RESEARCH ARTICLE

Association between sporadic Parkinson disease and interleukin-1β -511 gene polymorphisms in the Turkish population

Ahmet Arman[1], Nihal Isık[2], Ajda Coker[3], Fatma Candan[2], Kezban Serap Becit[4], Edward O. List[5]

[1] The Faculty of Engineering, Marmara University, Istanbul, Turkey
[2] The Department of Neurology, Göztepe Government Hospital, Istanbul, Turkey
[3] The Department of Molecular Biology and Genetics, Istanbul Kultur University, Istanbul, Turkey
[4] The Department of Biology, Science and Letters, Marmara University, Istanbul, Turkey
[5] The Edison Biotechnology Institute, Ohio University, Athens, OH, USA

Correspondence: Dr A. Arman, The Faculty of Engineering (FE), FE Building D, Molecular Genetics and Cell Culture Lab., Room #: 405, Goztepe Campus, Marmara University, 34722, Istanbul, Turkey
<ahmetarman@marmara.edu.tr>

Accepted for publication January 15, 2010

ABSTRACT. The pathogenesis of Parkinson Disease (PD) remains poorly understood; however, inflammation is thought to play an important role in disease progression. Recent reports suggest that IL-1, a major proinflammatory cytokine, might play a role in PD progression. The purpose of this study was to determine the relationship between IL-1 gene family polymorphisms [IL-1α (-889), IL-1Ra (VNTR) and IL-1β (-511, +3953)] and PD in the Turkish population. In this study, we examined the genotypes of IL-1 gene family polymorphisms in 365 individuals, of which 199 were healthy control subjects and 166 were PD patients. No significant differences were found in the genotype distribution or in the allele frequencies of IL-1α (-889), IL-1Ra (VNTR) and IL-1β (+3953) between PD cases and control subjects. However, distribution of the IL-1β -511 2/2 (T/T) genotype was found to be significantly lower in PD patients than in healthy controls ($p = 0.018$, x^2: 8.242, OR: 2.211, 95% CI: 1.261-3.877). In addition, the IL-1β -511 allele 1 (C) frequency was significantly elevated in PD patients versus controls ($p = 0.048$, x^2: 3.87, OR: 1.178, 95% CI: 0.999-1.388). These results suggest that IL-1α (-889), IL-1Ra and IL-1β (+3953) gene polymorphisms have no association with PD, while allele 1 (C) of IL-1β (-511) is associated with PD and may provide a susceptibility factor for this disease in the Turkish population. Furthermore, the 2/2 (T/T) genotype of IL-1β (-511) may protect individuals from PD.

Keywords: interleukin-1, cytokine, polymorphism, Parkinson disease

Parkinson Disease (PD), is the second most common neurodegenerative disease after Alzheimer's disease (AD), and was first described by James Parkinson in 1817 [1]. Tremor, akinesia, bradykinasia, hypomimia, decreased eye blinking, and hypophonia are the clinical features of PD [2]. These symptoms develop because of the dopaminergic neuron loss in the substantina nigra (SN) pars compacta region of the PD patient's brain [3]. According to the epidemiological studies, 95% of PD cases are sporadic, while 5% are familial based [4]. Mutations within genes such as parkin, ubiquitin C terminal L1, and alpha synuclein have been linked with familial PD [5]. Although the etiology of sporadic PD is not well established, it is suggested that environmental toxins, oxidative stress, mitochondrial dysfunction and genetic factors are involved [6-8]. Recently, chronic inflammation, caused by the action of activated microglia cells, has also been shown specifically in the SN area of the PD brain [9].

Interleukin-1 (IL-1) is a major pro-inflammatory cytokine and has been shown to be involved in sepsis, trauma, infection and inflammation [10, 11]. The IL-1 family consists of three members: interleukin-1 alpha (IL-1α), interleukin beta (IL-1β) and IL-1 receptor antagonist (IL-1Ra). In terms of activity, the IL-1 family has two agonists (IL-1α and IL-1β), and one antagonist (IL-1Ra). Thus, both IL-1α and IL-1β promote inflammation, while IL-1Ra inhibits IL-1-induced inflammation by binding to the IL-1 receptor type I (IL-1RI) and blocking IL-1α and IL-1β signaling [12]. IL-1α, IL-1Ra and IL-1β, which are expressed from the *IL-1A, IL-1RN* and *IL-1B* genes respectively, are highly polymorphic. Single nucleotide polymorphisms (SNPs) have been determined at promoter position -889 in the IL-1α gene [13], and at promoter position -511 C/T [14] and in exon 5 at position +3953 C/T of the IL-1β gene [15]. There is also a length variation within intron 2 caused by 86 base-pair variable number of tandem repeats (VNTR) in the IL-1RN gene

doi: 10.1684/ecn.2010.0186

[16-18]. Both IL-1α (-889) and IL-1β (-511) 2 (T) alleles lead to high expression of their respective proteins. Thus, these polymorphisms are thought to play an important role in IL-1-induced diseases [19]. This study was designed to determine the association between PD and IL-1 gene family polymorphisms (IL-1α (-889), IL-1Ra (VNTR) and IL-1β (-511, +3953)) in the Turkish population. Our results showed that neither the genotype nor the alleles of IL-1α (-889), IL-1Ra VNTR and IL-1 β (+3953) are associated with PD. However, IL-1β (-511) SNP was associated with PD in the Turkish population.

DONORS AND METHODS

Subjects

A total of 166 (100 males and 66 females) PD patients and a total of 199 age- and gender-matched healthy subjects (125 males and 74 females) were included in this study. All patients and healthy controls were of Turkish ancestry, and gave informed consent before participating. Subjects were excluded if they had evidence of hypertension, diabetes mellitus, cardiovascular problems, stroke, or rheumatoid arthritis. In addition to these criteria, healthy controls had no clinical evidence of neurological disease or familial history of Parkinsonism, and in order to minimize the presence of juvenile Parkinsonism, patients with disease onset under the age of 40 were excluded. Patients were selected from the Movement Disorder Outpatient Clinic of Goztepe Training Hospital Neurology Department. For the diagnosis of PD, the United Kingdom Parkinson's Disease Society Brain Bank (now known as the Queen-Square Brain Bank) clinical diagnostic criteria were used [20]. The Unified Parkinson's Disease Rating Scale (UPDRS) [21] and Hoehn & Yahr scores (H&Y) [22] of all participants were measured, in addition to physical and neurological examinations. Disease duration, age-at-onset of disease, predominant symptoms and duration of treatment (levodopa, dopamine agonists) were documented.

Genotyping

Blood samples were taken from all 365 participants and kept in tubes with EDTA. Genomic DNA isolation was done as previously described [23]. The IL-1α (-889) SNP was determined by PCR using forward and reverse primers, 5'-AAGCTTGTTCTACCACCTGAACTAGGC-3' and 5'-TTACATATGAGCCTTCCAT-3', respectively. PCR cycles were as follows: (94°C, 1 min) x 1; 94°C, 30 sec, 45°C, 30 sec, 72°C, 45 sec) x 35 cycles; 72°C, 10 min) x 1. Restriction digestion was performed overnight with 5 U Nco I at 37°C, followed by 3.5% agarose gel electrophoresis. Nco I digestions resulted in an 83 bp and a 16 bp fragment with allele 1 (allele C), whereas a single 99 bp fragment was amplified in the presence of allele 2 (allele T). The VNTR region in intron 2 of the IL-1Ra, IL-1β (-511) and IL-1β (+3953) genes were amplified as previously described [24].

Statistical analysis

Allele and genotype frequencies among cases and controls were compared with Hardy-Weinberg predictions using x^2-analysis. For comparisons of the age-at-onset of the disease, a Mann-Whitney U test was used. The association between disease and genotypes was shown by odds ratio (OR) and 95% confidence interval (CI). Statistical significance was set at a value of $p < 0.05$ (2-sided). SPSS 13.0 software program was used for all statistical analyses.

Ethics approval

This research was approved by the ethics committee of Marmara University, in Turkey. All human rights in this research were protected, and any necessary approval was secured from the ethics committee. All experiments performed on human subjects were conducted in accordance with the Declaration of Helsinki. All procedures were carried out with the adequate understanding and written consent of the subjects.

RESULTS

The mean age and gender of the PD cases and the healthy controls are given in *table 1*. None of the genotype frequencies observed deviated from the Hardy-Weinberg equilibrium. The genotype distribution and allele frequency of IL-1α (-889) and IL-1Ra VNTR are shown in *table 2*. Neither the IL-1α-889 genotype distribution ($p = 0.356$, OR: 0.911, 95% CI: 0.653-1.566), nor the allele frequency ($p = 0.283$, OR: 0.841, 95% CI: 0.621-1.155) differed between the PD patients and healthy controls *(table 2)*. Four genotypes of the IL-1Ra gene were commonly seen in the PD patients and control subjects. Among these genotypes, no significant difference was found between the PD patients and controls ($p = 0.588$, OR: 0.990, 95% CI: 0.391-2.510). For the IL-1Ra allele frequencies, no association was detected between the controls and PD patients ($p = 0.836$, OR: 0.926, 95% CI: 0.387-2.216) *(table 2)*.

The genotype distribution and allele frequency of IL-1β (-511) in the PD and control groups are shown in *table 3*. These data show that PD groups exhibited a low frequency of IL-1β (-511) 2/2 (T/T) genotype compared to healthy controls, and this difference was statistically significant (x^2: 8.242, df: 2; $p = 0.018$, OR: 2.211, 95% CI: 1.261-3.877). These data also show that IL-1β (-511) C allele (allele 1) was significantly higher in frequency when compared to healthy controls (x^2: 3.87, df: 1; $p = 0.048$, OR: 1.178, 95% CI: 0.999-1.388). When the genotype distribution of IL-1β (+3953) was compared between groups, no significant difference was observed between the PD and control groups ($p = 0.617$, OR: 1.280, 95% CI: 0.521-1.141). No significant difference was observed in the frequency of the IL-1β +3953 allele between PD cases and controls ($p = 0.901$, OR: 0.978, 95% CI: 0.694-1.380) *(table 3)*.

Since age is a major risk factor for PD, statistical analysis was performed to evaluate the PD group data with regard

Table 1

A) Age and gender distribution of PD patients and controls		
Age and gender	**Controls (n = 199)**	**PD (n =166)**
Age (years ± SD)	60.2 ± 8.6	63.8 ± 10.8
Gender		
- Male	125 (62.8%)	100 (60.3%)
- Female	74 (37.2%)	66 (39.7%)
B) Primer sets used for genotyping		
PCR primers/additional treatment	**Polymorphism**	**Reference**
F: 5'-AAGCTTGTTCTACCACCTGAACTAGGC-3'	IL-1 α (-889)	[13]
R: 5'-TTACATATGAGCCTTCCAT-3'		
NcoI digestion		
F: 5'- CTCAGCAA CACTCCTAT- 3'	IL-1Ra	[24]
R: 5'- TCC TGGTCTGCAGGTAA -3'		
F:5'-GTTTAGGAATCTTCCCACTT-3'	IL-1β (-511)	[24]
R:5'- TGGCATTGATCTGGTTCATC- 3'		
AvaI digestion		
F:5'- GTTGTCATCAGACTTTGACC- 3'	IL-1β (+3953)	[24]
R:5' -TTCAGTTCATATGGACCAGA -3'		
TaqI digestion		

Table 2
Genotype distribution and allele frequency of the IL-1 α (-889) and IL-1Ra VNTR polymorphisms in Turkish population

	Genotypes				**PD *versus* control**	**Alleles**			**PD *versus* control**
	1/1	**1/2**	**2/2**	**1/3**		**1**	**2**	**3**	
IL-1α (-889)[1]									
- Control	94 (47.2)	80 (40.2)	25 (12.6)		p = 0.356	0.673	0.327		p = 0.283
- PD	82 (50)	69 (42.1)	13 (7.9)			0.710	0.290		
IL-1Ra[2]									
- Control	109 (54.8)	61 (30.7)	18 (9)	11 (5.5)	p = 0.588	0.729	0.244	0.028	p = 0.836
- PD	89 (54.3)	56 (34.1)	9 (5.5)	10 (6.1)		0.744	0.226	0.030	

[1] P-values for IL-1α (-889) were calculated using the Chi-Square exact test with 2 x 3 contingency tables (genotype) and 2 x 2 table (allele).
[2] P-values of IL-1Ra VNTR were calculated using the Chi-Square exact test with 2 x 4 contingency tables (genotype) and 2 x 3 table (allele).
Genotypes were expressed as number of patients (proportion in % within brackets), p-values were from the Chi-Square exact test.
* P < 0.05 was taken as the level of significance.

Table 3
Genotype distribution and allele frequency of the IL-1 β (-511) and (+3953) SNP polymorphisms in PD and control groups in Turkish population

	Genotypes			**PD *versus* control**	**Alleles**		**PD *versus* control**
	1/1	**1/2**	**2/2**		**1**	**2**	
IL-1β (-511)[1]							
- Control	61 (30.7)	84 (42.2)	54 (27.1)*	p = 0.018	0.518	0.482	p = 0.048
- PD	55 (33.1)	86 (51.8)	25 (15.1)		0.590*	0.410	
IL-1β (+3953)[2]							
- Control	114 (57.3)	75 (37.7)	10 (5)	p = 0.617	0.761	0.239	p = 0.901
- PD	98 (59.8)	55 (33.5)	11 (6.7)		0.765	0.235	

[1] P-values of IL-1β (-511) and [2] p-values of IL-1β (+3953) were calculated using the Chi-Square exact test with 2 x 3 contingency tables (genotype) and 2 x 2 table (allele). Genotypes were expressed as number of patients (proportion in % within brackets), p-values were from the Chi-Square exact test. * P < 0.05 was taken as the level of significance.

to age-at-onset. However, no association between IL-1α -889 or IL-1Ra VNTR allele 2 and age-at-onset was found (p = 0.511 and p = 0.802, respectively). Although IL-1 β -511 C/C (1/1) carriers developed PD 3.10 years earlier than the IL-1 β -511 T/T (2/2) genotype carriers (61.51 ± 8.8 years *versus* 58.41 ± 7.4 years; p = 0.289), this difference did not reach statistical significance. Furthermore, no association was found between the IL-1β +3953 polymorphism and age-at-onset of PD in the Turkish population (p = 0.705) *(table 4)*.

Table 4
Comparisons of IL-1 α (-889), IL-1RN (VNTR), IL-1β (-511) and IL-1β (+3953) genotypes and age-at-onset of PD

	Genotypes		
IL-1α -889	**1/1**	**1/2**	**2/2**
- Age	67.53 ±8.5	66.14 ±8.2	67.61 ±9.1
- Age-at-onset	59.01 ±7.9	58.47 ±7.6	61.30 ±8.7
IL-1RN VNTR	**1/1**	**1/2**	**1/3**
- Age	67.22 ± 6.4	67.75 ± 7.3	63.11 ± 5.8
- Age-at-onset	58.97 ± 6.1	59.66 ± 4.7	57.22 ± 5.7
IL-1β -511	**1/1**	**1/2**	**2/2**
- Age	67.12 ± 7.3	65.91 ± 6.9	69.77 ± 7.2
- Age-at-onset	58.41 ± 7.4	58.50 ± 7.9	61.51 ± 8.8
IL-1β +3953	**1/1**	**1/2**	**2/2**
- Age	67.05 ± 5.6	65.83 ± 5.8	71.72 ± 5.2
- Age-at-onset	59.35 ± 6.1	57.20 ± 5.8	64.36 ± 7.1

Mean and ± standard deviation of age and age-at-onset of PD cases were given as years. For comparison of the age-at-PD-onset, the Mann-Whitney U test was used. * $P < 0.05$ was taken as the level of significance.

DISCUSSION [25, 26, 27]

The expression of IL-1, interleukin-6 (IL-6) and tumor necrosis factor alpha (TNF-α) from activated microglial cells in the SN region of PD patients has been reported [11]. PD patients have also been reported to have 7- to 15-fold higher levels of these cytokines in circulation [28-31]. IL-1 is a major proinflammatory cytokine; its role in PD progression has not been fully established. According to some studies, IL-1 acts as a neurotoxic agent [32], but according to the others IL-1 has a neuroprotective role [33, 34]. As polymorphisms in the IL-1 genes have been shown to alter expression levels of IL-1 protein, the association between IL-1 gene polymorphisms and PD in various population groups was investigated.

One of SNPs in the IL-1 family is within the promoter region (-889) of the IL-1α gene. This SNP (C-889T polymorphism) leads to high expression of IL-1α, which may have a protective effect on PD progression [19]. In order to determine the association between IL-1α C-889T polymorphism and PD in the Turkish population, we analyzed the IL-1α -889 genotypes in 166 PD patient and 199 healthy controls. Our results showed that neither genotype distribution nor allele frequency of IL-1α -889 polymorphism differed between PD cases and healthy controls. A lack of association was also reported in Finnish [35], German [36, 37], Taiwan [38] and Japanese [39] populations. Collectively, these results suggest that there could be other IL-1 polymorphisms with a significant association with PD. Since age is a major risk factor for PD, Wu and colleagues analyzed the IL-1α -889 genotype effect on a PD subgroup older than 70; they found that the IL-1α -889 C/T genotype had a protective role in late-onset PD. However, we could not find an association between the IL-1α -889 polymorphism and age-at-onset of PD. This result may be because the average age of the specific PD cases in our study was younger than that in the study of Wu *et al.*, or because the total subject number was smaller. Further studies with larger numbers of PD individuals could be performed to help resolve this issue.

IL-1Ra is an endogenous anti-inflammatory agent coded by the IL-1RN gene. The IL-1Ra gene has been shown to be interrupted with an 86 bp repeating sequence within the second intron, and according to the number of 86 bp repeats, six alleles have been implicated [16-18]. In our study, we found four alleles of IL-1Ra VNTR in the study groups. Our results showed no significant difference either in allele frequency or in genotype distribution between PD patients and controls. A similar lack of association between IL-1Ra VNTR and PD was also found in Finnish [35] and Japanese [39] populations. Thus, IL-1Ra VNTR polymorphism may not be involved in PD progression.

One of the SNPs in the IL-1β gene is the -511 C/T polymorphism. This region is located in the promoter region of the IL-1β gene and is important for regulating gene expression. It was shown that allele 2 (T allele) of IL-1β -511 leads to high levels of IL-1β expression. It has been reported that people carrying the IL-1β -511 allele 2 (T allele) have higher levels of IL-Ra, while people carrying allele 1 have lower levels of IL-1Ra [40]. The balance between IL-1 and IL-1Ra may be important for the development or severity of diseases. Thus, the IL-1β gene that may alter IL-1Ra expression, and individuals carrying the polymorphisms in the IL-1β gene, may have altered susceptibility to certain diseases that have been linked to IL-1, such as PD. However, epidemiological studies addressing the association between IL-1β -511 SNP and PD are controversial. In the US population, it has been reported that the IL-1β -511 2/2 (T/T) genotype is more frequently found in PD patients than in healthy controls [41]. An association between IL-1β -511 2/2 (T/T) genotype and PD was also reported in Caucasian [42] and in German [37] populations. However, an association between the IL-1β -511 C (1) allele and PD was found in the Finnish population [35]. A lack of association between IL-1β (-511) polymorphism and PD was found in Japanese [39] and Taiwanese [38] populations. In contrast to McGeer *et al.* and Möller *et al.*, we found that IL-1β -511 2/2 (T/T) genotype frequency was significantly less frequent in PD patients than in healthy controls ($p = 0.018$), and allele C (allele 1) of IL-1β -511 was more frequently seen in PD patients when compared to normal controls ($p = 0.048$). This result also implies that in the Turkish population the IL-1β -511 C allele is more likely to result in the development of PD. Taken together, it appears that ethnic background and geographic differences may be important factors in these epidemiological studies.

Another SNP in the IL-1 β gene is found in exon 5 at position +3953 [15]. The effect of this polymorphism on PD is poorly understood compared to the IL-1β -511 polymorphism, with the only report being a lack of association between IL-1β +3953 and PD in the Japanese population [39]. In our study, no significant difference between PD and IL-1β +3953 as regards allele and genotype distribution in Turkish population was found. Thus, IL-1β +3953 polymorphisms may have no effect on PD development.

As age is a major risk factor for PD progression, we investigated the association between the age at disease-onset and IL-1 polymorphisms. In our study, we found no

association between IL-1α -889 polymorphism and age-at-onset of PD. However, Wu *et al.* reported that the IL-1α -889 C/T genotype has a protective role in PD patients older than 70 years [38]. Lack of an association between the IL-1β -511 polymorphism and age-at-onset of PD was found in other studies [38, 35] as well as this one. In contrast to our study, Nishumura *et al.* reported that the IL-1β -511 C/C genotype leads to a significantly earlier age for PD onset in the Japanese population [39]. These results suggest that both the association between IL-1 polymorphisms and PD, and the effect of IL-1 polymorphisms on age-at-PD-onset should be investigated in different populations and with large study groups.

In summary, the risk of developing PD has been associated with IL-1 gene cluster polymorphisms. According to our study, IL-1α -889, IL-1Ra VNTR and IL-1β +3953 polymorphisms are not associated with PD in the Turkish population. However, we did find an association between IL-1β (-511) and PD. This is the first report showing the protective effect of the IL-1β -511 T allele (2 alleles) in the development of PD in a Turkish population.

Disclosure. *None of the author has any conflict of interest to disclose.*

Financial support*. This work was supported by a grant from The Marmara University Research Foundation. E.L. is supported by grants from the Diabetes Research Initiative at Ohio University, the World Anti-doping Agency, and the National Institutes of Health (DK075436-01) and (AG019899-06).*

REFERENCES

1. Kempster PA, Hurwitz B. Lees AJ. A new look at James Parkinson's Essay on the Shaking Palsy. *Neurology* 2007; 69: 482-5.
2. Deumens R, Blokland A, Prickaerts J. Modeling Parkinson's disease in rats: an evaluation of 6-OHDA lesions of the nigrostriatal pathway. *Exp Neurol* 2002; 175: 303-17.
3. Lang AE, Lozano AM. Parkinson's disease. Second of two parts. *N Engl J Med* 1998; 339: 1130-43.
4. Mizuno Y, Hattori N, Kitada T, *et al.* Familial Parkinson's disease. Alpha-synuclein and parkin. *Adv Neurol* 2001; 86: 13-21.
5. Gwinn-Hardy K. Genetics of parkinsonism. *Mov Disord* 2002; 17: 645-56.
6. Schapira AH. Evidence for mitochondrial dysfunction in Parkinson's disease a critical appraisal. *Mov Disord* 1994; 2: 125-38.
7. Ben-Shachar D, Zuk R, Glinka Y. Dopamine neurotoxicity: inhibition of mitochondrial respiration. *J Neurochem* 1995; 64: 718-23.
8. Rosenberg RN. Mitochondrial therapy for Parkinson disease. *Arch Neurol* 2002; 59: 1523.
9. McGeer PL, Yasojima K, McGeer EG. Inflammation in Parkinson's disease. *Adv Neurol* 2001; 86: 83-9.
10. Dinarello CA. Proinflammatory cytokines. *Chest* 2000; 118: 503-8.
11. Hirsch EC, Hunot S, Damier P, Faucheux B. Glial cells and inflammation in Parkinson's disease: a role in neurodegeneration? *Ann Neurol* 1998; 44 (3 Suppl. 1): S115-20.
12. Auron PE. The interleukin 1 receptor: ligand interactions and signal transduction. *Cytokine & Growth Factor Rev* 1998; 9: 221-37.
13. McDowell TL, Symons JA, Ploski R, Førre O, Duff GW. A genetic association between juvenile rheumatoid arthritis and a novel interleukin-1 alpha polymorphism. *Arthritis Rheum* 1995; 38: 221-8.
14. dı Gıovıne FS, Takhsh E, Blakemore AI, Duff GW. Single base polymorphism at -511 in the human interleukin-1 beta gene (IL1 beta). *Hum Mol Genet* 1992; 1: 450.
15. Pocıot F, Molvıg J, Wogensen L, Worsaae H, Nerup JA. TaqI polymorphism in the human interleukin-1 beta (IL-1 beta) gene correlates with IL-1 beta secretion *in vitro*. *Eur J Clin Invest* 1992; 22: 396-402.
16. Steinkasserer A, Koelble K, Sim RB. Length variation within intron 2 of the human IL-1 receptor antagonist gene (IL-1 RN). *Nucleic Acid Research* 1991; 19: 5095.
17. Tarlow JK, Blakemore AI, Lennard A, *et al.* Polymorphism in human IL-1 receptor antagonist gene intron 2 is caused by variable numbers of an 86-bp tandem repeat. *Human Genetics* 1993; 91: 403-4.
18. Vamvakopoulos JE, Taylor CJ, Morris-Stiff GJ, Green C, Metcalfe S. The IL-1 Receptor Antagonist gene: A single-copy variant of the intron 2 variable number tandem repeat (VNTR) polymorphism. *Eur J Immunogenet* 2002; 29: 337-40.
19. Arend WP. The balance between IL-1 and IL-1 Ra in disease. *Cytokine & Growth Factor Rev* 2002; 13: 323-40.
20. Gibb WR, Lees AJ. The relevance of the Lewy body to the pathogenesis of idiopathic Parkinson's disease. *J Neurol Neurosurg Psychiatr* 1988; 51: 745-52.
21. Fahn S, Elton RL, and Members of the UPDRS Development Committee. The Unified Parkinson's Disease Rating Scale. In: Fahn S, Marsden CD, Calne DB, Goldstein M, eds. *Recent developments in Parkinson's disease*. Florham Park, N.J.: Macmillan Healthcare Information, 1987: 153-64.
22. Hoehn MM, Yahr MD. Parkinsonism: onset, progression and mortality. *Neurology* 1967; 17: 427-42.
23. Miller SA, Dykes DD, Polesky HF. A simple salting out procedure for extracting DNA from human nucleated cells. *Nucleic Acids Res* 1988; 16: 1215.
24. Arman A, Yılmaz B, Coker A, Inanc N, Direskeneli H. Interleukin-1 Receptor Antagonist (IL-1RN) and Interleukin-1B gene Polymorphisms in Turkish patients with Rheumatoid Arthritis. *Clin Exp Rheumatol* 2006; 24: 643-8.
25. de Rijk MC, Tzourio C, Breteler MM, *et al.* Prevalence of parkinsonism and Parkinson's disease in Europe: the EUROPARKINSON Collaborative Study. European Community Concerted Action on the Epidemiology of Parkinson's disease. *J Neurol Neurosurg Psychiatry* 1997; 62: 10-5.
26. Hagan JJ, Middlemiss DN, Sharpe PC, Poste GH. Parkinson's disease: prospects for improved drug therapy. *Trends Pharmacol Sci* 1997; 18: 156-63.
27. Forno LS. Neuropathology of Parkinson's disease. *J Neuropathol Exp Neurol* 1996; 55: 259-72.
28. Mogi M, Harada M, Riederer PP, Narabayashi H, Fujita K, Nagatsu T. Tumor necrosis factor-alpha (TNF-alpha) increases both in the brain and in the cerebrospinal fluid from parkinsonian patients. *Neurosci Lett* 1994; 165: 208-10.
29. Nagatsu T, Mogi M, Ichinose H, Togari A. Cytokines in Parkinson's disease. *J Neural Transm Suppl* 2000; 58: 143-51.
30. Blum-Degen D, Müller T, Kuhn W, Gerlach M, Przuntek H, Riederer P. Interleukin-1 beta and interleukin-6 are elevated in the cerebrospinal fluid of Alzheimer's and *de novo* Parkinson's disease patients. *Neurosci Lett* 1995; 202: 17-20.

31. Müller T, Blum-Degen D, Przuntek H, Kuhn W. Interleukin-6 levels in cerebrospinal fluid inversely correlate to severity of Parkinson's disease. *Acta Neurol Scand* 1998; 98: 142-4.

32. Hirsch EC, Hunot S, Hartmann A. Neuroinflammatory processes in Parkinson's disease. *Parkinsonism Relat Disord* 2005; 11 (Suppl. 1): S9-15.

33. Wang J, Bankiewicz KS, Plunkett RJ, Oldfield EH. Intrastriatal implantation of interleukin-1. Reduction of parkinsonism in rats by enhancing neuronal sprouting from residual dopaminergic neurons in the ventral tegmental area of the midbrain. *J Neurosurg* 1994; 80: 484-90.

34. Ho A, Blum M. Induction of interleukin-1 associated with compensatory dopaminergic sprouting in the denervated striatum of young mice: model of aging and neurodegenerative disease. *J Neurosci* 1998; 18: 5614-29.

35. Mattila KM, Rinne JO, Lehtimäki T, Röyttä M, Ahonen JP, Hurme M. Association of an interleukin 1B gene polymorphism (-511) with Parkinson's disease in Finnish patients. *J Med Genet* 2002; 39: 400-2.

36. Schulte T, Schöls L, Müller T, Woitalla D, Berger K, Krüger R. Polymorphisms in the interleukin-1 alpha and beta genes and the risk for Parkinson's disease. *Neurosci Lett* 2002; 326: 70-2.

37. Möller JC, Depboylu C, Kölsch H, *et al.* Lack of association between the interleukin-1 alpha (-889) polymorphism and early-onset Parkinson's disease. *Neurosci Lett* 2004; 359: 195-7.

38. Wu YR, Chen CM, Hwang JC, *et al.* Interleukin-1alpha polymorphism has influence on late-onset sporadic Parkinson's disease in Taiwan. *J Neural Transm* 2007; 114: 1173-7.

39. Nishimura M, Mizuta I, Mizuta E, Yamasaki S, Ohta M, Kuno S. Influence of interleukin-1beta gene polymorphisms on age-at-onset of sporadic Parkinson's disease. *Neurosci Lett* 2000; 284: 73-6.

40. Hurme M, Santtila S. IL-1 receptor antagonist (IL-1Ra) plasma levels are co-ordinately regulated by both IL-1Ra and IL-1beta genes. *Eur J Immunol* 1998; 28: 2598-602.

41. Wahner AD, Sinsheimer JS, Bronstein JM, Ritz B. Inflammatory cytokine gene polymorphisms and increased risk of Parkinson disease. *Arch Neurol* 2007; 64: 836-40.

42. McGeer PL, Yasojima K, McGeer EG. Association of interleukin-1 beta polymorphisms with idiopathic Parkinson's disease. *Neurosci Lett* 2002; 326: 67-9.