Original article

Folia Neuropathologica

Association of monoamine oxidase B and catechol-O-methyltransferase polymorphisms with sporadic Parkinson's disease in an Iranian population

Anahita Torkaman-Boutorabi[1], Gholam Ali Shahidi[2], Samira Choopani[3], Mohammad Reza Zarrindast[1]

[1]Department of Neuroscience, School of Advanced Technologies in Medicine, Tehran University of Medical Sciences, Tehran, Iran, [2]Department of Neurology, Hazrat Rasool Hospital, Tehran University of Medical Sciences, Tehran, Iran, [3]Department of Physiology and Pharmacology, Pasteur Institute of Iran, Tehran, Iran

Folia Neuropathol 2012; 50 (4): 382-389 DOI: 10.5114/fn.2012.32368

Abstract

Genetic polymorphisms have been shown to be involved in dopaminergic neurotransmission. This may influence susceptibility to Parkinson's disease (PD). We performed a case-control study of the association between PD susceptibility and a genetic polymorphism of MAOB and COMT, both separately and in combination, in Iranians. The study enrolled 103 Iranian patients with PD and 70 healthy individuals. Polymerase chain reaction restriction fragment length polymorphism (PCR-RFLP) methods were used for genotyping. Our data indicated that the MAOB genotype frequencies in PD patients did not differ significantly from the control group. However, the frequency of MAOB GG genotype was significantly lower in female patients. It has been shown that the distribution of MAOB allele A was slightly higher in PD patients. No statistically significant differences were found in the COMT allele and genotype distribution in PD patients in comparison to the controls. The combined haplotype of the MAOB A, A/A and COMT LL genotype showed a slight increase in the risk of PD in female patients in this Iranian population. The data may suggest that the MAOB and COMT genetic polymorphisms do not play any role in the pathogenesis of PD in Iranians. In addition, the combined haplotype of MAOB and COMT genes did not significantly affect the susceptibility to PD. Future studies involving larger control and case populations will undoubtedly lead to a more thorough understanding of the role of the polymorphisms involved in the dopamine pathway in PD.

Key words: *COMT, Iranian, MAOB, Parkinson's disease, polymorphism.*

Introduction

Many investigations have been made to elucidate pathogenesis of Parkinson's disease (PD), but no unambiguous factors for its occurrence have been indicated [31]. Currently, a conception of 'double hit hypothesis' has been presented to describe involvement of genetic factors in occurrence of the disease when subjects are exposed to certain environmental neurotoxins. Dopamine is one of the major modulatory neurotransmitters in the central nervous system (CNS) [20]. As a dysfunction of dopaminergic neurotransmission in the CNS has been implicated in development of PD [17], it has been suggested that genetic polymorphisms involved in the biosynthesis and degra-

Communicating authors:
Anahita Torkaman-Boutorabi, Department of Neuroscience, School of Advanced Technologies in Medicine, Tehran, Iran, e-mail: anahitaboutorabi@yahoo.com; Mohammad Reza Zarrindast, Department of Neuroscience, School of Advanced Technologies in Medicine, Tehran, Iran, e-mail: zarinmr@ams.ac.ir

dation of dopamine and related compounds influence the susceptibility to PD. The candidate PD pathogenic genes include those that are linked to dopamine synthesis, transport and degradation, detoxification of xenobiotics and other toxins in dopaminergic neurons. Recent studies suggest that monoamine oxidase B (MAOB) A644G and catechol-O-methyltransferase (COMT) G1947A polymorphisms might influence the risk and treatment of PD.

Monoamine oxidase B (MAOB) is one of the primary enzymes regulating metabolism of neurotransmitters such as dopamine. It is well documented that MAOB inhibition may prevent degeneration of the dopaminergic system in PD [5,35]. Patients with PD are reported to have higher platelet MAOB activity than control individuals [34]. Furthermore, inhibition of MAOB activity in the brains of cigarette smokers has been suggested to have a protective effect against the development of PD [5]. Therefore, low MAOB activity may play a preventive role in PD development. The gene encoding MAOB is located on the X-chromosome (Xp11.4-p11.23) [19] and contains an A644G (rs1799836) SNP in intron 13 [25]. Although the MAOB A644G polymorphism is a synonymous substitution, this single nucleotide polymorphism (SNP) is associated with varying enzyme activity. As the G allele of MAOB A644G polymorphism is associated with lower brain MAOB activity, the G allele may be involved in PD susceptibility (protective). On the other hand, it has been shown that in the human brain the A allele has been associated with higher messenger Ribonucleic Acid (mRNA) levels of MAOB [1]. The positive association of the intron 13 A644G polymorphism in the *MAOB* gene with PD has been reported in Caucasian and Japanese populations [6,25,32,39] whereas other studies failed to find any correlation [12-14,18,28,29].

Catechol-O-methyltransferase (COMT) is an enzyme, which by O-methylation inactivates neurotransmitters or toxic catechols and some hydroxylated metabolites. The COMT gene in humans is localized to chromosome 22, band q11.2. The Val158Met SNP within COMT (rs4680) encodes a Valine→Methionine substitution at protein residue 158 of the membrane-bound COMT isoform that predominates in brain tissue. This substitution is linked to low COMT enzyme activity and is designated the L (low activity) allele, in contrast to the H (high activity) allele [18]. In the individuals with the L allele, the COMT protein is thermolabile. Decreased COMT activity may result in increased metabolism of dopamine to neuromelanin that can enhance the formation of cytotoxic radicals contributing to neuronal degeneration [21]. As the A allele of COMT G1947A is associated with low COMT activity of soluble COMT [37], the A allele of COMT G1947A may be linked to an increased risk of PD. Homozygosity for the COMT A allele has been reported to be a genetic risk of PD in Japanese people, but recent studies in whites and Chinese people failed to confirm any association between PD and COMT polymorphism [24,40,41].

To understand the pathogenesis of PD, extensive studies may be required. In fact, it is necessary to find out whether a cluster of related genes is involved in the nigrostriatal degeneration of dopamine neurons. Several studies have focused on a mutation in a separate gene of either MAOB or COMT associated with susceptibility to PD and there are a few reports indicating the interplay between these two genes in the pathogenesis of PD. Wu *et al.* [39] reported that the low activity allele of COMT augments the positive association of a single nucleotide variant in the MAOB gene with PD in a Taiwanese population. On the other hand, there is a report indicating that the combined haplotype of the MAOB G (G/G) and COMT HL genotype caused a fourfold increase in the risk of PD in a Polish female population [2], thus an interaction between these two dopamine-metabolizing enzymes may be correlated with the pathogenesis of PD.

The prevalence of PD varies worldwide. In general, this disease is less common in Asia than in Western countries. Thus, understanding the ethnicity-specific influence of susceptible genes on the PD risk in different races may provide valuable clues to potential causes of racial and individual susceptibility to PD. In the present study, we determined both the individual and combined effect of MAOB and COMT genetic polymorphisms on the PD risk in a population of Iranian patients (n = 103) with PD and in a control group (n = 70).

Material and methods

Human subjects

Patients of Iranian origin were included in the study after giving informed consent. The protocol of the study was approved by the human subjects research Ethnic Committee of the Tehran University of Medical Sciences, Iran. A total of 103 unrelated patients suffering from sporadic PD (72 males, 31 females) aged 36-83 years (mean age 57.46 ± 10.35 SD) were enrolled in the study. All patients were recruited from the Movement Dis-

orders Clinic at the Hazrat Rasool Hospital in Tehran, Iran. Diagnosis of idiopathic PD was based on clinical symptoms according to the UK Parkinson's Disease Society Brain Bank Clinical Diagnostic Criteria [8] and if at least two of the four main signs of the disease, i.e. tremor at rest, rigidity, bradykinesia and postural reflex impairment, were observed. All patients were examined during the "on" state for their baseline motor function and the activities of daily living using the Unified Parkinson's Disease Rating Scale (UPDRS) in the phase of good motor activity. The severity of the disease was evaluated using the Hoehen-Yahr (H-Y) score [16]. The control group consisted of 70 individuals (42 males, 28 females), aged 36-87 years (mean age 55.73 ± 11.69 SD) and recruited from the same hospital and without any previous diagnosis of a neurodegenerative or malignant disease. Controls and cases were matched for age and sex.

Genomic DNA was extracted from blood samples, using the NucleoSpin® blood XL kit (Macherey-Nagel, Germany). COMT and MAOB genotypes were determined using the polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) assay, as originally described by Kunugi *et al.* [24] and Sun *et al.* [36].

Genetic analysis

In the MAOB study, a 232 bp DNA fragment of the MAOB containing the intron 13 polymorphism was amplified. The forward primer 5-GGAACCTCTTATACCACAGG-3 and reverse primer 5-GACTGCCAGATTTCATCCTC-3 were used for partial MAOB DNA fragment amplification [30]. The PCR mixture in the MAOB study contained the same reagents used in COMT amplification and under previously described conditions [3]. To determine the MAOB polymorphism, the PCR amplified DNA product was digested with the restriction enzyme *Tsp* 45I. MAOB allele A (containing the *Tsp* 45I restriction site) was detected as two bands of 146 and 86 bp, whereas allele G (containing no *Tsp* 45I restriction site) was detected as a single 232-bp band [39].

The 217 bp region of the COMT gene, including exon 4, which contains the polymorphism site, was amplified with the following set of primers: 5-TCGTGGACGCCGTGATTCAGG-3 and the reverse primer 5-AGGTCTGACAACGGGTCAGGC-3 [24] under conditions described previously [3, 24]. The PCR product was digested with the restriction enzyme *NIa* III (Fermentase, Canada), which cleaves the Met-108 allele (COMT low activity) but not the Val-108 allele (COMT high activity), in addition to a constant cleavage site. Homozygotes for COMTH variant give fragments of 136 and 81-bp, heterozygotes fragments of 40, 81, 96 and 136-bp and homozygotes for COMTL fragments of 40, 81 and 96-bp [39].

Statistical analysis

Frequencies of genotypes and alleles were given with their 95% confidence intervals (95% CI). Chi-square and odds ratio were used to compare either allelic frequencies or the genotype frequencies of MAOB or COMT in the control and patient groups. When more than 20% of the cell numbers, or when the expected number of cases was less than 1.0 in a cell, Fisher's exact test was performed (SPSS, version 11.5). Since the MAOB gene is located on the X chromosome, the MAOB genotype was assessed separately in men and women. Conformity of genotype distributions to Hardy-Weinberg law was assessed using Chi-square test.

Results

The examination of MAOB and COMT gene's polymorphism was carried out in 70 healthy individuals and in 103 patients with diagnosed PD. The distribution of MAOB genes is presented in Table I. No statistically significant differences were found in the frequency of MAOB genotype in PD patients and controls. However, there is an insignificantly higher incidence of total A alleles in PD patients in comparison to the controls [odds ratio (OR) 0.57, 95% 0.31-1.02, $p = 0.06$]. Since the MAOB gene is located on chromosome X, both sexes were also analysed separately. A higher distribution of G/G genotype is shown in women from the control group compared to the women patients [odds ratio (OR) 8.18, 95% CI 0.91-72.91, $p < 0.05$].

Table II shows the allelic and genotype frequencies for COMT polymorphism. There were no significant differences between the two groups in the frequencies of either the homozygous (H/H or L/L) or heterozygous (H/L) genotypes. Similarly to the whole studied population, there were no sex differences in the distribution of COMT genotypes.

Evaluating the effect of the combined MAOB and COMT polymorphism on the risk of PD development, an insignificantly higher incidence of MAOB A or A/A combined with the COMT L/L genotype was seen in the patient group [odds ratio (OR) 0.48, 95% CI 0.21-1.20,

Table I. MAOB genotype frequencies

Genotype	Patients (n = 103)	Controls (n = 70)	χ^2	P-value	OR (95% CI)
All subjects					
A, A/A	75 (72.8%)	44 (62.9%)	1.92	0.16	0.63 (0.33-1.21)
AG	16 (15.5%)	12 (17.1%)	0.08	0.77	1.12 (0.49-2.55)
G,G/G	12 (11.7%)	14 (20%)	2.27	0.13	1.89 (0.81-4.39)
Total alleles					
A	105 (78.4%)	66 (67.3%)	3.54	0.06	0.57 (0.31-1.02)
G	29 (21.6%)	32 (32.7%)			
Males					
A	61 (84.7%)	34 (81.0%)	0.27	0.60	0.76 (0.28-2.08)
G	11 (15.3%)	8 (19.0%)			
Females					
A/A	14 (45.2%)	10 (35.7%)	0.54	0.46	0.67 (0.23-1.92)
A/G	16 (51.6%)	12 (42.9%)	0.45	0.50	0.70 (0.25-1.96)
G/G	1 (3.2%)	6 (21.4%)	4.66	0.03	8.18 (0.91-72.91)

Figures in parantheses indicate percentages or 95% CIs

Table II. COMT genotype frequencies

Genotype	Patients (n = 103)	Controls (n = 70)	χ^2	P-value	OR (95% CI)
All subjects					
H/H	20 (19.4%)	19 (27.1%)	1.42	0.23	1.54 (0.75-3.17)
H/L	50 (48.5%)	32 (45.7%)	0.13	0.715	0.89 (0.48-1.64)
L/L	33 (32%)	19 (27.1%)	0.47	0.49	0.79 (0.40-1.54)
Total alleles					
L	116 (56.3%)	70 (50%)	1.33	0.27	0.77 (0.50-1.019)
H	90 (43.7%)	70 (50%)			
Males					
H/H	13 (18.1%)	12 (28.6%)	1.71	0.19	1.81 (0.73-4.46)
H/L	38 (52.8%)	19 (45.2%)	0.60	0.43	0.73 (0.34-1.58)
L/L	21 (29.2%)	11 (26.2%)	0.11	0.73	0.86 (0.36-2.02)
Females					
H/H	7 (22.6%)	7 (25%)	0.048	0.82	1.14 (0.34-3.79)
H/L	12 (38.7%)	13 (46.4%)	0.35	0.54	1.37 (0.48-3.86)
L/L	12 (38.7%)	8 (28.6%)	0.67	0.41	0.63 (0.21-1.88)

Figures in parantheses indicate percentages or 95% CIs

Table III. MAOB and COMT haplotype frequencies

Haplotype	Patients (n = 103)	Controls (n = 70)	χ^2	P-value	OR (95% CI)
A, A/A, H/L	37 (35.9%)	22 (31.4%)	0.37	0.54	0.81 (0.42-1.55)
A, A/A, H/H	14 (13.6%)	13 (18.6%)	0.78	0.37	1.45 (0.63-3.30)
A, A/A, L/L	24 (23.3%)	9 (12.9%)	2.94	0.08	0.48 (0.21-1.20)
A/G, H/L	7 (6.8%)	5 (7.1%)	0.00	0.93	1.05 (0.32-3.46)
A/G, H/H	3 (2.9%)	2 (2.9%)	0.00	0.98	0.98 (0.16-6.02)
A/G, L/L	6 (5.8%)	5 (7.1%)	0.12	0.72	1.24 (0.36-4.24)
G, G/G, H/L	6 (5.8%)	5 (7.1%)	0.12	0.72	1.24 (0.36-4.24)
G, G/G, H/H	3 (2.9%)	4 (5.7%)	0.84	0.35	2.02 (0.43-9.31)
G, G/G, L/L	3 (2.9%)	5 (7.1%)	1.69	0.19	2.56 (0.59-11.09)

Figures in parantheses indicate percentages or 95% CIs

Table IV. Sex effect on MAOB and COMT haplotype frequencies

Haplotype	Patients (n = 103)	Controls (n = 70)	χ^2	P-value	OR (95% CI)
Females					
A, A/A, H/L	5 (16.1%)	5 (17.9%)	0.03	0.86	1.13 (0.29-4.40)
A, A/A, H/H	3 (9.7%)	4 (14.3%)	0.29	0.58	1.55 (0.31-7.65)
A, A/A, L/L	6 (19.4%)	1 (3.6%)	3.50	0.06	0.15 (0.01-1.37)
A/G, H/L	7 (22.6%)	5 (17.9%)	0.20	0.65	0.74 (0.20-2.68)
A/G, H/H	3 (9.7%)	2 (7.1%)	0.12	0.72	0.71 (1.11-4.64)
A/G, L/L	6 (19.4%)	5 (17.9%)	0.02	0.88	0.90 (0.24-3.37)
G, G/G, H/L	0 (0.0%)	3 (10.7%)	3.49	0.06	0.89 (0.78-1.01) undefined
G, G/G, H/H	1 (3.1%)	1 (3.6%)	0.00	0.92	1.14 (0.06-19.25)
G, G/G, L/L	0 (0.00%)	2 (7.1%)	2.29	0.13	0.92 (0.83-1.02) undefined
Males					
A, H/L	32 (44.4%)	17 (40.5%)	0.17	0.68	0.85 (0.39-1.83)
A, H/H	11 (15.3%)	9 (21.4%)	0.69	0.40	1.51 (0.56-4.02)
A, L/L	18 (25.0%)	8 (19.0%)	0.53	0.46	0.70 (0.27-1.80)
G, H/L	6 (8.3%)	2 (4.8%)	0.51	0.47	0.55 (0.10-2.85)
G, H/H	2 (2.8%)	3 (7.1%)	1.20	0.27	0.55 (0.10-2.85)
G, L/L	3 (4.2%)	3 (7.1%)	0.47	0.49	2.69 (0.43-16.8)

Figures in parantheses indicate percentages or 95% CIs

$p = 0.08$]. Moreover, it seems that this association is stronger in women in the total population, but was not seen in men.

Discussion

Several reports published so far aimed at evaluating the association between polymorphisms of MAOB and COMT enzymes and the incidence of PD. There are also a few reports showing the interaction between the two gene polymorphisms [2,3,39]. However, there are no available data on the MAOB and COMT genotype interplay in an Iranian population.

The role of a genetic polymorphism of MAOB in the etiopathogenesis of PD has been widely discussed in the literature with conflicting results. The results of the present study demonstrated that the presence of allele A of MAOB might be associated with an increased risk of PD. Similar to our data there is a report that in Caucasians allele A occurred slightly more frequently among PD patients than in controls [14]. Furthermore, a two-fold risk elevation associated with the polymorphism of intron 13 carries of allele A has been shown, which was detected by single-strand conformational polymorphism analysis [25]. Another investigation in a Japanese population indicated the predominance of MAOB allele A in PD patients [4,23]. On the contrary, a significant association between the G allele of MAOB and an increased PD risk was observed [6,33,39]. Other studies found no association between this polymorphism and the PD risk in Asian, Caucasian, Australian, Polish, British populations, and five other European countries (Italy, Malta, Romania, Scotland, and Sweden) [2,9,13,14,27,38]. Since the MAOB gene is located on the X chromosome; the distribution of the alleles was also evaluated in both sexes. In females diagnosed with PD, there is a lower incidence of G/G genotype. Thus, it seems that the G allele may play a protective role against PD in females. However, in both sexes, there were no significant differences between patient and control groups in the frequency of MAOB alleles and genotypes in Polish and Taiwanese populations. The role of the MAOB polymorphism in PD has not been fully established. There are reports indicating the MAOB allele G as the marker of lower enzymatic activity [25,27]. However, others reported contradictory results [13]. Al-though it was suggested that the MAOB (G/A) polymorphism of intronic origin does not directly affect the amino acid sequence, it can contribute to the varying expression of MAOB [7,11]. Undoubtedly, intensive oxidation processes in the nigrostriatal cells may both initiate and intensify the already existing deleterious processes.

A similar situation can be observed in the case of the COMT polymorphism. Most studies have not detected an association between the COMT polymorphism and the risk of PD [10,15,22,37,40]. Contrary to those studies, it has been reported that the AA genotype is a genetic risk factor for PD in the Japanese [24,41]. On the other hand, another study on a Polish population showed a significantly lower frequency of COMT L homozygotes in PD in comparison to the controls [2]. The results of the present study failed to confirm any significant association between the COMT polymorphism and the risk of PD. Furthermore, in PD subjects and in the controls, the distribution of the COMT allele studied was comparable both in men and women. The low-activity COMT allele (COMT L) is common in whites, with an allelic frequency of 40-50%, but less common in Asians and Africans, in whom the frequency is 20-30% [24,26,41]. The frequency of the COMT L allele in our study (50%) was similar to Caucasians. Since both COMT and MAOB metabolize dopamine and other catecholamines, we have also analysed the additive effect of MAOB and COMT polymorphisms and the risk of PD. We found an insignificantly higher risk of PD in individuals harboring the MAOB allele A or A/A (A for men and A/A for women) combined with the COMT genotype L/L. Low COMT enzyme activity results in dopamine being metabolized mainly by MAOB, which may increase oxidative stress on midbrain dopamine neurons as a result of free radical formation through MAOB high activity allele A [6,25,28]. There are limited reports addressing the issue of dopamine catabolism in relation to the PD risk by using a two-gene model. In the Taiwanese, it has been suggested that the association of PD with MAOB G allele is augmented in the presence of COMT L genotype [39]. Similarly, a research on the Polish population found that the frequency of the haplotype consisting of MAOB allele G or G/G combined with the COMT genotype H/L was significantly higher in patients with PD [2]. In contrast, in the US population of Caucasian population ancestry, no cross talk between MAOB and COMT was seen [13].

The present study, however, does have some limitations. First, although our results were negative, the findings may be restricted to the Iranian population as there may be ethnic differences. Moreover, our sample size may be small and may not be powerful enough,

especially for the analysis of a combination of genotypes, as the cells in the constructed contingency tables of the combinations become many and each cell thus has relatively small counts. Thus, larger sample sizes are required to detect smaller effects, probably of minor clinical significance.

Conclusions

To the best of our knowledge, this is the first report on the relation between MAOB and COMT genetic polymorphisms with PD in an Iranian population. Our results suggest that the MAOB and COMT genetic polymorphisms do not play a role in the pathogenesis of PD. In addition, the combined haplotype of MAOB and COMT genes did not significantly affect the susceptibility to PD in this population. However, further studies comprising larger control and case populations may show significant results.

Acknowledgement

This study was supported by the grant of the School of Advanced Technologies in Medicine, Tehran University of Medical Sciences.

The authors wish to thank Dr. Mohammad-Reza Khoshyand for his assistance in the statistical analysis of data.

References

1. Balciuniene J, Emilsson L, Oreland L, Pettersson U, Jazin EE. Investigation of the functional effect of monoamine oxidase polymorphisms in human brain. Hum Genet 2002; 110: 1-7.
2. Bialecka M, Drozdzik M, Honczarenko K, Gawronska-Szklarz B, Stankiewicz J, Dabrowska E, Kubisiak M, Klodowska-Duda G, Opala G. Catechol-O-methyltransferase and monoamine oxidase B genes and susceptibility to sporadic Parkinson's disease in a Polish population. Eur Neurol 2005; 53: 68-73.
3. Bialecka M, Drozdzik M, Klodowska-Duda G, Honczarenko K, Gawronska-Szklarz B, Opala G, Stankiewicz J. The effect of monoamine oxidase B (MAOB) and catechol-O-methyltransferase (COMT) polymorphisms on levodopa therapy in patients with sporadic Parkinson's disease. Acta Neurol Scand 2004; 110: 260-266.
4. Bialecka M, Klodowska-Duda G, Honczarenko K, Gawrońska-Szklarz B, Opala G, Safranow K, Droździk M. Polymorphisms of catechol-0-methyltransferase (COMT), monoamine oxidase B (MAOB), N-acetyltransferase 2 (NAT2) and cytochrome P450 2D6 (CYP2D6) gene in patients with early onset of Parkinson's disease. Parkinsonism Relat Disord 2007; 13: 224-229.
5. Castagnoli K, Murugesan T. Tobacco leaf, smoke and smoking, MAO inhibitors, Parkinson's disease and neuroprotection: are there links? Neurotoxicology 2004; 25: 279-291.
6. Costa P, Checkoway H, Levy D, Smith-Weller T, Franklin GM, Swanson PD, Costa LG. Association of a polymorphism in intron 13 of the monoamine oxidase B gene with Parkinson's disease. Am J Med Genet 1997; 74: 154-156.
7. Costa-Mallen P, Kelada SN, Costa LG, Checkoway H. Characterization of the in vitro transcriptional activity of polymorphic alleles of the human monoamine oxidase-B gene. Neurosci Lett 2005; 383: 171-175.
8. Danil SE, Lees AJ. Parkinson's Disease Society Brain Bank, London: overview and research. J Neural Transm 1993; 39: 165-172.
9. De Palma G, Dick FD, Calzetti S, Scott NW, Prescott GJ, Osborne A, Haites N, Mozzoni P, Negrotti A, Scaglioni A, Mutti A. A case-control study of Parkinson's disease and tobacco use: gene-tobacco interactions. Mov Disord 2010; 25: 912-919.
10. Eerola J, Launes J, Hellstrom O, Tienari PJ. Apolipoprotein E (APOE), PARKIN and catechol-O-methyltransferase (COMT) genes and susceptibility to sporadic Parkinson's disease in Finland. Neurosci Lett 2002; 330: 296-298.
11. Garpenstrand J, Ekblom K, Forslund G, Rylander L, Oreland L. Platelet monoamine oxidase activity is related to MAOB intron 13 genotype. J Neural Transm 2000; 107: 523-530.
12. Goudreau JL, Maraganore DM, Farrer MJ, Lesnick TG, Singleton AB, Bower JH, Hardy JA, Rocca WA. Case-control study of dopamine transporter-1, monoamine oxidase-B, and catechol-O-methyl transferase polymorphisms in Parkinson's disease. Mov Disord 2002; 17: 1305-1311.
13. Hernan MA, Checkoway H, O'Brien R, Costa-Mallen P, De Vivo I, Colditz GA, Hunter DJ, Kelsey KT, Ascherio A. MAOB intron 13 and COMT codon 158 polymorphisms, cigarette smoking, and the risk of PD. Neurology 2002; 58: 1381-1387.
14. Ho SL, Kapadi AL, Ramsden DB, Williams AC. An allelic association study of monoamine oxidase B in Parkinson's disease. Ann Neurol 1995; 37: 403-405.
15. Hoda F, Nicholl D, Bennett P, Arranz M, Aitchison KJ, al-Chalabi A, Kunugi H, Vallada H, Leigh PN, Chaudhuri KR, Collier DA. No association between Parkinson's disease and low-activity alleles of catechol Omethyltransferase. Biochem Biophys Res Commun 1996; 228: 780-784.
16. Hoehn MM, Yahr MD. Parkinsonism: onset, progression, and mortality. Neurology 1967; 17: 427-442.
17. Hornykiewicz O. Dopamine (3-hydroxytyramine) and brain function. Pharmacol Rev 1966; 18: 925-964.
18. Hosak L. Role of the COMT gene Val158Met polymorphism in mental disorders. A review. Eur Psychiatry 2007; 22: 276-281.
19. Hsu YP, Powell JF, Sims KB, Breakefield XO. Molecular genetics of monoamine oxidases. J Neurochem 1989; 53: 12-18.
20. Jaber M, Robinson SW, Missale C, Caron MG. Dopamine receptors and brain function. Neuropharmacology 1996; 35: 1503-1519.
21. Jellinger K, Kienzl E, Rumpelmair G, Riederer P, Stachelberger H, Ben-Shachar D, Youdim MB. Iron-melanin complex in substantia nigra of parkinsonian brains: an x-ray microanalysis. J Neurochem 1992; 59: 1168-1171.
22. Kalinderi K, Fidani L, Kourtesi G, Katsarou Z, Mioglou E, Bostantjopoulou S. No association of the Val158Met COMT polymorphism with Parkinson's disease in the Greek population. Eur J Neurol 2008; 15: e83.
23. Kiyohara C, Miyake Y, Koyanagi M, Fujimoto T, Shirasawa S, Tanaka K, Fukushima W, Sasaki S, Tsuboi Y, Yamada T, Oeda T, Shima-

da H, Kawamura N, Sakae N, Fukuyama H, Hirota Y, Nagai M; Fukuoka Kinki Parkinson's Disease Study Group. Genetic polymorphisms involved in dopaminergic neurotransmission and risk for Parkinson's disease in a Japanese population. BMC Neurol 2011; 11: 89.
24. Kunugi H, Nanko S, Ueki A, Otsuka E, Hattori M, Hoda F, Vallada HP, Arranz MJ, Collier DA. High and low activity alleles of catechol-Omethyltransferase gene: ethnic difference and possible association with Parkinson's disease. Neurosci Lett 1997; 221: 202-204.
25. Kurth JH, Kurth MC, Podsulo SE, Schwankhaus JD. Association of a monoamine oxidase B allele with Parkinson's disease. Ann Neurol 1993; 33: 368-372.
26. McLeod HL, Syvanen AC, Githang A, Indalo A, Ismail D, Dewar K, Ulmanen I, Sludden J. Ethnic differences in catechol-O-methyltransferase pharmacogenetics: Frequency of the codon 108/158 low activity allele is lower in Kenyan than Caucasian or South-west Asian individuals. Pharmacogenetics 1998; 8: 195-199.
27. Mellick GD, Buchanan DD, McCann SJ, James KM, Johnson AG, Davis DR, Liyou N, Chan D, Le Couteur DG. Variations in the monoamine oxidase B (MAOB) gene are associated with Parkinson's disease. Mov Disord 1999; 14: 219-224.
28. Morimoto Y, Murayama N, Kuwano A, Kondo I, Yamashita Y, Mizuno Y. Association analysis of a polymorphism of the monoamine oxidase B gene with Parkinson's disease in a Japanese population. Am J Med Genet 1995; 60: 570-572.
29. Nanko S, Ueki A, Hattori M. No association between Parkinson's disease and monoamine oxidase A and B gene polymorphisms. Neurosci Lett 1996; 204: 125-127.
30. Reilly DK, Rivera-Calimlim L, Van Dyke D. Catechol-O-methyltransferase activity: a determinant of levodopa response. Clin Pharmacol Ther 1980; 2892: 278-286.
31. Samii A, Nutt JG, Ransom BR. Parkinson's disease. Lancet 2004; 363: 1783-1793.
32. Shao M, Liu Z, Tao E, Chen B. Polymorphism of MAO-B gene and NAD(P)H: quinone oxidoreductase gene in Parkinson's disease. Zhonghua Yi Xue Yi Chuan Xue Za Zhi 2001; 18: 122-124.
33. Singh M, Khan AJ, Shah PP, Shukla R, Khanna VK, Parmar D. Polymorphism in environment responsive genes and association with Parkinson disease. Mol Cell Biochem 2008; 312: 131-138.
34. Steventon GB, Sturman SG, Heafield MTE, Waring RH, Napier J, Williams AC. Platelet monoamine oxidase-B activity in Parkinson's disease. J Neural Transm Park Dis Dement Sect 1989; 1: 255-261.
35. Strolin Benedetti M, Dostert P. Monoamine oxidase, brain ageing and degenerative diseases. Biochem Pharmacol 1989; 38: 555-561.
36. Sun B, Zhang WY, Zhao YH. Association between catechol-methyltransferase gene polymorphism and pregnancy induced hypertension. Zhonghua Fu Chan Ke Za Zhi 2004; 39: 21-23.
37. Syvanen AC, Tilgmann C, Rinne J, Ulmanen I. Genetic polymorphism of catechol-O-methyltransferase (COMT): correlation of genotype with individual variation of S-COMT activity and comparison of the allele frequencies in the normal population and parkinsonian patients in Finland. Pharmacogenetics 1997; 7: 65-71.
38. Tan EK, Chai A, Lum SY, Shen H, Tan C, Teoh ML, Yih Y, Wong MC, Zhao Y. Monoamine oxidase B polymorphism, cigarette smoking and risk of Parkinson's disease: a study in an Asian population. Am J Med Genet B Neuropsychiatr Genet 2003; 120B: 58-62.
39. Wu RM, Cheng CW, Chen KH, Lu SL, Shan DE, Ho YF, Chern HD. The COMT L allele modifies the association between MAOB polymorphism and PD in Taiwanese. Neurology 2001; 56: 375-382.
40. Xie T, Ho SL, Li SW, Ma OC. G/A 1947 polymorphism in catechol-O-methyltransferase (COMT) gene in Parkinson's disease. Mov Disord 1997; 12: 426-427.
41. Yoritaka A, Hattori N, Yoshino H, Mizuno Y. Catechol-O-methyltransferase genotype and susceptibility to Parkinson's disease in Japan. Short communication. J Neural Transm 1997; 104: 1313-1317.