showed that PD cases with the positive GSTT1 gene had considerably lower UPDRS scores.

Images of gel electrophoresis for the HindIII PAI-1 C>G variant and the homozygous deletion of GSTT1, performed on a 2% agarose gel stained with ethidium bromide, are shown in Figure 1. Images illustrating the rs11808092 (EVI5: c.1884G>T) variant are presented in Figure 2.

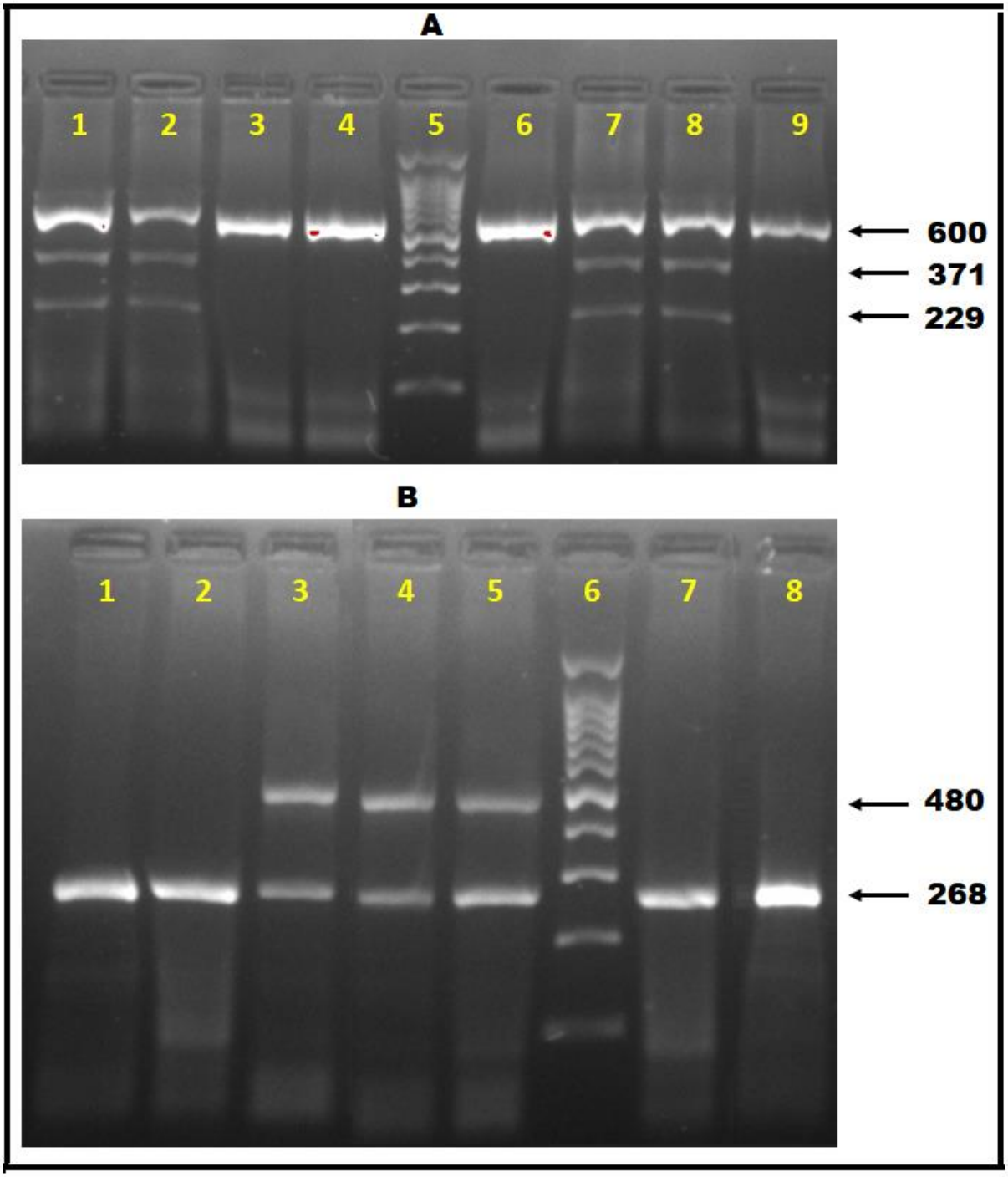

Figure 1.showsa gel electrophoresis image of the *Hind III* PAI-1 C>G and homozygous deletion of *GSTT1*using 2% agarose. A) There is a band of 600 bp in lanes 3, 4, 6, and 9 representing the GG genotype, while three bands of 600 bp, 371 bp, and 229 bp were present in lanes 1, 2, 7, and 8, indicating the GC genotype. Lane 5 had the 100 bp marker. **B)** Lanes 1, 2, 7, and 8 show a single band of 268 bp, indicating the existence of the β-globin gene without the *GSTT1* gene. Lanes 3, 4, and 5 had two bands of 268 and 480, implying the presence of the *GSTT1* gene. Lane 6 had the 100 bp marker.

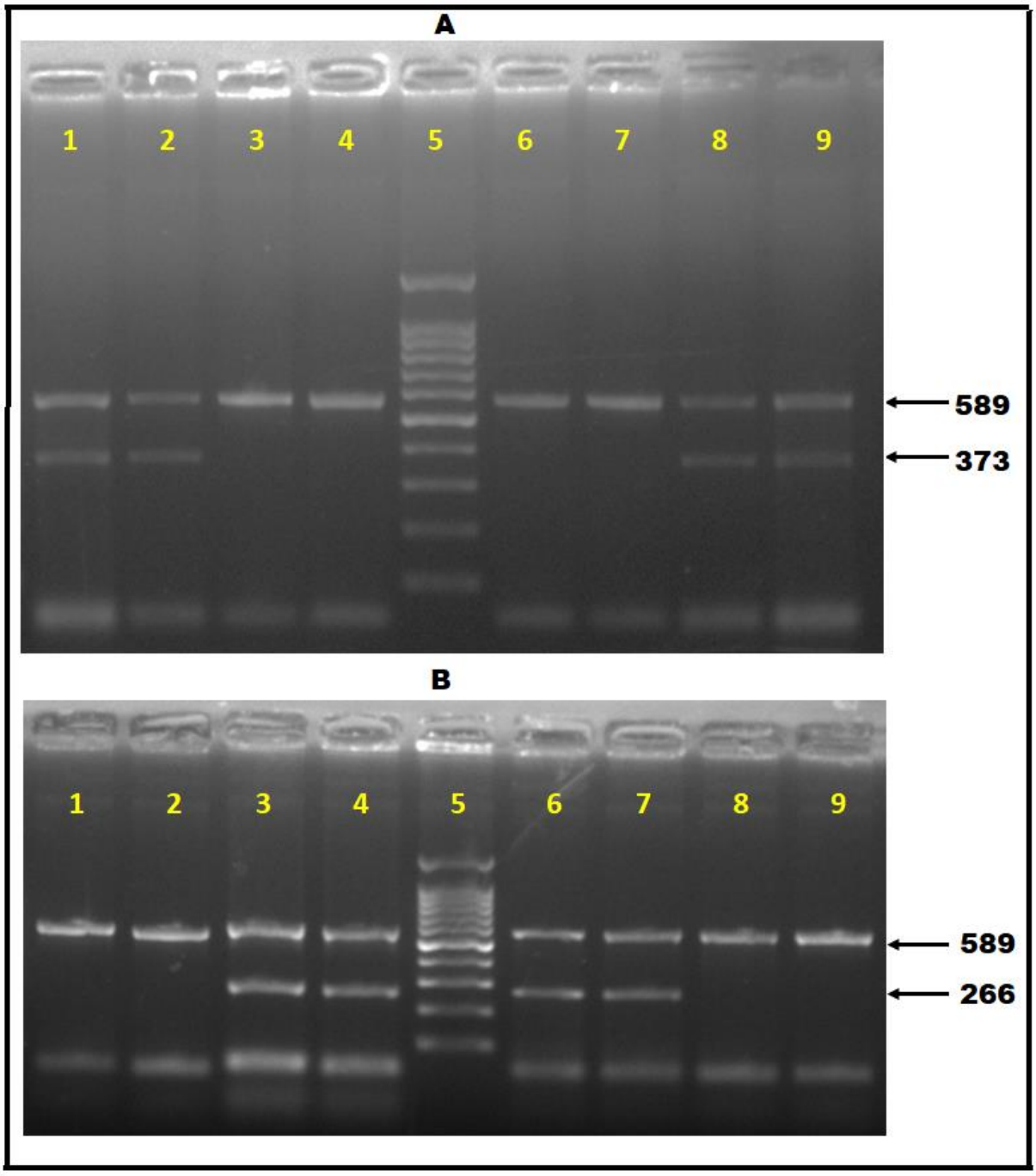

Figure 2.showsa gel electrophoresis image of the rs11808092: *EVI5*: c.1884G>T using 2% agarose. A) Lanes 1, 2, 8, and 9 revealed two bands of 589 bp and 373 bp, indicating the presence of the T allele in the rs11808092 SNP, while lanes 3, 4, 6, and 7 had a band of 589 bp, so the T allele is not present in the rs11808092 SNP. Lane 5 represents a 100 bp marker. **B**) Lanes 1, 2, 8, and 9 show a band of 589 bp, revealing the absence of the G allele in the rs11808092 SNP, while lanes 3, 4, 6, and 7 had two bands of 589 bp and 266 bp, showing the existence of the G allele in the rs11808092 SNP. Finally, a 100 bp marker is in lane 5.

Discussion

Parkinson's disease (PD) is a progressive neurodegenerative disorder that primarily impairs the motor system. In our study population, the main motor symptoms observed were tremors, bradykinesia, and rigidity. Tremors were present in 48% of cases, which is lower than the 70% prevalence of resting tremors reported by Burton (2008) [16]. Non-motor manifestations were also common in our cohort: constipation was reported in 62% of cases, consistent with Pedrosa et al. (2018) [17], who noted that two-thirds of PD patients experience constipation. Insomnia affected 66% of our patients, whereas

Duan et al. (2025) [18] reported that insomnia occurs in up to 90% of PD cases. Anosmia was observed in 6% of our patients, which contrasts with the findings of Tarakad et al. (2017) [19], who reported anosmia in approximately 50% of PD cases.

Hypertension was observed as a non-motor manifestation in 40% of our PD cases, consistent with the findings of Hou et al. (2018) [20], who identified hypertension as a susceptibility factor during the motor stage of PD. Additionally, 20% of our PD cases had type II diabetes mellitus, aligning with Cheong et al. (2020) [21], who described diabetes mellitus as a susceptibility factor for PD and suggested that neurodegeneration may occur through activation of the insulin signaling pathway.

In our study, Parkinson's disease was predominantly sporadic, with only 14% of cases reporting a family history. This finding is consistent with Papapetropoulos et al. (2007) [22], who reported that only 10–15% of PD cases had a family history, while the majority were sporadic.

PD cases exhibit a marked loss of dopaminergic neurons in the substantianigra pars compacta [23]. Consequently, dopamine agonists or drugs that inhibit dopamine degradation are central to PD treatment strategies. In the current study, the following medications were administered to PD patients: Sinemet® (levodopa, carbidopa) in 86% of cases, Parkintreat® (monoamine oxidase B inhibitor) in 40%, Ramixole® (dopamine agonist) in 22%, and Stalevo® (levodopa, carbidopa, entacapone; catechol-O-methyltransferase inhibitor) in 18%. These therapies increase central nervous system (CNS) dopamine levels, which remains the primary approach for PD management [4]. Overall, these treatments maintained controlled PD in 52% of cases.

This study included 100 healthy controls and 50 PD patients, matched for age and gender, with no statistically significant difference between groups ($p > 0.05$; Table 2). The female-to-male (F:M) ratio among our PD cases was 1.38, consistent with ratios reported by Kimura et al. (2002) [24] and Park et al. (2019) [25] in Japanese and Korean populations, respectively. In contrast, a global study of PD cases in 2016 found a male-to-female (M:F) ratio of 1.4 [26].

The mean age of onset among our PD cases was 64.5 ± 3.5 years. Pagano et al. (2016) [27] reported that 13.7% of PD cases had an onset age of less than 50 years, while the proportions for the age ranges 50–59, 60–69, and 70 years or older were 27.7%, 39.8%, and 18.7%, respectively. In our study, the mean disease duration was 6.1 ± 3.1 years. The mean severity scores for PD, as assessed by UPDRS 1, UPDRS 2, UPDRS 3, and UPDRS 4 were 17.0 ± 11.5, 20.6 ± 13.5, 35.3 ± 17.4, and 6.8 ± 6.6, respectively (Table 3). The aetiology of classical PD involves both environmental and genetic factors [28], whereas early-onset Parkinsonism is primarily attributed to mutations in monogenic genes, as reviewed by Riboldi et al. (2022) [29].

The pathobiology of several central nervous system (CNS) diseases, including Parkinsonism, is influenced by oxidative stress. Oxidants contribute to significant neuronal degeneration, and reactive oxygen species (ROS) are key elements in the molecular pathways underlying neurodegeneration. As a result, therapeutic strategies for PD often include synthetic antioxidants [9]. The GSTT1 gene encodes a phase II biotransformation enzyme that eliminates ROS and protects against lipid peroxidation and neuronal damage [11]. In the current study, the GSTT1 null polymorphism showed a strong association with PD susceptibility (OR=0.34, 95% CI: 0.17–0.70, P=0.003) compared to the control group. This finding consistent with Rebai et al. (2021) [11], who reported a significant relationship between homozygous GSTT1 deletion and PD cases from North Africa (OR=5.45, 95% CI: 2.90–10.30, p=10−6). Additionally, Stroombergen and Waring (1999) and Singh et al. (2008) found a significant association between the GSTT1 null genotype and PD cases [30, 31].

Conversely, some studies have found no association between PD susceptibility and the GSTT1 null genotype [32, 33]. In our study, however, the GSTT1 null genotype was significantly associated with non-controlled PD cases compared to those with the GSTT1 gene (OR = 4.50, 95% CI: 1.37–14.78, P = 0.011; Table 5). PD cases with the GSTT1 null genotype also had significantly higher UPDRS scores (Table 6). Aggregation of alpha-synuclein (α-syn) protein in the substantianigra leads to the formation of Lewy body inclusions, which contribute to degeneration of dopaminergic neurons and the pathogenesis of Parkinson's disease. Plasmin, a protease, has been found to degrade extracellular α-syn and reduce Lewy body inclusions, thereby lowering susceptibility to parkinsonism. Plasminogen, the precursor of plasmin, requires activation by plasminogen activators to become active plasmin. Plasminogen activator inhibitor-1 (PAI-1) inhibits the activation of plasminogen, so increased PAI-1 levels reduce plasmin activity, leading to greater α-synuclein accumulation and increased susceptibility to PD [34]. Polymorphisms in the PAI-1 gene, such as the HindIII C>G variant, modulate PAI-1 expression [8]. The HindIII C/G PAI-1 polymorphism has been shown to be highly associated with multiple sclerosis, another neurological disorder [35], and is also linked to higher PAI-1 concentrations, which may increase PD susceptibility [10]. Consistent with these findings, our study demonstrated that the HindIII C>G PAI-1 GC genotype (OR = 0.32, 95% CI: 0.14–0.72, P = 0.005) and the C allele (OR = 0.60, 95% CI: 0.37–0.99, P = 0.046) were significantly associated with PD cases. No association was found between the HindIII C>G PAI-1 GC genotype or the C allele and controlled parkinsonism or UPDRS scores (Tables 5 and 6).

Parkinson's disease (PD) and multiple sclerosis (MS) are chronic, progressive disorders characterized by degeneration of brain and spinal neurons [12]. The EVI5 rs11808092 SNP has a well-established association with MS susceptibility [13]. In the current study, we evaluated the association of this SNP with PD susceptibility. No significant association was found between EVI5 rs11808092 and PD susceptibility, clinical manifestations, or UPDRS scores. This lack of association may be attributed to ethnic variability, limited sample size, or disease specificity.

Limitations of this study

This study is limited by a modest sample size, its focus on only three SNPs, and the absence of functional assays. Future research should involve larger cohorts, investigate additional genetic markers, and include mechanistic studies to validate these associations.

Conclusion

Our findings revealed significant associations between the GSTT1 null polymorphism, the HindIII C>G PAI-1 GC genotype, and the C allele with increased incidence of PD in the Egyptian cohort. In contrast, no association was observed between the EVI5 rs11808092 SNP and PD susceptibility. This is the first study in Egypt to screen these SNPs, providing new insights into the genetic diagnosis and pathogenesis of Parkinson's disease in the Egyptian population.

Authors' contributions

This work was carried out in collaboration between all authors. T.H.A.A. designed, wrote the protocol and coordinate the study. H.T.E., G.M.R., H.E., and K.H. performed the clinical study for the patients and their families and recruited the patients samples. T.H.A.A. and E.E.A.M. performed the molecular analysis, results interpretation, literature searches. T.H.A.A. wrote the first draft of the manuscript. H.M.H. provided statistical data analysis. All authors read, revised, and approved the submitted manuscript. T.H.A.A. (guarantor) has the responsibility for the integrity of the work as a whole from inception to published article. The manuscript has been read and approved by all the authors, that the requirements for authorship as stated earlier in this document have been met, and that each author believes that the manuscript represents honest work.

Conflict of interest

The Authors declare that there is no conflict of interest.

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