Association of functional *RAGE* gene polymorphisms with Parkinson's disease in a Turkish cohort.

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Abstract

Background: There is an increasing deal about the role of inflammation in Parkinson's disease (PD) pathogenesis after the observation of clear evidence of immune responses close to the basal ganglia of PD patients. Although receptor of advanced glycation end-products (RAGE) has been implicated in several studies as an inflammation marker in PD; *RAGE* gene polymorphisms is infrequently examined. Thirty single-nucleotide polymorphisms (SNPs) including G82S (rs2070600) located in 3rd exon, -374T/A (rs1800624), -429T/C (rs1800625) and 63bp ins/del in the promoter region of the gene which may have marked effects on the expression or function of *RAGE* have been described to date.

Objective: To evaluate the association of *RAGE* gene polymorphisms with PD in a Turkish cohort.

Methods: Totally, 174 PD patients and 150 healthy-individuals were included into the study. Genotype analyses were performed using PCR-RFLP and ARMS methods.

Results: 429T>C, 374T>A, and 82G>S polymorphisms showed significant differences between PD patients and controls (p<0.001, p<0.05, p<0.001, respectively). For 82G>S polymorphism, the patients carrying mutant S allele in homozygous (p<0.00, OR=16.094) or heterozygous (p<0.00, OR=22.379) states have the highest risk for PD development.

Conclusion: The *RAGE* gene polymorphisms that are involved in gene expression may be associated with the susceptibility of PD and homozygous/heterozygous mutant S genotypes for the exonic 82G>S polymorphism may be an informative risk factor for PD. However, larger and different ethnical cohorts are needed to validate the results for different populations.

Keywords: Parkinson's disease, *RAGE* gene, Polymorphism, Turkey.

Introduction

A slow but irreversible detorioration of brain functions is a major characteristic feature of age-related neurodegenerative diseases [1]. Following Alzheimer's disease, Parkinson Disease (PD) is the second most common progressive neurodegenerative disease with a prevelance of about 1% in individuals over 60 years of age to approximately 4% in cases over the age 85 [2]. The disease causes severe morbidity by motor (tremor, bradykinesia, muscle rigidity, postural instability) and non-motor symptoms such as cognitive and behavioural symptoms, autonomic dysfunction, sensory symptoms, sleep disorders, and fatigue [1-5]. These specific clinical features can be explained by progressive degeneration of dopaminergic neurons in the substantianigra pars compacta (SNpc) and the widespread presence of accumulation of intracellular protein aggregates, Lewy bodies and Lewy neurites in the surviving neurons of the brain [6]. Most of the

studies [7-10] have suggested that inflammation and excitotoxicity both play central roles in the initiation and progression of PD. The genetic and functional studies have strongly suggested the important roles of genetic factors and/or epigenetic changes in regulation of immune pathways and inflammatory reactions for the neuronal dysfunction and subsequent neurodegeneration [11-16].

Similar to other neurodegenerative diseases of aging, PD has a complex etiology and presents as both a familial/genetic disorder and a sporadic/idiopathic disease whose exact etiology has yet to be elucidated although the genomic background of the disease has begun to be understood progressively [2,5,17-21]. Recently, Cacabelos [12] has listed the pathogenic mechanisms associated with genomic, epigenetic and environmental factors. All of these mechanisms are leading to misfolding of the proteins, therefore changing their membrane-

binding ability, favouring self-aggregation and formation of Lewy bodies (LBs).

RAGE, is a multiligand receptor of immunoglobulin superfamily and binds broad reportoire of ligands that tend to accumulate and aggregate during aging and development of neurodegenerative diseases including PD. The accumulation of these ligands including AGEs, β-amyloid (Aβ), S100/ calgranulin family, high mobility group protein B1 (HMGB1) within pathological levels stimulates RAGE expression and then diverse condition-specific signaling cascades are activated [22-24]. During the inflammation, AGE-RAGE binding strongly stimulates the activation of NF-κB pathways in neurons and microglial cells [25,26]. The gene for RAGE, comprising 11 exons, is located on chromosome 6p21.3 near the major histocompatibility complex locus. Previous studies [27,28] have shown associations between the *RAGE* gene polymorphisms and various diseases including Alzheimer's disease. Although the involvement of AGE-RAGE relation and their expression states are known in PD, surprisingly the role of *RAGE* gene polymorphisms in PD has only been reported in Chinese Han population [29]. It is well-known that Single Nucleotide Polymorphisms (SNPs) may influence gene expression, protein function and disease susceptibility. Therefore, this study was aimed to evaluate the association of *RAGE* gene polymorphisms with PD in a Turkish cohort to determine whether there are polymorphic markers that play significant associations with susceptibility of PD in Turkish population.

Materials and Methods

The study protocol and procedure were approved by the Institutional Ethics Review Committee and all the procedures pertaining to the study were conducted in accordance with the Declaration of Helsinki, local laws and regulations. After explaining the aim of the study, written informed consent was obtained from each patient and control subject.

Subjects (patients and controls)

This study included 174 consecutive, unrelated sporadic late onset (diagnosed>50 years of age) PD patients (93 Male; 81 Female). The physical examinations of the patients were performed by movement disorder specialists at the Department of Neurology of the Eskisehir Osmangazi University Hospital (Author S.O.). The United Kingdom Parkinson's Disease Society Brain Bank Clinical Diagnostic Criteria was used for clinical diagnosis and the disease severity was rated according to the Unified Parkinson's Disease Rating Scale (UPDRS) and Hoehn and Yahr staging (Hughes, Daniel & Lees 2001). None of the patient had a family history of Parkinsonism/ neurological/psychiatric conditions other than PD in one or more first- or second-degree relatives. One hundred and fifty unrelated, healthy control subjects were selected from Health Examination Center of the university. The PD cases and controls were at the same ethnicity.

Genotyping

Genomic DNA was isolated from peripheral blood samples with a Vivantis DNA Blood Extraction Kit (Vivantis Technology, USA) according to the manufacture's recommendations and DNA was stored at -20°C. The average genomic DNA concentration was measured with NanoDrop2000 (Thermo Scientific, Wilmington, DE, USA).

An Hexaprimer-Amplification Refractory Mutation System-PCR (H-ARMS-PCR) was designed for the simultaneous genotyping of -374A/T, -429A/G, and 63 bp deletion (-407 to -345 deletion) polymorphisms of *RAGE* gene in a single step whereas G82S polymorphism of *RAGE* gene was determined by the method of PCR-RFLP. The primers were as previously described [29-31].

–374A/T, –429A/G, and 63 bp Ins/Del polymorphisms

For the simultaneous detection of RAGE polymorphisms, 15 µL genomic DNA template, 5 µL of 10X PCR buffer A (Vivantis technology, USA), 0.25 µL dNTP mixture (Vivantis technology, USA) containing 0.2 mM of each nucleotide, 10 pmol of each F/R primer pairs specific to three polymorphisms and 0.2 µL Taq polymerase (Vivantis technology, USA) enzyme were added into the PCR tube.

The PCR cycling conditions were denatured at 95°C for 2 min, followed by seven cycles of 25 s at 94°C, 30 s at 60°C, and 1 min at 72°C; 14 cycles of 25 s at 94°C, 30 s at 52°C, and 1 min at 72°C; 14 cycles of 25 s at 94°C, 30 s at 51°C, and 1 min at 72°C with a final extension at 72°C for 7 min. The PCR products were separated on a 3% agarose gel electrophoresis stained by ethidium bromide and visualized in UV transilluminator.

G82S polymorphism

The PCR amplification of G82S polymorphism was performed in a total volume of 50 µL containing 50 ng genomic DNA, 10 pmol of each primer, 0.5 U Hotstar-Taq DNA polymerase (Vivantis technology, USA), 0.2 µL of dNTP (25 Mm) (Vivantis technology, USA) and 5 µL 10 × Buffer A. The PCR conditions for the G82S polymorphism were as follows: denaturation at 94°C for 2 min, 35 cycles were performed with denaturation for 30 s at 94°C, anneling for 30 s at 60°C, and extension for 1 min at 72°C, and a final prolonged extension at 72°C for 2 min. The PCR products were digested with 5 U restriction endonuclease *Alu I* (BioLabs NEB, New England) and then incubated at 37°C for 16 h. The digested products were separated by 2.5% agarose gel electrophoresis stained by ethidium bromide and visualized on an UV transilluminator with 50 bp DNA ladder to assess the size of the PCR-RFLP products.

Statistical analyses

The statistical analyses were performed using IBM SPSS 21 and MINITAB 16 package programmes. The qualitative variables were given as frequency and percentage. The

relationship between qualitative variables that have two categories and more than two categories were used Pearson Chi-Square test. The distribution of *RAGE* gene polymorphisms and ORs (Odds Ratio) for the null gene polymorphisms in the patients and controls were given in Table

1. Two Proportion Test was used in the comparisons of allele frequencies of *RAGE* gene in patients and controls group. A significance level of $p<0.05^{*}$ was considered statistically significant.

Table 1. *Genotype frequencies of RAGE gene polymorphisms in normal and PD individuals.*

Genotype	PD (%)	Control (%)	OR	95% CI	P
Rs1800624 (-374T/A)					<0.05
TT	29 (16.5)	52 (34.5)	1	-	-
AT	136 (78.3)	90 (60)	2.71	(1.60-4.58)	<0.001
AA	9 (5.2)	8 (5.5)	2.017	(0.702-5.794)	>0.05
AA+AT	145 (83.3)	98 (65.3)	2.653	(1.575-4.470)	<0.001
Rs1800625 (-429T/C)					<0.001
TT	12 (7)	52 (34.5)	1	-	-
CT	153 (88)	82 (54.5)	8.085	(4.086-16.001)	<0.001
CC	9 (5)	16 (11)	2.438	(0.870-6.828)	>0.05
CT+CC	162 (93.1)	98 (65.3)	7.163	(3.644-14.082)	<0.001
Rs2070600 (82GS)					<0.001
GG	29 (16.7)	121 (80.7)	1	-	-
GS	118 (67.8)	22 (14.7)	22.379	(12.167-41.16)	<0.001
SS	27 (15.5)	7 (4.6)	16.094	(6.383-40.578)	<0.001
GS+SS	145 (83.3)	29 (19.3)	20.862	(11.816-36.83)	<0.001
63 bp Ins/Del					>0.05
Del-	171 (98.3)	150 (100)	-	-	-
Del+	3 (1.7)	0 (0.0)	-	-	-

Results

In this study, we examined rs1800624 (-374T>A), rs1800625 (-429T>C), and rs2070600 (Gly82Ser) SNPs and a 63bp deletion allele (-407 to -345) polymorphisms of the *RAGE* gene in 174 PD patients (F: 81, M: 93) (Mean age: 72 ± 3.9) and 150 healthy-controls group (F: 70, M: 80) (Mean age: 70 ± 2.1). The allellic and genotypic distributions of the four polymorphisms and their correlations with PD patients and controls are summarized in Table 1. Allele frequencies of the *RAGE* gene in the patients and controls are shown in Table 2.

Table 2. *Allele frequencies of RAGE gene in patients and controls.*

Allele	PD	Control	P
Rs1800624 (-374T/A)			
T (%)	194 (56.0)	194 (65.0)	<0.05
A (%)	154 (44.0)	106 (35.0)	<0.05
Rs1800625 (-429T/C)			
T (%)	177 (50.0)	186 (62.0)	<0.01
C (%)	171 (49.0)	114 (38.0)	<0.01
Rs2070600 (82GS)			
G (%)	176 (50.0)	264 (88.0)	<0.001
S (%)	172 (50.0)	36 (12.0)	<0.001

Significant differences between PD patients and controls were observed in allele and genotype distributions of rs1800624 (-374T>A) polymorphism (P<0.05). If TT genotype was used as the reference group, the AT genotype was associated with a higher risk of PD (p<0.001, OR=2.710, 95% CI=1.60-4.58). The frequency of genotype with A (AT+AA) was significantly higher in the patient group than the control group (p<0.001, OR=2.653, 95% CI=1.575-4.70). However, no significant difference was detected for homozygous AA genotype between the patient and control groups.

When we compared genotype and allele frequencies of rs1800625 (-429T>C) polymorphism of the *RAGE* gene between the PD patients and the controls, the difference was also statistically significant (p<0.001). The heterozygote CT

genotype was associated with a higher risk of PD (p<0.001, OR=8.085, 95% CI=4.086-16.001). In the patient group, the frequency of genotype with C (CT+CC) was significantly higher than the corresponding value for control group (p<0.001, OR=7.163, 95% CI=3.644-14.082). Although the homozygous CC frequency was lower in the patient group than the control group, the difference was not statistically significant (p>0.05, OR=2.438, 95% CI=0.87-6.828).

A significant association between the 82S allele (encoding amino acid Ser of the non-synonymous SNP rs2070600) and risk of PD was observed (p<0.001). If compared to Gly/Gly genotypes, Gly/Ser and Ser/Ser genotypes associated with significantly higher (for Gly/Ser genotype OR=22.379, 95% CI=12.167-41.16, p<0.001; for homozygous Ser/Ser genotype OR=16.094, 95% CI=6.383-40.578, p<0.001) chance of PD in 174 cases and 150 controls. Having S allele in a homozygote or heterozygote state (GS+SS genotypes) seems to be a risk factor for development of PD (p<0.001, OR=20.862, 95% CI=11.816-36.83).

The 63 bp Ins/del polymorphism of the *RAGE* gene was only found in 1.7% of PD patients but not in healthy controls (p=0.154).

Discussion

The glycation of α-synuclein exerts toxic effects in neuronal cells through multiple mechanisms, such as altering membrane permeability and causing neuronal cell dysfunction, causing neuronal cell death through generation of ROS and increasing oxidative stress. Besides, glycated α-synuclein activates microglia that are resident innate immune cells of the CNS. Activated microglia produces neurotoxic molecules including cytokines, chemokines, complement proteins, and nitric oxide and incites neuro-inflammation that is a critical driving force in the pathology of PD [32,33]. The glycated α-syn may also interact with RAGE and trigger the release of NF-kB. These signaling proteins activate signaling cascades in the brain and damage neuronal cells [15]. NF-kB also regulates RAGE expression by inducing the expression of RAGE proteins. The meaning of increased expression of RAGE receptors is binding of more glycated α-synuclein and releasing of NF-kB that activates inflammatory pathway and the end product is neuronal death [34,35].

Previously, the role of RAGE has been investigated in different aspects of AD pathology, including transport of AD-specific amyloid (A) peptides. Ray et al. [28] have reviewed emerging role of RAGE in the pathogenesis of amyotrophic lateral sclerosis (ALS). Besides, a few studies [27,36,37] have also focused on the effects of *RAGE* gene polymorphisms on AD susceptibility. Although both PD and AD are frequently observed neurodegenerative diseases and are thought to share common pathogenic mechanisms, surprisingly, only the study by Gao et al. [29] has focused on the potential association of three *RAGE* gene polymorphisms with PD susceptibility in Chinese Han population. To the best of our knowledge, this is the first study evaluating the role of RAGE genetic variants in the risk with PD in a Turkish cohort.

In this preliminary case-control study, we investigated the association between four different functional *RAGE* gene polymorphisms (-429T>C, -374T>A, G82S and 63 bp Ins/Del) and sporadic late onset PD.

The expression levels of *RAGE* gene is regulated by -374T>A and -429T>C polymorphisms in the promoter region of RAGE. In our survey of 174 late onset sporadic PD patients and 150 healthy controls, analysis of genotype distribution of -429T/C polymorphism revealed significant association of mutant variant with the PD (p<0.001, OR: 7.163). The mutant PD population has seven fold more chances of developing PD in comparison to PD patients with wild genotype. Previously, it has also been reported a statistically significant association between the PD susceptibility and the *RAGE* -429T/C polymorphism [29]. However, their data has revealed that heterozygous CT and homozygous CC allele frequencies in PD patients were significantly lower than controls and they have suggested that the -429C allele may down-regulate RAGE expression. Consequently, -429T/C polymorphism may prevent the development of PD, and -429C allele may be a protective factor of PD. In contrast, in our cohort, the C allele frequency and heterozygous CT genotypes were significantly higher (p<0.01, p<0.001, respectively) in PD patients. Although the frequency of the patients with homozygous CC genotype was lower than the corresponding value of controls, the difference was not statistically significant. The -429T/C promoter polymorphism have been shown to increase *RAGE* gene transcript [38,39]. The increased expression of RAGE receptors causes binding of more glycated α-synuclein and releasing of NF-kB that activates downstream signaling cascades and favors inflammatory pathway and eventually neuronal death.

The data of Gao et al. [29] has revealed no -374T/A SNP association with PD. However, the frequency of mutant A allele was found to be significantly higher (p<0.05) in PD group as compared to healthy controls in our study. The frequency of the patients, carrying mutant A allele in heterozygous and homozygous states (AT+AA genotypes) was significantly higher (p<0.001, OR=2.653) compared to healthy controls. Transcription factor binding assays have revealed that the substitution of the T-to-A at the -374 position of the *RAGE* gene promoter leads to reduced binding of a nuclear factor to a regulatory element of the *RAGE* gene promoter, thus resulting in enhanced transcriptional activity [39]. It has been shown that both the –429C and –374A alleles had a marked effect on transcriptional activity of the RAGE. We suggested that revealing significant associations of these two polymorphisms with the PD susceptibility may provide important data for further studies.

In contrast to the data of the previous study by Gao et al. [29], we also observed significant association between Ser82 allele and the tendency to PD. The wild type (GG) genotype was significantly low in the patient group. We suggested that the patients carrying mutant S allele in homozygous (p<0.001

OR=16.094) or heterozygous (p<0.001 OR=22.379) states have the highest risk for PD development if we compare with the other polymorphic genotypes. The G82S polymorphism, located in exon3 of the *RAGE* gene encodes V-domain of the gene and may affect the ligang-binding activity of the gene and subsequent cellular signaling. Previous studies have shown that cells bearing the 82S isoform have a higher affinity for ligands such as S100A12 and that leads to the activation of *RAGE* and increased production of inflammatory mediators [40,41]. The higher tendency of the individuals with 82S genotype to some diseases such as gastric cancer, Alzheimer's Disease (AD) [27,37,42], coronary artery disease and ischemic stroke [43] has been suggested in many studies.

The polymorphisms in the promoter region of the *RAGE* gene (-429C, -374A and 63 bp del alleles) resulted in an increase of gene expression of two-, three- and four-fold, respectively have already been reported by Hudson et al. [39]. We also analysed the 63 bp del polymorphism in this study. Interestingly, the presence of the 63 bp deletion affects the polymorphic site -374T>A in the *RAGE* gene promoter region and is not a frequent polymorphism, varying from 0 to 6% in different population [44]. This deletion was only observed in three cases (1.72%) with PD, no mutation was detected in the healthy controls. Although this finding didn't reach a statistical significance, we suggested that this polymorphism should also be evaluated in neurodegenerative diseases, including PD.

The frequencies of *RAGE* gene polymorphisms and their possible roles on the susceptibility of PD development were not in line with the data of Gao et al. [29]. However, presence of these differences might be due to the genetic heterogeneity in different cohorts. One of the limitations of the present study includes a limited number of patients with PD.

In conclusion, the presence of significant associations among two promoter-located and one exonic polymorphisms that are involved in gene expression with the late-onset PD indicated that *RAGE* gene may play an important role in the physiopathology of PD. The highest risk for susceptibility of PD in our Turkish cohort seems to be the individuals who are carriers of mutant S allele in the 82th position of 3rd exon of the *RAGE* gene. However, the other promoter region polymorphisms (- 429C and -374A) may also be associated with increased risk of PD. The studies with larger samples from different ethnical cohorts are necessary to validate the potential roles of *RAGE* gene polymorphisms in the pathophysiology of PD.

Acknowledgement

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