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Research article

The impacts of prominent gene polymorphisms in DNA repair enzymes on Parkinson's disease

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ABSTRACT

Parkinson's Disease (PD), a chronic and progressive neurodegenerative disease of the brain, is associated with the loss of dopaminergic neurons. Its pathogenesis remains unclear; however, oxidative DNA damage due to reactive oxygen species (ROS) is believed to play a major role in the etiology of PD. DNA repair systems can mitigate oxidative DNA damage and help to maintain genomic stability and thus prevent neuronal death. However, gene polymorphisms on DNA repair enzymes may alter the functions of enzymes and increase the risk of PD. The present study aims to investigate a possible link between the *OGG1*, *XRCC1*, and *MTH1* gene polymorphisms and PD risk in 97 patients with PD and 102 controls in the Turkish population. Our genotyping study utilizing polymerase chain reaction-restriction fragment length polymorphism revealed no relationship between two gene polymorphisms (*OGG1Ser326*Cys and *MTH1Val83Met*) and PD risk. Participants with the *XRCC1* variant genotypes had a two to three and a half fold higher risk of PD than controls (p = 0.046, OR = 1.910, 95 % CI= [1.013–3.603] and p = 0.006, OR = 3.742, 95 % CI= [1.470–9.525], respectively). Our results suggested that *XRCC1 Arg399Gln* polymorphism is a risk factor for PD.

1. Introduction

Parkinson's disease (PD) is a neurodegenerative process that affects approximately 1 % of the population over 65 years old. PD is a neurological disease with a multifactorial etiology that includes environmental (such as cigarette smoke, pesticides, herbicides, and heavy metals) and genetic factors [1–3]. The pathogenesis of PD still remains obscure; however, current evidence supports that an age-related increase in oxidative DNA damage may be the main risk factor [4]. Studies have shown that reactive oxygen species (ROS) are generated excessively in the brains of patients with PD and may attack macromolecules like DNA [5–7]. Many studies have also confirmed that ROS and oxidative DNA damage are part of pathological processes during PD [7,8], but it has not yet been determined whether this is a major event or a result of other cellular dysfunctions. Genetic polymorphisms may alter or decrease DNA repair capacity and affect the susceptibility to PD. Analysis of the polymorphisms of DNA repair enzymes can clarify whether PD may arise from a genetic predisposition to oxidative stress [8]. Enhanced production of 8-hydroxy-2´-deoxyguanosine (8-OHdG), a marker of DNA damage induced by ROS in the midbrain of patients with PD, creates laboratory evidence of oxidative damage [5]. It is an oxidized form of guanine, yielding G:C to T:A transversion. Organisms have many protective mechanisms against oxidative DNA damage, including the base excision repair (BER) pathway. In BER, 8-oxoG DNA glycosylase (*hOGG1*), which is encoded by the human *OGG1* gene, recognizes and removes the altered base (8-OHdG) [6,9]. *OGG1* is polymorphic and has several polymorphisms. The higher expression levels of *OGG1* enzymes have been found in patients with PD [6].

Another repair enzyme that also has a major role in BER is X-ray repair cross-complementing 1, encoded by the *XRCC1* gene. The protein participates in the repair of DNA single-strand breaks and interacts with *OGG1*, poly (ADP-ribose) polymerase (PARP), DNA ligase III, and DNA polymerase β in BER [10–12]. Three polymorphisms (*Arg/Gln*, *Arg/His*, and *Arg/Trp*) have been described in the *XRCC1* gene. One of them is the *Arg399Gln* polymorphism that has been shown to alter DNA repair capacity [13]. The codon 399 polymorphism has been shown to affect DNA repair capacity, while the significance of the other two polymorphisms is not yet known in genotoxic measurement [14].

Human *MTH1*, an oxidized purine nucleoside triphosphatase, has a major role in BER, in that it hydrolyzes 8-oxo-dGTP and 2-hydroxy-dATP in the nucleotide pool. *MTH1* is considered a potential marker of oxidative DNA damage since its function is to reduce the accumulation of oxidized nucleotides in DNA [15]. Its activity can, therefore, be used

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to understand the association between oxidative stress and genomic instability. *MTH1* is overexpressed in neuron cells in patients with PD [16].

Many studies have been conducted on *OGG1, XRCC1*, or *MTH1* single nucleotide polymorphisms in human populations, allowing us to compare our results against them [6,11,17–19]. Previous studies investigating the association of the *OGG1*, *Ser326Cys*, and *XRCC1 Arg399Gln* variant polymorphisms with PD have produced inconsistent results. Some studies have found a significant association between the polymorphisms in these genes and PD. Other studies have shown no significant association. One study showed no significant association between the *MTH1 Val83Met* polymorphism and PD risk [15]. However, to our knowledge, no study has yet investigated the impacts of all three polymorphisms, which have major roles in BER, together on the risk of PD. Therefore, we investigated the relationship between the *OGG1 Ser326Cys*, *XRCC1 Arg399Gln*, and *MTH1 Val83Met* gene polymorphisms and the risk of PD. Moreover, we also carried out a subgroup modeling analysis.

2. Materials and methods

2.1. Patient selection

This study was conducted on 102 patients (46 females and 56 males) with a mean age of 65.5 ± 11.6 years (range 38–91 years) who were diagnosed with PD. A matched control group, consisting of 97 healthy participants (48 females and 49 males) with a mean age of 62.1 ± 9.6 years (range 31–82 years) and a similar lifestyle, was also recruited. Table 1 shows the differences in age between the patients and the controls. All participants were asked questions about their lifestyle, including questions about smoking, caffeine consumption, alcohol consumption, and history of diabetes mellitus (DM). The literature has shown that DM is a major contributor to PD. The exclusion criteria of our study group included repeated strokes and head injury, antipsychotic or dopamine-depleting drugs, definite encephalitis and/or oculogyric crisis not caused by drugs, and exposure to known neurotoxins. In this study, the controls were randomly selected from patients who had visited the neurologic clinic of Ankara Numune Hospital and were diagnosed as not having PD by neurologists. DNA isolation was performed from peripheral blood samples in PD and healthy participants. *OGG1 Ser326Cys*, *XRCC1 Arg399Gln*, and *MTH1 Val83Met* gene polymorphism measurements were performed in PD and healthy participants using polymerase chain reaction (PCR) and restriction fragment length polymorphism (RFLP). This study was approved by the Gazi University Ethical Committee for Clinical Research on Human Subjects (ethical number 2016/346).

Table 1
Demographic and clinical characteristics of patients with PD and controls.

	Controls (n = 97)	PD patients (n = 102)	P value
Mean Age ± SD(years)	62.1 ± 9.6	65.5 ± 11.6	0.027†
Age, *n (%)*			0.013‡
< 65	53 (54.6)	37 (37.0)	
≥65	44 (45.4)	63 (63.0)	
Gender, *n (%)*			0.536‡
Women	48 (49.5)	46 (45.1)	
Man	49 (50.5)	56 (54.9)	
Smoking Habit, *n (%)*			0.211‡
Non-smokers	49 (52.7)	61 (61.6)	
Smokers	44 (47.3)	38 (38.4)	
DM History, *n (%)*			0.095¶
Yes	82 (88.2)	62 (77.5)	
No	11 (11.8)	18 (22.5)	

† *Student's t test*, ‡ *Pearson's* χ^2 test, ¶ Continuity corrected χ^2 test, $ *Fisher's exact* test.

2.2. Genotyping analyses

2.2.1. OGG1 gene polymorphism

Approximately 100 ng of genomic DNA was added to the 15 µl PCR containing 0.2 mM dNTP, 2 mM $MgCl_2$, 0.6 pmol primer *F* (5′- ACTGT CACTAGTCTCACCAG -3′) and *R* (5′-TGAATTCGGAAGGTGCTTGGGG AAT-3′) 1*U Taq* polymerase, and 10x*Taq* buffer $(NH_4)_2SO_4$. The initial denaturation of 2 min at 94 °C was followed by 33 cycles of amplification beginning with denaturation for 15 s at 94 °C, annealing for 30 s at 60 °C, and extension for 35 s at 72 °C. The reaction was completed by a final extension for 10 min at 72 °C.

2.2.2. XRCC1 gene polymorphism

Approximately 50 ng of genomic DNA was added to the 15 µl PCR containing 0.2 mM dNTP, 2 mM $MgCl_2$, 0.6 pmol primer *F* (5′-CAGTG GTGCTAACCTAATC-3′) and *R* (5′-AGTAGTCTGCTGGCTCTGG-3′), 1*U Taq* polymerase, and 10x*Taq* buffer $(NH4)_2SO_4$. The initial denaturation of 2 min at 94 °C was followed by 35 cycles of amplification beginning with a denaturation step for 30 s at 94 °C, annealing for 45 s at 58 °C, and extension for 1 min at 72 °C. The reaction was completed by a final extension for 7 min at 72 °C.

2.2.3. MTH1 Val83Met gene polymorphism

Approximately 200 ng of genomic DNA was added to the 15 µl PCR containing 0.2 mM dNTP, 2 mM $MgCl_2$, 0.6 pmol primer *F* (5′-CATGG CACCATGCCCTGA-3′) and *R* (5′-GAGATGGGACCC GCATAG-3′), 1*U Taq* polymerase, and 10x*Taq* buffer $(NH_4)_2SO_4$. The initial denaturation for 5 min at 94 °C was followed by 35 cycles of amplification beginning with a denaturation step for 90 s at 94 °C, annealing for 60 s at 58 °C, and extension for 1 min at 72 °C. The reaction was completed by a final extension for 7 min at 72 °C.

For all three (*OGG1, XRCC1* and *MTH1*) gene polymorphisms, the amplified products are 207 bp, 871 bp, and 247 bp, respectively, and were resolved on a 2% agarose gel containing 5 µg/mL ethidium bromide and visualized under UV light.

2.3. Restriction enzyme digestion of PCR product

Enzyme digestions of the PCR products were performed in a final volume of 15 µl at 37 °C for 16 h using 0.08 µl of *SatI* for *OGG1 Ser326Cys* [9], 0.5 µl *HpaII* for *XRCC1 Arg399Gln* [13], and 0.5 µl of *NsiI* for *MTH1 Val83Met* [20]. The enzyme *SatI* recognizes the variant-type alleles of *codon 326*. It has a single recognition site on the 207 bp fragment. The variant allele results in two fragments of 107 and 100 bp; the wild-type allele is present as an undigested 207 bp fragment. The enzyme *HpaII* recognizes the wild-type alleles and variant-types alleles of *codon 399*. It has two recognition sites for wild type and one recognition site for variant types on the 871 bp fragment. Thus, the wild-type allele of *codon 399* generates three fragments of 461, 278, and 132 bp, while the variant allele leads to two fragments of 593 and 278 bp.

The enzyme *NsiI* recognizes the variant-type alleles of *codon 83*. It has a single recognition site on the 247 bp fragment. The variant allele results in two fragments of 150 and 97 bp; the wild-type allele is present as an undigested 247 bp fragment.

2.4. Statistical analyses

Statistical analysis of the data was performed using the IBM SPSS Statistics 17.0 (IBM Corporation, Armonk, NY, USA) package program. The mean differences in ages between groups were compared using Student's *t*-test. Pearson's Chi-square test was used in the analysis of categorical data unless otherwise stated. In the 2 × 2 contingency tables for comparison of the categorical variables, the continuity corrected Chi-square test was used when one or more of the cells had an expected frequency of 5–25; otherwise, Fisher's exact test was used when one or more of the cells had an expected frequency of 5 or less.

Table 2
Allele frequency distributions of *OGG1*, *XRCC1* and *MTH1* genes and risk of PD.

Polymorphism	Control (n = 97)	PD (n = 102)	p value†	OR (95 % CI)
OGG1 allele frquency				
Ser	145 (74.7 %)	156 (82.1 %)	Ref	1.000
Cys	49 (25.3 %)	34 (17.9 %)	0.081	0.645 (0.394 − 1.055)
XRCC1 allele frequency				
Arg	137 (73.7 %)	106 (57.6 %)	Ref	1.000
Gln	49 (26.3 %)	78 (42.4 %)	< 0.001	2.057 (1.328 − 3.188)
MTH1 allele frequency				
Val	179 (95.2 %)	186 (95.9 %)	Ref	1.000
Met	9 (4.8 %)	8 (4.1 %)	0.753	0.855 (0.323 − 2.266)

Ref: *Ser* allele for *OGG1*, *Arg* allele for *XRCC1* and *Val* allele for *MTH1* were assumed as reference categories which their odds ratios were set at 1.000. † Univariate logistic regression analysis, PD: Parkinson's Disease, OR: Odds Ratio, CI: Confidence Interval.

We used the Chi-squared ($\chi 2$) test to verify the Hardy–Weinberg equilibrium of the alleles analyzed. Odds ratios (ORs) and 95 % confidence intervals (95 % CIs) were also calculated to detect allele and genotype differences in PD. We tested whether or not the gene polymorphisms had a statistically significant effect on PD through multiple logistic regression analyses after adjustment for all possible confounding factors. All results were considered statistically significant ($p < 0.05$).

3. Results

The allele frequencies in the controls were consistent with those predicted from the Hardy–Weinberg equilibrium (for *OGG1 Ser326Cys*, $\chi^2 = 0.950$ and $p = 0.330$; for *XRCC1 Arg399Gln*, $\chi^2 = 0.682$ and $p = 0.409$; for *MTH1 Val83Met*, $\chi^2 = 0.238$ and $p = 0.626$). The frequencies of the alleles and genotypes were evaluated in PD patients and controls (Tables 2 and 3). Fig. 1 shows a representative gel for the *OGG1 Ser/Cys* polymorphism. We did not find any significant differences for the *OGG1* allele ($p = 0.081$, OR = 0.645, 95 %CI = 0.394–1.055) and genotype frequencies ($p = 0.092$, OR = 0.6, 95 % CI = 0.331–1.087) between the patients with PD and the healthy controls. The *OGG1 Ser326Ser* genotype in healthy participants was 57.7 %, the *Ser/Cys* genotype was 34 %, and the *Cys/Cys* genotype was 8.3 %. Our result is in accordance with data reported in European Caucasians (56 %, 38 %, 6% and 60 %, 43 %, 2 %, respectively) [21,22]. In patients with PD, the *Ser/Ser* genotype was 69.4 %, the *Ser/Cys* genotype was 25.3 %, and the *Cys/Cys* genotype was 5.3 % (Tables 2 and 3). There was no significant difference between the groups regarding smoking, caffeine consumption, gender, and DM history (not shown, $p > 0.05$).

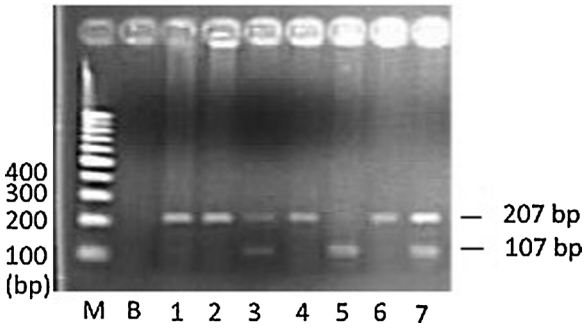


Fig. 1. *OGG1* gene polymorphisms in patients with PD. Polymorphic regions of the *codon 326* were amplified by a multiplex PCR; the products were digested with *Sat1* and separated by gel electrophoresis. Lanes 1,2,4 and 6 demonstrate patients with *Ser326Cys* genotype; Lane 3 and 7 *Ser326Cys*; Lanes 5: *Cys326Cys*. M is the 100 bp. DNA size marker (bp, base pairs).

Fig. 2 shows a representative gel for the *XRCC1 Arg399Gln* polymorphism. There were statistically significant differences in *XRCC1 Arg399Gln* genotypes between the patients with PD and the controls. In patients with PD, the *XRCC1 Arg/Arg* genotype was 35.9 %, the *Arg/Gln* genotype was 43.5 %, and the *Gln/Gln* genotype was 20.6 % (Table 2 and 3). *XRCC1 Gln/Gln* genotypes in patients with PD were more than three times higher (OR = 3.742; 95 % CI = 1.470–9.525; $p = 0.006$) than in controls. In controls, the *XRCC1 Arg/Arg* genotype was 55.9 %, the *Arg/Gln* genotype was 35.5 %, and the *Gln/Gln* genotype was 8.6 %. The frequencies of Gln alleles in patients with PD were also twice as high as in controls (OR = 2.057, 95 % CI = 1.328–3.188, $p = 0.001$). Our results are similar to the results obtained previously in the Brazilian

Table 3
Genotype frequency distributions of *OGG1 Ser326Cys*, *XRCC1 Arg399Gln* and *MTH1 Val83Met* genes and risk of PD.

Polymorphism	Control (n = 97)	PD (n = 102)	p value†	OR (95 % CI)
OGG1 genotype frequency				
Ser/Ser	56 (57.7 %)	66 (69.4 %)	Ref	1.000
Ser/Cys	33 (34.0 %)	24 (25.3 %)	0.136	0.617 (0.327 − 1.164)
Cys/Cys	8 (8.3 %)	5 (5.3 %)	0.289	0.530 (0.164 − 1.713)
Ser/Cys + Cy/Cys	41 (42.3 %)	29 (30.6 %)	0.092	0.600 (0.331 − 1.087)
XRCC1 genotype frequency				
Arg/Arg	52 (55.9 %)	33 (35.9 %)	Ref	1.000
Arg/Gln	33 (35.5 %)	40 (43.5 %)	0.046	1.910 (1.013 − 3.603)
Gln/Gln	8 (8.6 %)	19 (20.6 %)	0.006	3.742 (1.470 − 9.525)
Arg/Gln + Gln/Gln	41 (44.1 %)	59 (64.1 %)	0.007	2.268 (1.256 − 4.094)
MTH1 genotype frequency				
Val/Val	85 (%90.4)	89 (%91.8)	Ref	1.000
Val/Met	9 (%9.6)	8 (%8.2)	0.748	0.849 (0.313 − 2.302)

Ref: *Ser/Ser* genotype for *OGG1, Arg/Arg* genotype for *XRCC1 a*nd *Val/Val* genotype for *MTH1* were assumed as reference categories which their odds ratios were set at 1.000. [According to the HWE $\chi^2 = 0.950$, $p = 0.330$ for *OGG1*, $\chi^2 = 0.682$, $p = 0.409$ for *XRCC1*, $\chi^2 = 0.238$, $p = 0.626$ for *MTH1* in controls and $\chi^2 = 1.869$, $p = 0.171$ for *OGG1*, $\chi^2 = 1.110$, $p = 0.292$ for *XRCC1*, $\chi^2 = 0.179$, $p = 0.672$ for *MTH1* in PDs], † Univariate logistic regression analysis, PD: Parkinson's Disease, OR: Odds Ratio, CI: Confidence Interval.

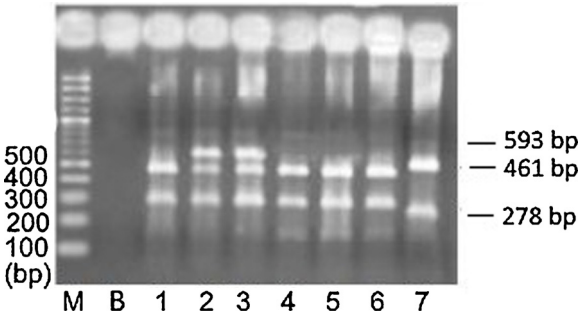


Fig. 2. *XRCC1* gene polymorphisms in patients with PD. Polymorphic regions of the codon 399 were amplified by a multiplex PCR, the products were digested with *HpaII* and separated by gel electrophoresis. Lanes 1,4,5 and 6 demonstrate patients with *Arg399Arg* genotype; Lane 2 and 3 *Arg399Gln;* Lanes 7: *Gln399Gln.* M is the 100 bp. DNA size marker (bp, base pairs).

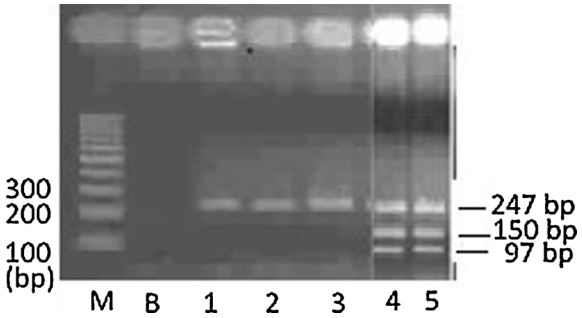


Fig. 3. *MTH1* gene polymorphisms in patients with PD. Polymorphic regions of the *codon 83* were amplified by a multiplex PCR; the products were digested with *NsiI* and separated by gel electrophoresis. Lanes 1,2 and 3 demonstrate patients with *Val83Val* genotype; Lane 4 and 5 *Val83Met.* M is the 100 bp. DNA size marker (bp, base pairs).

population, as published by Rossit et al. [23] (49 %, 34 %, and 13 %, respectively).

Fig. 3 shows a representative gel for the *MTH1 Val83Met* polymorphism. We did not find any significant differences for the *MTH1* allele (p = 0.753, OR = 0.855, 95 % CI = 0.323–2.266) and genotype frequencies (p = 0.748, OR = 0.849, CI = 0.313–2.302) between patients with PD and healthy controls. The *Val/Val* genotype of *MTH1* polymorphism in healthy participants was 90.4 %, the *Val/Met* genotype was 9.6 %, and the *Met/Met* genotype was 0%. The very low frequency of *codon 83 Val/Val* and *Met/Met* genotypes in our healthy participants is in accordance with the data reported in Karahalil et al. (93.3 % 6.7 %, and 0%, respectively) [20]. In patients with PD, the *Val/Val* genotype was 91.8 %, the *Val/Met* genotype was 8.2 %, and the *Met/Met* genotype was 0%, respectively (Table 2 and 3).

According to the multiple logistic regression analyses, *OGG1 Ser326Cys* [OR = 0.812, 95 % CI = 0.425–1.551] and *MTH1 Val83Met* [OR = 0.703, 95 % CI = 0.126–2.290] polymorphisms were not found to be statistically significant predictors for the risk of PD (with adjustment for age, gender, smoking status, and DM) (p = 0.528 and p = 0.559, respectively). The *Arg/Gln + Gln/Gln* genotype was 2.133 times (95 % CI = 1.116–4.077) more likely to be associated with PD, after adjustment for all possible confounding factors (age, gender, smoking, and history of DM), in multiple logistic regression analysis (p = 0.022) (Table 4).

4. Discussion

Genetic polymorphisms in the DNA repair genes may impair their function and enhance PD susceptibility [6]. Thus, given the role of BER in PD, the effects of the *OGG1 Ser326Cys*, *XRCC1 Arg399Gln*, and *MTH1 Val83Met* polymorphisms were evaluated in the risk of PD.

Table 4
Multiple logistic regression analyses. *OGG1*, *MTH1* and *XRCC1* genotype and DATA adjusted for age, gender, DM and smoker.

	OR	%95 CI		p-value
		LL	*UL*	
OGG1 Ser326Cys				
≥65(Age)	1.596	0.826	3.085	0.165
Male factor	1.383	0.665	2.873	0.385
Smoking History	1.628	0.305	1.292	0.207
History of DM	1.991	0.847	4.680	0.014
Ser / Cys + Cys / Cys	0.812	0.425	1.551	0.528
MTH1 Val83Met				
≥65 ages	1.579	0.816	3.055	0.175
Male factor	1.459	0.701	3.036	0.312
Smoking History	0.621	0.302	1.279	0.196
History of DM	1.999	0.856	4.669	0.110
Val / Met	1.703	0.216	2.290	0.559
XRCC1 Arg399Gln				
≥65 (Age)	1.257	0.637	2.483	0.509
Male factor	1.456	0.696	3.045	0.318
Smoking History	0.632	0.306	1.308	0.216
History of DM	1.954	0.821	4.647	0.130
Arg / Gln + Gln / Gln	2.133	1.116	4.077	**0.022**

OR: Odds ratio, CI: Confidence interval, LL: Lower limit, UL: Upper limit is to find out variables in a model are significant.

OGG1 has two isoforms: *OGG1-1a* and *OGG1-2a* [6]. Lack of association between the *326Cys* allele and PD in the present study is in accordance with the data previously published by Coppedè et al. [11], Cornetta et al. [18], and Gencer et al. [19]. However, exposure to some pesticides may affect the BER pathway, causing mtDNA damage and leading to the risk of PD [24]. Warner and Schapira [3] suggest that there is evidence to support the effects of environmental exposure, including pesticide and head injuries, and potentially protective factors, such as smoking and drinking alcohol or caffeinated drinks in the causation of PD. Fukae et al. [6] detected higher expression levels of *OGG1-2a* in the mitochondria of patients with PD. However, the findings obtained in this study did not show polymorphic changes. Our results do not provide evidence for an association between the *OGG1* gene polymorphisms and the risk of PD in the Turkish population. These data are in concordance with the subgroups in our studies. Data from our study showed consistent results with the results found by Parildar-Karpuzoglu et al. [10] in the Turkish population affected by Alzheimer's disease.

To our knowledge, an association between the *83MTH1* polymorphism and PD risk has been suggested by only one study in the literature so far [15], which reported a lack of association between PD risk and the *83Met* polymorphism.

The *XRCC1* gene encodes the enzyme involved in the repair of DNA base exchange and single-strand breaks resulting from exposure to ionizing radiation and alkylating agents. A lack of association between the *399Gln* allele and PD is in accordance with the data previously published by Kaleagasi et al. [17] and Cornetta et al. [18]. However, in our study, the *XRCC1 Gln/Gln* genotype among patients with PD was significantly higher than in the healthy controls (p = 0.006, OR = 3.742, 95 % CI = 1.470–9.525), while the frequency of the *XRCC1 Arg/Gln* genotype was slightly higher (p = 0.046, OR = 1.910, 95 % CI = 1.013–3.603). Comparing the allele frequencies of control participants and patients with PD, the risk of PD was 2.057 times higher in those carrying the *Gln* allele than those carrying the *Arg* allele, and the difference was statistically significant. Similarly, the risk of PD increased 1.9 times (p < 0.046) in those carrying the *Arg/Gln* genotype, whereas the risk of PD increased 3.7 times in those carrying the *Gln/Gln*

genotype ($p < 0.006$) (Table 3). Concerning *XRCC1, OGG1*, and *MTH1* together, to our knowledge, no data are available in the literature for PD. Data from our study showed results for both *OGG1* and *XRCC1* that were consistent with those found by Gencer et al. [19] in the Turkish population affected by PD.

The variant *399Gln* allele is much more common than the variant *326Cys* and *83Met* alleles in patients with PD and in controls. The allele frequency of the *codon 83* variant was very low in patients with PD and in controls. The distribution of both gene variants for *OGG1* and *MTH1* alleles was similar among the patients with PD and the healthy controls. The frequency of both of these variant alleles among the patients with PD is slightly lower than that in healthy controls. A similar distribution of the variant alleles showed a lack of any significant association between the *OGG1* and *MTH1* polymorphisms and PD risk, in both in homozygotes and in heterozygotes and in the two combined.

Various epidemiological studies have reported an inverse relationship between cigarette smoking and the development of PD [25]. However, we suggested an interaction between *XRCC1 Arg399Gln* polymorphism and smoking, since *Gln/Gln* variant genotype carriers among smokers had a 9.8 times higher risk of PD. The sample size in the subgroups was low, but *XRCC1 Arg399Gln* gene polymorphism showed statistically significant increases in total and in *Arg/Gln* and *Gln/Gln* genotypes compared to controls, and although the sample size in smokers with the *Gln/Gln* genotype was low, it may contribute to this significance. We also suggested that participants with DM had a higher risk of PD. Our study is in accordance with data on those previously published by Pagano et al. [26]. According to Pagano et al. [26], DM may be prone to a Parkinson's-like pathology and may induce a more aggressive phenotype when it presents in patients with PD. Wooten et al. [27], in their meta-analysis study, found an interaction gene and gender. They reported a significantly higher incidence of PD among men, with the relative risk being 1.5 times higher in men than in women. In our study, the impacts of gender on the development of PD and among men with the *Gln/Gln* variant genotype increased the risk of PD 5.10 times ($p = 0.025$) but showed no association among women. Furthermore, we found that an age higher than 65 had an impact on the development of PD. However, we had small subgroups for smoking, gender, age, and DM. Therefore, we could not conclusively find any relationships. Our results do not provide evidence for an association between the *OGG1* and *MTH1* gene polymorphisms and gender, age, DM history, and smoking.

The main limitation of this study is that ROS derivatives or oxidative damage products, especially the activity of 8-oxo-Gua, have not been studied. However, we have three gene polymorphisms that perform the most important key roles in BER and a sufficient number of samples to perform genome analysis. The distribution of *OGG1 Ser326Cys*, *XRCC1 Arg399Gln*, and *MTH1 Val83Met* gene polymorphisms in our study was found to be similar to those in the Caucasian population. This data confirms the accuracy of the methodology we used.

In conclusion, *XRRC1 Arg399Gln* polymorphism is a risk factor, in that it increases the oxidative DNA damage that may cause the loss of dopaminergic neurons in the SN and, finally, the development of PD. Moreover, we found that *OGG1 Ser326Cys* polymorphism and *MTH1 Val83Met* polymorphism are not associated with PD. The *Met83* allele frequency was almost the same between the groups (0.41 in patients with PD and 0.48 in controls, $p = 0.753$) and was similar in genotype frequencies (0.82 in patients with PD and 0.96 in controls, $p = 0.748$). Further studies are needed to explain the impacts of these DNA repair genes on PD.

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CRediT authorship contribution statement

Nergis Selma Aslan: Conceptualization, Methodology, Software, Writing - review & editing, Writing - original draft, Formal analysis, Data curation. **Gürdal Orhan:** Visualization, Investigation, Supervision, Writing - review & editing. **Bensu Karahalil:** Software, Validation, Project administration, Writing - review & editing.

Declaration of Competing Interest

None.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.neulet.2020.135203.

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