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Research article

Alzheimer's disease susceptibility genes modify the risk of Parkinson disease and Parkinson's disease-associated cognitive impairment

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ABSTRACT

The pathogenic mechanism underlying Parkinson's disease (PD) and PD- Cognitive impairment (CI) remains elusive. Its potential link to the risk factors in Alzheimer's disease (AD) is unclear. In this study, we analyzed 16 CE-associated single nucleotide polymorphisms (SNPs) in twelve genes in a Chinese cohort of 450 PD cases and 449 controls. Among our 298 cases clinically evaluated for CI, 113 cases did not show CI signs (PD-NC), 86 cases had mildly cognitive impairment (PD-MCI) and 99 cases had dementia (PD-D). We found that the *APOE* ε4 allele is associated with a higher risk for PD-D. Gene-gene interaction analysis revealed that three significant gene–gene interactions, including *BDNF* and *CLU*, *APOE* and *CR1*, and *DYRK1A* and *CD2AP* increase the risk for PD. Because these SNPs are known genetic risk factors for AD, their contribution to PD and PD-D shown in this study suggests that PD/PD-D and AD may share convergent pathways in their pathogenesis through gene–gene interactions.

1. Introduction

PD is clinically characterized by resting tremor, bradykinesia, rigidity and a variety of other motor and non-motor symptoms. Cognitive impairment (CI), ranging from mild cognitive impairment (MCI) to dementia, is one of the major non-motor symptoms in PD. Patients with PD are at almost six fold increased risk for dementia compared to the general population[1]. The prevalence of dementia increases with duration of the disease. Dementia is associated with a reduced quality of life and increased mortality [1].

The pathogenic mechanisms of PD and PD-CI remain elusive. Genetic association studies identified several putative susceptibility genes for PD and PD-CI [2–6]. However, negative data have also been reported using the same SNPs as well [7–9].

Previous genome-wide association studies (GWAS) have revealed a number of putative risk genes for Alzheimer's disease (AD), the most common form of progressive dementia in the elderly. AD and PD appear to share some overlapping environmental and aging factors, and have pathological hallmarks of protein aggregates, although the compositions of the protein aggregates are different [10]. Some studies have found familial co-aggregation of the two diseases [11]. In addition, there is increasing evidence showing the similarities among AD, PD and PD-CI in pathological characteristics and clinical features in recent years [12,13]. These data suggest that AD, PD and PD-CI may have some common genetic modifiers/pathways. Indeed, some previous studies suggest that two SNPs (rs11136000 at the *CLU* and ε4 allele of *APOE*), known AD risk loci, were associated with PD risk [14,15].

However, there are also conflicting results about common genetic risk of PD and AD [16]. We have previously investigated whether a total of 13 SNPs of 9 CE GWAS-linked top hit genes also confer increased risk to PD or PD-CI, but we failed to detect any association [17]. One plausible explanation is that the effect of a single gene variant is

Abbreviations: CI, cognitive impairment; PD, Parkinson's disease; AD, Alzheimer's disease; SNP, single nucleotide polymorphism; PD-D, Parkinson's disease with dementia; MCI, mild cognitive impairment; GWAS, genome-wide association study; HWE, Hardy-Weinberg equilibrium; OR, odds ratio; CI, confidence interval

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too small to be detected or gene–gene interactions are involved.

Gene-gene interaction is also known as epistasis that occurs when the phenotype for a genotype at one locus is dependent on genotypes at one or more other loci [18]. The phenomenon is a ubiquitous component of the genetic susceptibility of ploygene disease, especially AD [19]. The existence of gene–gene interaction leads to inconsistent results in genetic association studies among different ethnicities and regions. We have reported the combined effects in PD genetic risk [20]. Many epistatic effects have been discovered in these GWAS-linked top hit genes with AD risk [21]. Recently, interaction effects of some susceptibility genes have been reported in AD, PD and PD-D [22,23].

In this study, we generate a complete dataset, including those for both AD and PD-CI related genes. We analyzed the gene–gene interaction between every two SNPs. Our results suggest that PD/PD-D and AD may share convergent pathways in their pathogenesis through gene–gene interactions.

2. Subjects and methods

2.1. Subjects

The source and diagnostic method of subjects have been described in our previous study, according to the diagnostic criteria described by the UK brain bank criteria and the MDS Task Force diagnostic criteria [17]. We supplemented some PD cases and controls from the identical source, and diagnosed them with the same criterions and doctors in this study. But part of subjects was excluded for failed genotyping or too young at enrollment. Finally, 298 cases underwent a series of neuropsychological assessments, including 113 cases had normal cognitive function (PD-NC), 86 cases had mildly cognitive impairment (PD-MCI) and 99 cases had dementia (PD-D). Other 152 PD cases without neuropsychological assessments were only included in PD risk analyses.Additionally, 449 ethnically-matched healthy people were enrolled as controls.The work was approved by the ethics board of xiangya Hospital and obtained informed consent from all the involved subjects.

2.2. Genotyping method

In our previously study, the majority of subjects had been examined with 13 representative SNPs from 9 CE GWAS linked top ten hit genes: 1) BIN1 gene: rs744373; 2) CLU gene: rs11136000, rs2279590 and rs9331888; 3) ABCA7 gene: rs3764650; 4) CR1 gene: rs3818361 and rs6656401; 5) PICALM gene: rs3851179 and rs541458; 6) MS4A6A gene: rs610932; 7) CD33 gene: rs3865444; 8) MS4A4E gene: rs670139; and 9) CD2AP gene: rs9296559 for analysis [17]. In addition, two SNPs from the primary AD risk gene *APOE*: rs7412 and rs429358 were selected [24]. Meanwhile we also chose 4 representative SNPs of 4 genes, which have been reported to be associated with both AD and PD-CI: 1) *MAPT* gene: H1 Haplotype; 2) *COMT* gene: rs4680; 3) *BDNF* gene: rs6265; 4) *DYRK1A* gene: rs8126696 [4,6,25–28]. Subsequently, rs6656401 of *CR1* gene and H1 Haplotype of *MAPT* gene were excluded for lower minor allele frequency(< 5%) based on the 1000 genomes data [29]. We completed the genotyping in all the subjects with other 17 SNPs in this study.

Genotyping method is the same as our previous studied [17]. The MassArray system (Sequenom, San Diego, CA, USA) was used to genotype all SNPs. Ten percent of the DNA samples from both patients and controls were randomly selected for Sanger sequencing to validate the outcomes of MassArray study.

2.3. Statistical analyses

Chi-square test was used for Hardy-Weinberg equilibrium (HWE) to all SNPs in controls. Differences in alleles and genotypes between controls and cases or between different PD subgroups (PD-NC, PD-MCI, and PD-D) were tested by logistic regression with two-sided alpha of 0.05. Gene-gene interactions were searched using synergy analysis with dominant and recessive model between controls and cases or PD-NC and PD-D subgroups. The method of synergy analysis was previous described [19]. Because of limitation in sample sizes and methods, we limited this study to binary epistasis. Power value was calculated when gene–gene interaction reached to a significant level below 0.05. While the power value was more than 0.8, logistic regression was also used to have clearer odds ratio (OR), 95%confidence interval (CI) and p value on different genotypes of SNP pairs.

Chi-square test and synergy analysis were performed by Microsoft Office Excel 2003. Logistic and linear regressions were carried out by SPSS statistics (version 17.0). Power value was calculated by Quanto (version 1.2.4).

3. Results

The allele distribution of SNP rs3865444 in *CD33* gene was significantly deviated from HWE, and thus for the reason of quality assurance, the data from this SNP were excluded. Each of other 16 SNPs had an allele distribution consistent with Hardy-Weinberg Equilibrium (HWE) in the controls group (Supplement1.Table 1). Demographic characteristics of the samples are summarized in Supplement1.Table 2.

3.1. Monogenic association

The association between eleven AD related SNPs and PD or PD-CI were examined in our previously study [17]. The result of other 5 SNPs was shown in Table 1 and Supplement1.Table 3. No significant difference in allele or genotype frequencies was displayed in these 5 SNPs between controls and PD cases. In the analysis between every two subgroups of PD, the ε4 allele or genotype that has at least one ε4 allele were all associated with higher risk to PD-D comparing with PD-MCI in *APOE* gene, but the association was not significant between PD-NC and PD-D (Table 2). It was observed that GA heterozygotes of rs4680 at *COMT* gene abnormally increased in PD-MCI group comparing with the other two groups, while AA genotype was at lower risk of MCI in PD cases (Supplement1.Table 4). No significant association was found in other 3 SNPs.

Table 1
Allele frequencies in PD cases and controls.

SNPs	Chromosome_*Gene*	Allele		Minor allele frequency, n(%)		Allele association analysis	
		major	minor	PD cases	Controls	OR(95%CI)[a]	p value[a]
rs7412	Chr19_*APOE*	–	ε2	68 (7.56)	68 (7.57)	1.012 (0.713–1.437)	0.946
rs429358	Chr19_*APOE*	–	ε4	79 (8.78)	87 (9.69)	0.903 (0.655–1.245)	0.534
rs6265	Chr11_*BDNF*	C	T	430 (47.78)	446 (49.67)	0.930 (0.773–1.120)	0.444
rs4680	Chr22_*COMT*	G	A	235 (26.11)	240 (26.73)	0.969 (0.785–1.196)	0.770
rs8126696	Chr21_*DYRK1A*	C	T	441 (49.00)	413 (45.99)	1.134 (0.942–1.366)	0.183

Abbreviations: SNP, single nucleotide polymorphism; OR, odds ratio; CI, confidence interval.
[a] Adjusted for gender and age at enrollment.