의학석사 학위논문

Genetic association study of *LRRK2* exonic variants with susceptibility to Parkinson disease in Korean ethnicity

한국인의 *LRRK2* 유전자 엑손 변이와 파킨슨병의 발병 위험도의 관계에 대한 유전 연관 연구

2012 년 12 월

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December 2012

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A thesis submitted to the Department of neurology in partial fulfillment of the requirements for the Degree of Master in Medicine (Neurology) at Seoul National University College of Medicine

December 2012

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논문 제목: Genetic association study of *LRRK2* exonic variants with susceptibility to Parkinson disease in Korean ethnicity

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제 출 일: 2012 년 12 월 25 일

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ABSTRACT

Introduction: The number of *LRRK2* allelic variant has been reported more than one hundred thirty. Only a few representative allelic variants were studied in Korean ethnicity regarding the contribution of each variant to Parkinson disease (PD). Due to the ethnicity-specific distribution of variants, it is implausible to apply the results of studies conducted in other ethnicity to Korean ethnicity. Through sequencing 122 markers of *LRRK2* we investigated the frequency and the susceptibility to PD of each allelic variant in Korean ethnicity.

Methods: A total of 1069 unrelated subjects consisting of 663 sporadic PD patients and 406 healthy controls were included. As we are a participant of GEO-PD (the genetic epidemiology of Parkinson's disease consortium) project, 122 markers of *LRRK2* were genotyped. Pearson's chi-squared test was used to assess allelic association with PD. Then, we analyzed them through logistic regression analysis adjusting for age and sex to ascertain which markers modulate the risk of PD and to determine the extent to which the markers modulate the risk of PD.

Results: None of *LRRK2* exonic variants showed statistically significant association with the risk of PD. Presumptively, *LRRK2* p.N551K (rs7308720; OR 0.69, 95% CI 0.52-0.92; p=0.012), p.R1398H (rs7133914; OR 0.68, 95% CI 0.51-0.91; p=0.009), p.K1423K (rs11175964; OR 0.69, 95% CI 0.52-0.93; p=0.014), p.M2397T (rs3761863; OR 0.73, 95% CI 0.56-0.95; p=0.020) carriers showed lower risk of PD than non-carriers; *LRRK2* p.A419V

(rs34594498; OR 2.21, 95% CI 1.11-4.38; p=0.023) carriers presented higher risk of PD than non-carriers using dominant model-based logistic regression analysis. In linkage disequilibrium analysis, p.N551K, p.R1398H, p.K1423K were in strong LD together (r2>0.8).

Conclusions: In Korean population, presumptively, p.R1398H, p.N551K, p.K1423K variants constituting a haplotype modulate the risk of PD favorably, whereas p.A419V is associated with increased risk of PD. Although this result did not show statistically significant association, further study with sufficient number of subjects can confirm the result of this study.

Keywords: Parkinson disease, LRRK2, exonic variant.

Student number: 2008-21949

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INTRODUCTION

Parkinson disease (PD) has traditionally been considered a sporadic, neurodegenerative disorder. Nevertheless, PD is a heterogeneous, multifactorial syndrome with age-associated penetrance for which genetic susceptibility contributes to risk (1, 2). In the last 10 years, several chromosomal loci (termed PARK), genes, and mutations have been linked to familial parkinsonism through classic linkage approaches. In 2002, genetic linkage analysis of a Japanese family with dominantly inherited parkinsonism reminiscent of L-dopa responsive late-onset PD allowed Funayama and colleagues to map a novel PARK locus, PARK8, to chromosome 12q12.3 In that locus, subsequent studies identified pathogenic amino acid substitutions in a novel gene, leucine-rich repeat kinase 2 (*LRRK2*; Lrrk2). Seven definite pathogenic *LRRK2* mutations (encoding *LRRK2* N1437H, R1441C, R1441G, R1441H, Y1699C, G2019S, and I2020T) have been described so far (4).

LRRK2 gene has been widely investigated due to its role in pathogenesis of PD. Mutations in the *LRRK2* are now recognized as the most common genetic determinant of familial and sporadic PD.5 Various studies reported that *LRRK2* mutations account for roughly 10% of the familial and 1-5% of sporadic PD (6).

LRRK2 encompasses approximately 144 kilobases with 51 exons encoding a 2527 amino acid protein, 286 KDa. LRRK2 is a multidomain protein containing several protein interaction motifs as well as dual enzymatic domains of GTPase and protein kinase activities, including a leucine-rich

repeat domain, armadillo and ankyrin repeats, GTPase (Roc), Roc spacer (COR), WD40, and a kinase domain (MAPK) toward the C terminal. All are potentially associated with protein-protein interactions (1). The alteration of the enzymatic activity caused by genetic variants might induce neuronal cell toxicity, hence predisposes to PD.

The number of polymorphic variants of *LRRK2* is also considerable, the national center of biotechnology information (NCBI) dbSNP build 132 reports as many as one hundred thirty allelic variants in *LRRK2* as of 2011. Some variants such as p.G2019S were designated as pathogenic variants, while others are not reported to be clinically relevant (7). The ethnicity-specific distribution of pathogenic variants also hinders particular pathogenic *LRRK2* variants from being accepted as a general risk factor of PD, as a number of studies found that specific variants affecting the risk of PD in particular ethnic groups do not seem to even exist in other ethnicity even among Asian populations; several studies with ethnic Chinese subjects reported that *LRRK2* p.G2385R, p.R1628P are associated with increased risk of PD; however, two separate studies with Japanese and Korean subjects showed extremely rare frequency of subjects carrying *LRRK2* p.R1628P variant (8-12). Therefore, it is implausible to generalize the clinical impact of polymorphic variants of specific ethnicity to other ethnic groups.

So far, two Korean ethnic studies with regard to the relationship between *LRRK2* variants and the risk of PD were aimed to evaluate the clinical impact of at most one or two targeted SNPs (12, 13). Among a number of polymorphic variants of *LRRK2*, the question as to which variants have

impact that might be deleterious or protective on PD has yet to be elucidated in Korean population. Thus, with Korean population, we aimed to evaluate the effect of polymorphic variants of *LRRK2* on the risk of PD through sequencing 122 markers in *LRRK2*. Being a participant of "*LRRK2* variants and Parkinson's disease susceptibility" project of the genetic epidemiology of Parkinson's disease consortium (GEO-PD), we obtained gene sequencing data by aid of GEO-PD.

MATERIALS AND METHODS

Materials

The sporadic PD patients were defined as PD diagnosed by use of the UK Parkinson's Disease Society Brain Bank criteria with typical clinical symptoms, late onset, and no family history up to third degree relatives. All PD patients were personally examined and have been followed regularly by senior neurologist (BSJ) at Seoul national university hospital since 1993. The healthy controls were either healthy spouses of PD patients or those who presented for routine health examinations. All PD patients and controls were native Koreans, and none of them were from consanguineous families. The patients were screened with SNCA, PARK2, PINK1, DJ-1, SCA2, and SCA17, and those who were positive were excluded from the study.

A total of 663 PD patients and 406 healthy controls were included in the study. All DNA samples from subjects were collected after ethics approval had been obtained from Seoul national university hospital Institutional Review Board Committee, and were used in accordance with the terms of the written informed consent provided by the participants.

Genetic analysis

As being a participant of GEO-PD project "LRRK2 variants and Parkinson's disease susceptibility," we sent Korean study population samples to GEO-PD; and samples were analyzed by aid of GEO-PD project. GEO-PD study group identified *LRRK2* exonic variants through searches of available literature up to

April 1, 2010, from personal communications with consortium members, and from in-house sequencing studies that had identified novel variants (Appendix). Genotyping was performed using MassArray iPLEX platform (Sequenom, San Diego, CA, USA) at the Mayo Clinic neurogenetics laboratory, FL, USA.

Statistical analysis

The software STATA/SE version 11 (StataCorp. 2009. Stata Statistical Software: Release 11. College Station, TX: StataCorp LP.) and HAPLOVIEW were used through the analysis (14). The control groups of each marker were assessed for departure from Hardy-Weinberg equilibrium. Pearson's chi-squared test was used to assess allelic association with PD. Statistical significance level of Pearson's chi-squared test was set at 0.05, so that the study sample size (case: 663, control: 406) has at least 90% power to detect allelic effect corresponding to odds ratio of 0.67 or 1.5 at minor allele frequency (MAF) 20%. Analysis of linkage disequilibrium (LD) was performed using HAPLOVIEW. Along with Pearson's chi-squared test, fixed-effects logistic regression analysis was also performed to adjust for the effect of age and sex. With this regression model, we assumed that allelic effect worked as dominant mode of inheritance, namely dominant model (homozygote of ancestral allele vs. heterozygote plus homozygote of minor allele), because LRRK2 mutations cause an autosomal dominantly inherited form of PD and homozygotes for many of the variants are rare. Thereafter, with markers selected by aforementioned analysis we performed logistic

regression analysis according to additive model that separates the genotypes into three groups in order to give weight to the number of variant allele (none, one variant allele, and two variant alleles).

We adjusted for multiple testing by use of Bonferroni correction according to the number of polymorphic variants which are subject to further statistical analysis

RESULTS

A total of 122 markers in *LRRK2* were genotyped in the study group consisting of 663 unrelated PD patients and 406 healthy controls. The mean ages of case (64.5 ± 9.2) and control (63.2 ± 9.1) were different using Student's t-test at significance level, 0.05 (p=0.031); however, the extent of difference was clinically negligible, and the difference of sex proportion between groups was not significant (Table 1).

Among 122 markers, ninety-seven markers were monomorphic across all 1069 subjects. Table 2 summarizes the remaining twenty-five markers which are polymorphic and their characteristics. The polymorphic markers, all of which are in Hardy-Weinberg equilibrium, were subject to further analyses.

We adjusted for multiple testing by use of Bonferroni correction to assess the level of significance that controls the family-wise error rate at 0.05. After this adjustment, p=0.002 was judged to be significant for the number of polymorphic variants were twenty-five. Firstly, to examine the difference between the allelic frequencies of case and control group, we conducted chi-squared test with each of the twenty-five markers. All of 25 markers were statistically non-significant with significance level 0.002. However, presumptive seven markers based on p-value (p.A419V, p=0.010; p.N551K, p=0.012; p.R1398H, p=0.013; p.K1423K, p=0.020; p.L1653L, p=0.020, p.G2385R, p=0.057; p.M2397T, p=0.054) were selected for further analysis. With these seven markers, genotypes were dichotomized as presence versus absence of the minor allele (dominant model). Using logistic regression

analysis adjusting for age and sex, we obtained odds ratios (OR). From the dominant model we assumed, the OR also proved to be non-significant in all markers with significance level 0.002 (p.A419V (OR 2.24, 95% CI 1.13-4.46; p=0.021), p.N551K (OR 0.69, 95% CI 0.52-0.92; p=0.012), p.R1398H (OR 0.68, 95% CI 0.51-0.91; p=0.010), p.K1423K (OR 0.69, 95% CI 0.52-0.93; p=0.015), p.L1653L (OR 0.19, 95% CI 0.04-0.90; p=0.037), p.M2397T (OR 0.72, 95% CI 0.55-0.94; p=0.014); p.G2385R (OR 1.63, 95% CI 0.95-2.79; p=0.073)). Further analysis was performed with the above seven polymorphic markers based on additive model (Table 3). In linkage disequilibrium (LD) analysis, among seven markers, p.N551K, p.R1398H, p.K1423K were in strong LD together (r2>0.8) (Figure 1). Therefore, these three exonic variants constitute a haplotype which harbors protective effect on the occurrence of PD.

Table 1. Study characteristics of cases and controls

	No.	Age (mean±SD)	Sex (male/female)
cases	663 (38%)	64.5 ± 9.2	293 / 370 (0.79)
controls	406 (62%)	63.2 ± 9.1	174 / 232 (0.75)

Age difference between two groups was significant with Student's t-test (p=0.031); sex ratio difference was not significant with proportion test (p=0.503).

Table 2. Twenty-five *LRRK2* polymorphic variants in study population.

rs number	aminoacid substitution	minor allele	function	MAF (case)	MAF (control)	p-value of chi-squared test
rs10878245	L153L	C	synonymous	0.263	0.272	0.664
rs28365216	N238I	T	missense	0.001	0.001	0.730
rs34594498	**A419V**	**T**	**missense**	**0.032**	**0.014**	**0.010**
rs7308720	**N551K**	**G**	**missense**	**0.115**	**0.153**	**0.012**
rs10878307	I723V	G	missense	0.011	0.009	0.641
rs34410987	P755L	T	missense	0.006	0.008	0.720
rs7966550	L953L	C	synonymous	0.188	0.199	0.513
rs111341148	R1067Q	A	missense	0.001	0.000	0.434
rs77018758	R1320S	T	missense	0.016	0.011	0.400
rs72546338	R1325Q	A	missense	0.003	0.001	0.387
rs7133914	**R1398H**	**A**	**missense**	**0.109**	**0.146**	**0.013**
rs11175964	**K1423K**	**A**	**synonymous**	**0.108**	**0.143**	**0.020**
rs34995376	R1441H	A	missense	0.001	0.000	0.427
rs74681492	P1446L	T	missense	0.002	0.002	0.996
rs111501952	V1450I	A	missense	0.002	0.001	0.853
rs1427263	G1624G	A	synonymous	0.429	0.454	0.260
rs33949390	R1628P	C	missense	0.002	0.001	0.567
rs11176013	K1637K	G	synonymous	0.398	0.431	0.142
rs11564148	S1647T	A	missense	0.256	0.260	0.850
rs111503579	**L1653L**	**G**	**synonymous**	**0.002**	**0.009**	**0.020**
rs10878371	G1819G	C	synonymous	0.399	0.370	0.184
rs10878405	E2108E	A	synonymous	0.261	0.257	0.875
rs34778348	**G2385R**	**A**	**missense**	**0.041**	**0.025**	**0.057**
rs33962975	G2385G	G	synonymous	0.019	0.012	0.255
rs3761863	**M2397T**	**C**	**missense**	**0.390**	**0.433**	**0.054**

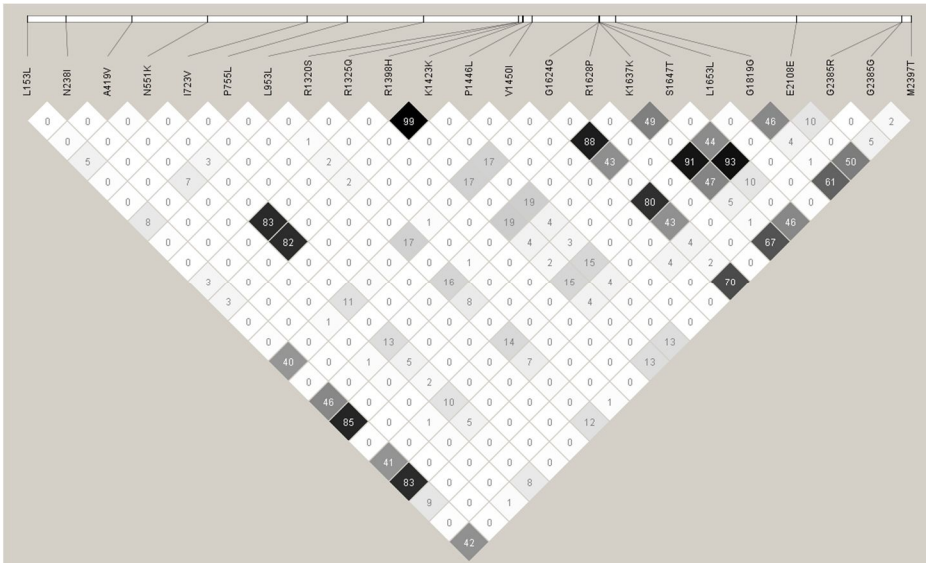
Among 25 polymorphic variants, none of them was significant with significance level 0.002. However, *LRRK2* p.A419V, p.N551K, p.R1398H, p.K1423K, p.L1653L p.G2385R, p.M2397T showed marginal significance.

Table 3. Seven polymorphic variants assorted from twenty-five polymorphic variants through chi-squared test.

	aminoacid	dominant model		additive model	
rs number	substitution	OR of carriers	p-value	OR	p-value
rs34594498	A419V	2.24 (1.13-4.46)	0.021	2.25 (1.17-4.35)	0.016
rs7308720	N551K	0.69 (0.52-0.92)	0.012	0.72 (0.56-0.94)	0.015
rs7133914	R1398H	0.68 (0.51-0.91)	0.010	0.72 (0.55-0.94)	0.017
rs11175964	K1423K	0.69 (0.52-0.93)	0.015	0.73 (0.56-0.96)	0.024
rs111503579	L1653L	0.19 (0.04-0.90)	0.037	0.19 (0.04-0.90)	0.037
rs34778348	G2385R	1.63 (0.95-2.79)	0.073	1.65 (0.97-2.79)	0.064
rs3761863	M2397T	0.72 (0.55-0.94)	0.014	0.84 (0.71-1.01)	0.064

Comparing the OR (odds ratio) and p-values of dominant model to that of additive model, they are very similar with each other. All the presented ORs were adjusted for age and sex using logistic regression analysis.

Figure 1.



Linkage disequilibrium (LD) plot involving 23 markers of LRRK2. The numbers of the entries indicate r2 between two corresponding markers. (R1398H-N551K: D´=0.94, r2 =0.835; R1398H-K1423K: D´=1.0, r2=0.995; N551K-K1423K: D´=0.931, r2 =0.825). The markers of which MAF was less than 0.001 were excluded.

DISCUSSION

We analyzed as many as 122 *LRRK2* exonic variants in Korean ethnicity, which is the largest genetic association study with *LRRK2* and PD so far. The result revealed that a single gene, *LRRK2,* harbors many rare and common exonic variants that allow variable susceptibility to PD in Korean ethnicity. Although there was no statistically significant association between *LRRK2* exonic variants with PD with this Korean study population, we found a clue that p.A419V is hazardous, and a three-variant haplotype (p.N551K-p.R1398H-p.K1423K) is protective for PD.

The statistical analysis procedure was based on dominant model, which designates heterozygote or minor allele homozygote as a carrier. Taking the gene dosage effect into account, additive model is more plausible with regard to explaining the causal relationship between allelic variants and phenotype, herein PD. Hence analyses based on additive model were conducted with seven variant markers.

The Chinese ethnic study reported that p.A419V was not relevant to the risk modulation, however in this study with Korean ethnicity, p.A419V was associated with increased risk of PD (15). Although the minor allele frequency of case and control was relatively low (0.032, 0.014), the statistical significance was consistent through the analyses including dominant and additive model.

We found that the *LRRK2* p.R1398H was associated with lower risk of PD than was wild type. The recent study with Chinese ethnicity showed that

p.R1398H had decreased kinase activity compared to wild type in in-vitro experiment (10). In that study, p.R1398H showed decreased risk (OR 0.75), which is similar to our result. This protective effect was also shown in p.N551K and p.K1423K by similar effect size. Interestingly, all these three exonic variants were in strong LD allowing them to be called a haplotype. Among the three-variant haplotype (p.N551K-p.R1398H-p.K1423K), which one has the main protective function is not clear. The p.N551K is located in armadillo repeat region which may participate in signaling complex, and p.K1423K is synonymous mutation, but it can lead to alternative splicing and different copy number of protein using different tRNA; therefore, the characteristic of the protective effect of this haplotype needs further investigation.

Several Asian, especially Chinese-population based studies have reported that p.G2385R and p.R1628P variants are associated with approximately twofold increase of risk independently. These two exonic variants were not found to be a risk factor in the study of European-population based researches (9, 15-18). However, p.G2385R was also reported to increase risk for PD in Korean and Japanese populations; whereas p.R1628P was absent or extremely rare in these populations (11-13). Recently, comprehensive genetic studies of LRRK2 in respect to susceptibility to PD were performed in Han Chinese and Japanese populations. Except for p.G2385R, the frequencies of polymorphic variants were strikingly different between the two populations, and also varied from that of our study (Table 4). The p.G2385R was found to increase the risk of PD (OR 1.63), but not statistically significant (p=0.073). The minor allele

frequency of p.G2385R was very similar to the result of other Korean and Han Chinese study, in which minor allele frequency of patients and controls were 4.6%, 2.5% and 5%, 2%, respectively; those of our study population were 4.1% and 2.5% (12). The lack of significance is presumed to be led by insufficient number of subjects of our study population.

If p.R1398H reduces the risk of PD, the subjects with p.G2385R will differ in the risk of PD depending on whether the subjects also have p.R1398H or not, taking that the LD between p.G2385R and p.R1938H was negligible into account. Although our samples did not present significant result of p.G2385R, subjects with both p.G2385R and p.R1398H showed lower OR than those with p.G2385R but not p.R1398H (subjects with p.G2385R and p.R1398H: OR 0.94, 95% CI 0.15-5.68; p=0.944; subjects with only p.G2385R: OR 1.55, 95% CI 0.88-2.74; p=0.127).

The p.G2019S was absent in our study population. The p.R1628P and the p.R1441H were extremely rare (MAF < 0.01) as with the result of Japanese population study (11). The influence of p.L1653L to the risk of PD is questionable due to the scarcity of minor allele frequency in both control and case group allowing for the number of subjects included in each group. For our study sample sizes and proportions of minor allele, the normal approximation to the binomial distribution may not be accurate, thus the result of statistical test may not be reliable. Regarding the p.L1653L, due to the extremely rare frequency of minor allele, it is hard to confer clinical meaning on this variant. The p.M2397T showed confusing result, which was not

significant in additive model, which might be caused by relatively low frequency of homozygote of minor allele.

In conclusion, we found a propensity that p.N551K, p.R1398H, p.K1423K variants constituting a haplotype may reduce the risk of PD, and the p.A419V may be a risk factor of PD in Korean ethnicity. Although the p.G2385R represented a risk factor of PD in previous reports, statistical significance was not validated in this study maybe due to the insufficient number of study subjects. A lack of number of study subjects was the main cause of negative results of this study. Therefore, further study that encompasses sufficient number of subjects can confirm the presumptive results of this study.

Table 4. Comparison of *LRRK2* polymorphic variants among Asian ethnic groups (Han Chinese, Japanese, and Korean population).

63 cases; 1251 controls)		Japanese population (631 cases; 1641 controls)			
		case	control		
(95% CI)	p-value	MAF	MAF	OR (95% CI)	p-value
(1.04-1.32)	0.006		not found in case		
(0.61-0.92)	0.005		not found in case		
(0.60-0.91)	0.004		not found in case		
(1.44-2.93)	0.00004		not found in case		
(2.19-4.63)	2.2×10^{-9}	0.115	0.062	1.83 (1.31-2.54)	3.3×10^{-4}
iscovery set		0.003	0.001		
iscovery set		0.012	0.02		
iscovery set		0.002	0.002		
iscovery set		0.003	0		
iscovery set			not found in case		
iscovery set			not found in case		

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APPENDIX

Exon	Accession number	dDNA	Aminoacid	Domain
1	··	28G>A	E10K	··
1	rs2256408	149G>A	R50H	··
2	rs72546335	155C>T	S52F	··
2	rs75054132	224G>A	A75A	··
4	rs33995463	356T>C	L119P	··
4	rs41286468	364T>C	L122L	··
5	rs10878245	457T>C	L153L	··
5	rs35517158	546A>G	K182K	··
6	rs112794616	632C>T	A211V	··
6	rs56108242	683G>C	C228S	··
7	rs28365216	713A>T	N238I	··
7	rs72546315	824C>T	H275H	··
8	rs17490713	867T>C	N289N	··
8	rs57355477	893T>C	A298A	··
8	rs41286466	936G>T	A312A	··
9	rs78501232	1000G>A	E334K	··
9	rs36016791	1055delC	A352fsX357	··
9	rs72546336	1088A>G	N363S	··
9	rs113065049	1096G>A	V366M	··
11	rs34594498	1256C>T	A419V	··
12	rs35847451	1383C>T	S461S	··
13	rs75711334	1464A>T	L488L	··
13	rs34090008	1543insG	P514fsX529	··
14	rs35328937	1561A>G	R521G	··
14	rs79996249	1630A>G	K544E	··
14	rs7308720	1653C>G	N551K	··
15	rs77424631	1647G>A	G558G	··
17	rs78154388	1987T>C	S663P	··
17	rs72546319	2022A>C	V674V	··
17	rs35611877	2198insA	L708fsX718	Ankyrin

18	..	2134A>G	M712V	Ankyrin
18	..	2147C>T	A716V	Ankyrin
18	rs10878307	2167A>G	I723V	Ankyrin
19	rs34410987	2264C>T	P755L	Ankyrin
19	rs72546337	2428A>G	I810V	Ankyrin
19	rs76890302	2481T>C	S827S	Ankyrin
20	..	2611A>G	K871E	..
21	rs58559150	2769G>C	Q923H	..
21	..	2789A>G	Q930R	..
22	rs17519916	2830G>T	D944Y	..
22	rs7966550	2857T>C	L953L	..
23	rs75148313	2918G>A	S973N	..
23	rs113217062	3018A>G	I1006M	LRR
23	rs55783828	3021C>T	S1007S	LRR
24	rs111341148	3200G>A	R1067Q	LRR
24	rs76535406	3287C>G	S1096C	LRR
24	rs78365431	3333G>T	Q1111H	LRR
24	rs35808389	3342A>G	L1114L	LRR
25	rs34805604	3364A>G	I1122V	LRR
25	rs74985840	3451G>A	A1151T	LRR
25	..	3494T>C	L1165P	LRR
26	..	3574A>G	I1192V	LRR
27	rs72546324	3647A>G	H1216R	LRR
27	rs80179604	3683G>C	S1228T	LRR
27	rs60185966	3683G>T	S1228I	LRR
28	rs4640000	3784C>G	P1262A	LRR
29	rs77018758	3960G>C/T	R1320S	..
29	rs72546338	3974G>A	R1325Q	..
29	rs17466213	4111A>G	I1371V	Roc
29	rs28365226	4125C>A	D1375E	Roc
30	rs7133914	4193G>A	R1398H	Roc
30	rs72546327	4229C>T	T1410M	Roc
30	rs113589830	4258G>A	D1420N	Roc
30	rs11175964	4269G>A	K1423K	Roc
30	rs111435410	4290C>T	A1430A	Roc

30	rs74163686	4309A>C	N1437H	Roc
31	rs33939927	4321C>T	R1441C	Roc
31	rs33939927	4321C>G	R1441G	Roc
31	rs34995376	4322G>A	R1441H	Roc
31	rs112998035	4323C>T	R1441R	Roc
31	..	4324G>C	A1442P	Roc
31	rs74681492	4337C>T	P1446L	Roc
31	rs111501952	4348G>A	V1450I	Roc
31	rs35363614	4387insA	R1462fsX1468	Roc
31	..	4402A>G	K1468E	Roc
31	rs113431708	4448G>A	R1483Q	Roc
32	rs35507033	4541G>A	R1514Q	COR
32	rs33958906	4624C>T	P1542S	COR
32	rs17491187	4666C>A	L1556I	COR
33	rs721710	4793T>A	V1598E	COR
34	..	4838T>C	V1613A	COR
34	rs1427263	4872C>A	G1624G	COR
34	rs33949390	4883G>C	R1628P	COR
34	rs11176013	4911A>G	K1637K	COR
34	rs35303786	4937T>C	M1646T	COR
34	rs11564148	4939T>A	S1647T	COR
34	rs111503579	4959A>G	L1653L	COR
35	rs35801418	5096A>G	Y1699C	COR
35	rs79909111	5163A>G	S1721S	COR
36	rs11564176	5173C>T	R1725X	COR
36	..	5183G>T	R1728L	COR
36	rs145364431	5183G>A	R1728H	COR
37	rs111910483	5385G>T	L1795F	COR
37	rs10878371	5457T>C	G1819G	COR
38	..	5605A>G	M1869V	COR
38	rs35602796	5606T>C	M1869T	COR
38	..	5610G>T	L1870F	COR
38	..	5620G>T	E1874X	COR
39	rs77428810	5822G>A	R1941H	MAPKKK
41	..	6016T>C	Y2006H	MAPKKK

41	rs34015634	6035T>C	I2012T	MAPKKK
41	rs34637584	6055G>A	G2019S	MAPKKK
41	rs35870237	6059T>C	I2020T	MAPKKK
41	rs78029637	6091A>T	T2031S	MAPKKK
42	rs111739194	6187delCTCTA	L2063X	MAPKKK
42	rs33995883	6241A>G	N2081D	MAPKKK
43	rs10878405	6324G>A	E2108E	MAPKKK
43	rs12423862	6356C>T	P2119L	MAPKKK
44	rs111691891	6422C>T	T2141M	..
44	rs34869625	6510C>A	G2170G	WD40
44	rs35658131	6566A>G	Y2189C	WD40
46	rs12581902	6782A>T	N2261I	WD40
48	rs113511708	7067C>T	T2356I	WD40
48	rs34778348	7153G>A	G2385R	WD40
48	rs33962975	7155A>G	G2385G	WD40
48	rs79546190	7168G>A	V2390M	WD40
49	rs78964014	7183G>A	E2395K	WD40
49	rs111272009	7187insGT	T2356fsX2360	WD40
49	rs3761863	7190C>T	M2397T	WD40
49	rs60545352	7224G>A	M2408I	WD40
50	..	7397T>A	L2466H	WD40
50	rs55633591	7435A>G	N2479D	WD40

국문 초록

서론: *LRRK2* 유전자는 염색체 12p12 에 위치하며, 상염색체 우성 유전 양식을 보이는 가족성 파킨슨병을 일으키는 원인 유전자 중의 하나이다. 인종에 따라 유전 변이의 분포가 상이함을 고려하면 다른 인종을 대상으로 한 *LRRK2* 유전자의 유전 변이 연구 결과를 한국인에게 그대로 적용하는 것은 적절하지 못한다. 한국인을 대상으로 한 연구는 *LRRK2* 유전자 중 극히 일부 유전 변이들에 대한 파킨슨병의 감수성만 연구되었다. 따라서 한국인을 대상으로 *LRRK2* 유전자의 122 개 유전 변이를 분석하여 각 유전 변이가 가지는 파킨슨병에 대한 감수성에 대한 분석이 필요하다.

방법: 한국인의 산발성 파킨슨병 663 명, 환자와 혈연관계가 아닌 정상인 406 명으로 총 1069 명을 대상으로 하였다. 122 개의 *LRRK2* 엑손 변이에 대한 단일염기다형성 분석을 하였고, 이들 중 다형성이 있는 엑손 변이를 선별하였다. 카이제곱검정으로 환자군과 대조군의 빈도가 유의한 차이를 보이는 엑손 변이를 선별한 후, 로지스틱 회귀분석으로 통하여 각 엑손 변이형이 가지는 파킨슨병의 발병 위험도에 대한 오즈비를 도출하였다.

결과: 다중 검정에 대한 본페로니 수정으로 도출한 유의수준 (p=0.002) 으로 검정하였을 때, 통계적으로 유의한 결과를 보

인 엑손 변이는 없었다. 하지만 *LRRK2* p.N551K (rs7308720; OR 0.69, 95% CI 0.52-0.92; p=0.012), p.R1398H (rs7133914; OR 0.68, 95% CI 0.51-0.91; p=0.009), p.K1423K (rs11175964; OR 0.69, 95% CI 0.52-0.93; p=0.014), p.M2397T (rs3761863; OR 0.73, 95% CI 0.56-0.95; p=0.020) 엑손 변이 보인군에서 그렇지 않은 군에 비하여 낮은 위험도를 보였고, *LRRK2* p.A419V (rs34594498; OR 2.21, 95% CI 1.11-4.38; p=0.023) 보인군은 그렇지 않은 군에 비하여 높은 위험도를 보였다. 연관 불균형 분석 (linkage disequilibrium analysis) 결과 p.N551K, p.R1398H, p.K1423K 의 세가지 엑손 변이가 강한 연관 불균형 (r2>0.8) 을 보였다.

결론: 한국인을 대상으로 한 122 개 *LRRK2* 엑손 변이 분석 결과 통계적으로 유의하게 파킨슨병의 발병위험도를 높이는 *LRRK2* 엑손 변이는 없었다. 하지만 이러한 연구 결과의 원인은 *LRRK2* 엑손 변이와 파킨슨병 간의 연관성이 없어서라기 보다는 연구 대상의 수가 부족하여 통계적으로 유의한 결과를 도출하지 못하였을 가능성이 크므로, 충분한 수의 환자, 정상인을 대상으로 한 연구가 필요하다.

주요어 : 파킨슨병, *LRRK2*, 엑손 변이.

학 번 : 2008-21949