Neurotoxicity Research (2019) 36:463–471
https://doi.org/10.1007/s12640-019-00031-z

ORIGINAL ARTICLE

Genetic Association Between *NGFR*, *ADAM17* Gene Polymorphism, and Parkinson's Disease in the Chinese Han Population

Wei-Wei Li[1] · Ying-Ying Shen[1] · Dong-Wan Chen[1] · Hui-Yun Li[1] · Qian-Qian Shi[1] · Jing Mei[1] · Heng Yang[1] · Fa-Ying Zhou[1] · An-Yu Shi[1] · Tao Zhang[1] · Xiu-Qing Yao[1] · Zhi-Qiang Xu[1] · Fan Zeng[1] · Yan-Jiang Wang[1]

Received: 13 February 2019 / Revised: 16 March 2019 / Accepted: 22 March 2019 / Published online: 2 April 2019

Abstract

Parkinson's disease (PD) is a common neurodegenerative disease characterized by neuronal loss in the substantia nigra. The p75 neurotrophin receptor (p75NTR, encoded by *NGFR*) was found to play an important role in the selective neuronal death of dopamine neurons in the substantia nigra, as well as the pathogenesis and development of PD. To assess the association between *NGFR* gene polymorphism and the susceptibility of PD, this case-control study consisting of 414 PD patients and 623 age- and sex-matched controls in a Chinese Han cohort was conducted. Twelve tag-single nucleotide polymorphisms (tag-SNPs) were selected from the *NGFR* gene through the construction of linkage disequilibrium blocks. One tag-SNP from the *ADAM17* gene was also selected owing to its function of encoding tumor necrosis factor α-converting enzyme, which is responsible for the shedding of the extracellular domain of p75NTR. A multiplex polymerase chain reaction-ligase detection reaction (PCR-LDR) method was applied for genotyping. The associations between tag-SNPs and the risk of PD with the adjustment for age and sex were analyzed by unconditional logistic regression, and five genetic models including codominant, dominant, recessive, over-dominant, and additive models were applied. The results showed that among the 13 tag-SNPs, rs741073 was associated with a reduced risk of PD in the codominant (OR = 0.71, 95% CI = 0.54–0.93, $P = 0.037$), dominant (OR = 0.76, 95% CI = 0.58–0.98, $P = 0.033$), and over-dominant models (OR = 0.71, 95% CI = 0.54–0.92, $P = 0.010$), and rs1804011 was also associated with a reduced risk of PD in the codominant (OR = 0.69, 95% CI = 0.50–0.95, $P = 0.049$), dominant (OR = 0.69, 95% CI = 0.50–0.93, $P = 0.014$), over-dominant (OR = 0.70, 95% CI = 0.51–0.96, $P = 0.025$), and additive models (OR = 0.72, 95% CI = 0.54–0.94, $P = 0.016$). However, these associations did not retain after Bonferroni correction. Conclusively, our study failed to reveal the association between the selected tag-SNPs within *NGFR*, *ADAM17*, and the susceptibility of PD. The role of p75NTR and its gene polymorphisms in the pathogenesis of PD needs to be further studied.

Keywords NGFR · ADAM17 · Parkinson's disease · Gene polymorphism

Introduction

Parkinson's disease (PD) is one of the most common neurodegenerative diseases whose prevalence was reported to be 10–1500 per 100,000 worldwide and increases nearly exponentially with age (Lorraine and Anthony 2015). Despite the typical pathologies of PD, including the prominent death of dopaminergic neurons in the substantia nigra pars compacta (SNpc) and Lewy pathology consists of abnormal aggregates of α-synuclein protein, have been well acknowledged, its underlying mechanism remains unclear. Previous studies have successfully identified several genes responsible for the mendelian forms of PD, including *synuclein alpha* (*SNCA*), *leucine rich repeat kinase 2* (*LRRK2*), and *vacuolar protein sorting 35 retromer complex component* (*VPS35*) in the autosomal dominant form, as well as *Parkin*, *phosphatase and tensin homolog induced kinase 1* (*PINK1*) and *Parkinsonism associated deglycase* (*PARK7* or *DJ-1*) in the autosomal recessive form (Lorraine and Anthony 2015). However, the non-mendelian form of PD (sporadic PD) which

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s12640-019-00031-z) contains supplementary material, which is available to authorized users.

✉ Fan Zeng
zengfan326@163.com

[1] Department of Neurology and Centre for Clinical Neuroscience, Daping Hospital, Third Military Medical University, Chongqing 400042, China

lack in penetrant genetic mutations is far more common. Growing evidences showed that genetic variants play a crucial role in the pathogenesis of PD. To date, an array of single nucleotide polymorphisms (SNPs) located in genes like *SNCA* (Maraganore et al. 2006), *MAPT* (encoding microtubule-associated protein tau) (Goris et al. 2007), and *GBA* (encoding acid betaglucosidase) (Sidransky et al. 2009) as well as some PD related loci discovered by genome-wide association studies (GWAS) and GWAS-meta-analysis have been found to have significant impact on the susceptibility of PD (Hamza et al. 2010; Nalls et al. 2014; Satake et al. 2009; Simon-Sanchez et al. 2009). Despite these progresses, approximately 40% or more of the population-attributable risk remained unexplained by the most promising PD related loci at present (Nalls et al. 2011). To this end, the genetic association study is still a potentially useful strategy for genetics researches of PD.

The mechanism for the selective cell death of nigral dopamine neurons is still unknown yet critical for the prevention and treatment of PD (Fernandez-Espejo 2004; Olanow and Tatton 1999). The p75 neurotrophin receptor (p75NTR, encoded by the *NGFR* gene) is a low-affinity receptor of neurotrophins that was found to regulate cell death and neuronal degeneration in the central nervous system. It is reported that p75NTR was also expressed in the nigral dopamine neurons, and the upregulation of p75NTR in the substantia nigra was demonstrated to mediate degenerative death of nigral dopamine neurons in rat or mouse models of PD (Chen et al. 2008a; Wang et al. 2008). Additionally, dynamic p75NTR expression was observed in substantia nigra of the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) mouse model, and the upregulation of p75NTR was coincident with the progressive neuronal degeneration in the same brain region, suggesting that p75NTR signaling is likely to be involved in the mechanism for the selective cell death of nigral dopamine neurons (Bian et al. 2007; Chen et al. 2008b). Besides, the pro-nerve growth factor (proNGF) was well recognized to trigger neuronal cell apoptosis by binding with high affinity to p75NTR and its co-receptor sortilin (Al-Shawi et al. 2007; Barrett 2000). A recent study also revealed the presence of the proNGF-sortilin signaling complex in nigral dopamine neurons and its response to the insult of lactacystin and 6-hydroxydopamine (6-OHDA), which were widely used to induce PD animal models (Xia et al. 2013). Taken together, p75NTR may contribute to the selective neuronal death of dopamine neurons in the substantia nigra, as well as the pathogenesis and development of PD.

Given the important roles of p75NTR and genetic polymorphism in the pathogenesis of PD, it is necessary to investigate the relationship between *NGFR* polymorphism and the risk of PD. In the present study, 12 tag-SNPs covering the entire *NGFR* gene including its potential promoter regions were selected and analyzed for their associations with PD. Meanwhile, one tag-SNP from the *ADAM17* gene was also selected owing to its function of encoding tumor necrosis factor α-converting enzyme (TACE, also known as an α-secretase of amyloid precursor protein), which is responsible for the shedding of the extracellular domain of p75NTR (p75ECD) (Esler and Wolfe 2001; Weskamp et al. 2004).

Materials and Methods

Study Population

A total of 414 PD patients were consecutively recruited from the Registry of Neurodegeneration of Daping Hospital from January 2015 to December 2018, and 623 age- and sex-matched controls were randomly recruited from the hospital during the same period. The diagnosis of PD was made according to the "Chinese diagnostic criteria of Parkinson's disease" (1999) (Luo 1999), which is essentially the same as UK Parkinson's Disease Society Brain Bank Clinical Diagnostic Criteria (1992). The demographic data and medical history were collected. These procedures were administered by experienced neurologists.

All subjects in this study were ethic Han people and lived in the south of China. The subjects were not eligible if they have (1) a family history of PD; (2) a concomitant neurodegenerative disorder (e.g., Alzheimer's disease); (3) severe cardiac, pulmonary, hepatic, renal diseases, or any kind of tumor; and (4) declined to participate in the study. The study was approved by Institutional Review Board of Daping Hospital. Written consents for genetic screening were obtained from all participants or their legal representatives. Their confidentiality was preserved according to the guidelines for studies of human subjects.

Tag-SNP Selection and Genotyping

The entire sequence of studied genes included the full length of human *NGFR* and *ADAM17* genes plus 3 kb upstream and 1 kb downstream (totally 23.728 kb and 70.526 kb for each gene). The genetic variation data was obtained from HapMap project (http://hapmap.ncbi.nlm.nih.gov/) for 45 unrelated Chinese Han people in Beijing (CHB). Eighteen SNPs with a minor allele frequency (MAF) ≥ 0.1 were selected from *NGFR*. As for *ADAM17*, the MAFs of all 65 SNPs obtained were less than 0.1, then 21 SNPs with a MAF ≥ 0.05 were selected. After converting the original data to linkage format, Haploview software (version 4.2) was applied to choose tag-SNPs with linkage disequilibrium (LD) threshold $r^2 \geq 0.8$ (Barrett et al. 2005). In each LD block, priority was given to the tag-SNP which was most frequently cited in other genetic association studies or predicted to be of important biological function according to online software FASTSNP and SNPinfo

(Xu and Taylor 2009; Yuan et al. 2006). The SNPs that did not form any LD blocks with others were also selected as tag-SNPs in order to cover the entire gene as comprehensively as possible.

Venous blood was sampled into sterile anti-coagulation tubes. The genomic DNA was extracted using Wizard Genomic DNA Purification Kit (Promega, Madison, WI, USA) according to the product instruction. A multiplex polymerase chain reaction-ligase detection reaction (PCR-LDR) method was utilized for genotyping each tag-SNP as described in our previous study (Zeng et al. 2013). Briefly, for each SNP, the alleles were distinguished by different fluorescent labels of allele-specific oligonucleotide probe pairs. Different SNPs were distinguished by different extended lengths at 3′ end. The primers for all tag-SNPs were shown in Supplementary Table 1.

The genotyping was carried out in a blind way to group status. A random sample accounting for approximately 5% ($n = 52$) of the total studied subjects was genotyped twice by different researchers for quality control, yielding a reproducibility of 100%.

Statistical Analysis

The age and the proportion of sex of the two groups were compared with t test and χ^2 test respectively. The genotype distributions of each tag-SNP in the control group were analyzed by χ^2 test for deviations from the Hardy-Weinberg equilibrium (HWE). The associations between tag-SNPs and the risk of PD with the adjustment for age and sex were analyzed by unconditional logistic regression, and five genetic models including codominant, dominant, recessive, over-dominant, and additive models were applied. The statistical analysis was carried out by PASW version 18.0 for windows (SPSS, Inc., Chicago, IL) and SNPStats online software (Sole et al. 2006). The statistical power of the case-control dataset was evaluated using Power and Sample Size software version 3.0 (http://biostat.mc.vanderbilt.edu/PowerSampleSize). All statistical tests were two-sided, and $P < 0.05$ was defined as statistically significant. Bonferroni correction method was utilized for multiple testing correction.

Results

Characteristics of the Study Population

Among the 414 PD patients and 632 controls recruited, there were no significant differences in age (65.84 ± 10.21 vs. 65.30 ± 11.24, $P = 0.44$) and sex (female proportion 47.1% vs. 44.9%, $P = 0.49$) between PD and control groups. The detailed information was shown in Table 1.

Table 1 Demographics of Parkinson's disease patients and controls

	PD ($n = 414$)	Control ($n = 632$)	P values
Age	65.84 ± 10.21	65.30 ± 11.24	0.44
Female, n (%)	195 (47.1)	280 (44.9)	0.49

Data are presented as absolute numbers with percentages or as mean ± SD. P values for categorical variables were calculated using χ^2 test and P values for continuous variables were calculated using t test. *PD*, Parkinson's disease

Construction of LD Blocks and Selection of Tag-SNPs

According to the obtained SNP information and LD blocks constructed by Haploview software, 12 tag-SNPs within *NGFR* and 1 tag-SNP within *ADAM17* were finally selected, which were located in the promoter (rs603769 and rs2584665), intron1 (rs9908234 and rs3785931), intron3 (rs2537706 and rs534561), exon4 (rs2072446), and exon6 (rs7219709, rs1804011, rs734194, rs741072, and rs741073) of *NGFR*, and in exon15 (rs1048610) of *ADAM17* respectively. Each tag-SNP and the SNPs they represented were showed in Fig. 1.

Allele Frequencies and Genotype Distributions of the Tag-SNPs

The genotyping of 13 tag-SNPs generated an average call rate of 99.32% in this study. The MAF of each tag-SNP was similar to the data from the HapMap database, and genotype distributions of each SNP were in agreement with HWE ($P > 0.05$). The locus information, MAF, and HWE P values of each SNP were shown in Table 2.

SNPs Within the *NGFR*, *ADAM17* Gene and the Risk of PD

Five genetic models, including codominant, dominant, recessive, over-dominant, and additive models were applied to assess the association between tag-SNPs and the risk of PD. After adjustments for age and sex, rs741073 was associated with a reduced risk of PD in the codominant (OR = 0.71, 95% CI = 0.54–0.93, $P = 0.037$), dominant (OR = 0.76, 95% CI = 0.58–0.98, $P = 0.033$), and over-dominant models (OR = 0.71, 95% CI = 0.54–0.92, $P = 0.010$), and rs1804011 was also associated with a reduced risk of PD in the codominant (OR = 0.69, 95% CI = 0.50–0.95, $P = 0.049$), dominant (OR = 0.69, 95% CI = 0.50–0.93, $P = 0.014$), over-dominant (OR = 0.70, 95% CI = 0.51–0.96, $P = 0.025$), and additive models (OR = 0.72, 95% CI = 0.54–0.94, $P = 0.016$). However, these associations did not retain after Bonferroni correction ($P > 0.05$) (Table 3).

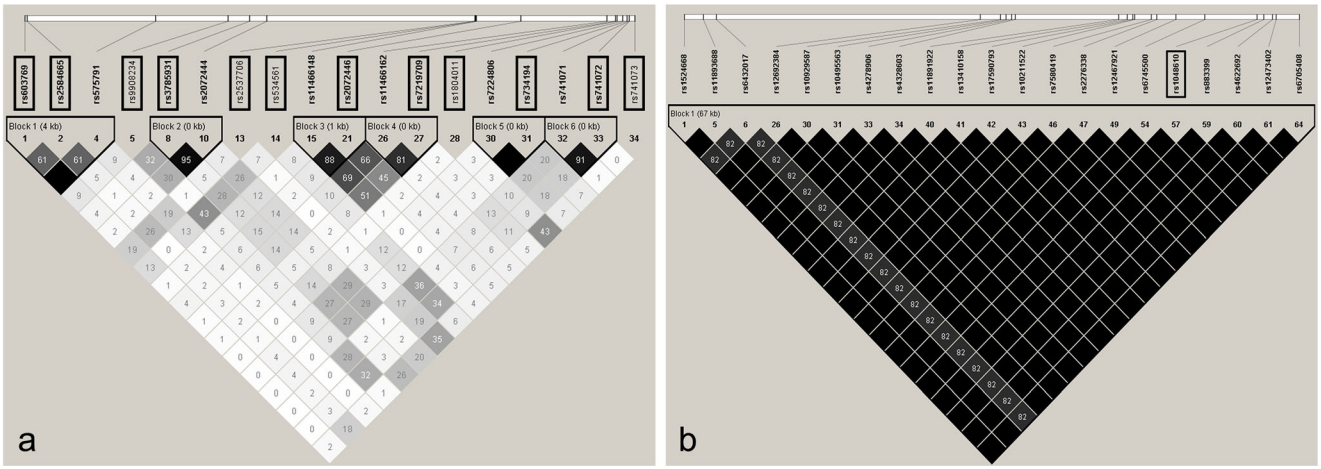

Fig. 1 Construction of linkage disequilibrium blocks and selection of tag-SNPs within the *NGFR* and *ADAM17* genes. The entire sequence of studied genes included the full length of human *NGFR* and *ADAM17* genes plus 3 kb upstream and 1 kb downstream. The linkage disequilibrium (LD) plot was generated using genetic variation data from HapMap project by Haploview software. Twelve tag-SNPs within *NGFR* (**a**) and one tag-SNP within *ADAM17* (**b**) were finally selected (indicated by black rectangles). The level of pairwise r^2 values indicating the correlation between every two SNPs was shown in gray scale (darker color indicates stronger correlation) with its value described as the percentage in each cell

Discussion

Up until now, SNPs within the *NGFR* gene have been found to confer the susceptibility of several diseases including atopic asthma (Szczepankiewicz et al. 2012), depressive disorder, and antidepressant treatment response (Fujii et al. 2011; Gau et al. 2008; Kunugi et al. 2004), while those within the *ADAM17* gene were reported to be associated with the survival of follicular lymphoma patients (Gibson et al. 2012), obesity, and insulin resistance-related phenotypes (Junyent et al. 2010). To the best of our knowledge, this is the first study investigating the relationship between gene polymorphism of *NGFR*, *ADAM17*, and the risk of PD. In order to cover the SNPs of the entire *NGFR* gene, 12 tag-SNPs considered to represent all SNPs (with MAFs > 0.1) were selected and analyzed in our study. One tag-SNP from the *ADAM17* gene was also selected due to its function of encoding TACE, the sheddase of p75ECD which was found important in modulating p75NTR-induced neurotoxicity in neurodegenerative diseases including Alzheimer's disease (AD) and frontotemporal lobar degeneration (FTLD) (Shen et al. 2018; Weskamp et al. 2004; Yao et al. 2015).

Table 2 Information of 13 tag-SNPs and HWE test

Gene	tag-SNP	Location [a]	Allele (major/minor)	MAF in CHB [b]	MAF in controls	*P* value of HWE
NGFR	rs603769	Promotor	A/G	0.208	0.216	0.24
NGFR	rs2584665	Promoter	A/C	0.128	0.137	0.61
NGFR	rs9908234	Intron1	A/G	0.263	0.230	0.91
NGFR	rs3785931	Intron1	C/T	0.500	0.423	0.46
NGFR	rs2537706	Intron3	G/A	0.122	0.126	0.062
NGFR	rs534561	Intron3	C/G	0.344	0.293	0.63
NGFR	rs2072446	Exon4	C/T	0.148	0.101	0.82
NGFR	rs7219709	Exon6	C/T	0.136	0.109	0.68
NGFR	rs1804011	Exon6	C/A	0.135	0.142	0.74
NGFR	rs734194	Exon6	T/G	0.186	0.295	0.39
NGFR	rs741072	Exon6	C/T	0.408	0.359	0.66
NGFR	rs741073	Exon6	G/A	0.250	0.233	0.74
ADAM17	rs1048610	Exon15	A/G	0.062	0.079	0.16

MAF, minor allele frequency; *HWE*, Hardy-Weinberg equilibrium

[a] The genomic coordinates were shown based on the human assembly GRCh37, and relative locations were referred to the *NGFR* and *ADAM17* genes

[b] Data were obtained from HapMap database for Chinese Han in Beijing (CHB, $n = 45$)

Table 3 Genotype distributions of the tag-SNPs and their associations with the risk of Parkinson's disease

tag-SNP	Genotypes	Control group	PD group	Genetic models[a]	OR value	95% CI	*P* value[b]
rs603769	A/A	385 (62.2%)	258 (62.5%)	Codominant	0.97	0.74–1.27	0.91
	A/G	200 (32.3%)	130 (31.5%)		1.10	0.64–1.89	
	G/G	34 (5.5%)	25 (6.0%)	Dominant	0.99	0.77–1.28	0.94
				Recessive	1.11	0.65–1.90	0.70
				Over-dominant	0.96	0.74–1.26	0.78
				Additive	1.01	0.82–1.24	0.93
rs2584665	A/A	465 (74.6%)	313 (75.6%)	Codominant	0.91	0.67–1.23	0.49
	A/C	145 (23.3%)	88 (21.3%)		1.47	0.67–3.23	
	C/C	13 (2.1%)	13 (3.1%)	Dominant	0.96	0.72–1.28	0.76
				Recessive	1.51	0.69–3.29	0.31
				Over-dominant	0.90	0.66–1.21	0.48
				Additive	1.01	0.79–1.29	0.95
rs9908234	A/A	367 (59.1%)	243 (59.0%)	Codominant	1.04	0.80–1.36	0.56
	A/G	222 (35.8%)	153 (37.1%)		0.74	0.40–1.38	
	G/G	32 (5.2%)	16 (3.9%)	Dominant	1.01	0.78–1.30	0.97
				Recessive	0.73	0.39–1.34	0.30
				Over-dominant	1.07	0.82–1.38	0.63
				Additive	0.96	0.78–1.19	0.74
rs3785931	C/C	201 (32.5%)	136 (33.0%)	Codominant	0.92	0.69–1.22	0.45
	C/T	311 (50.3%)	194 (47.1%)		1.14	0.79–1.63	
	T/T	106 (17.1%)	82 (19.9%)	Dominant	0.97	0.75–1.27	0.84
				Recessive	1.20	0.87–1.65	0.27
				Over-dominant	0.87	0.68–1.12	0.29
				Additive	1.04	0.87–1.25	0.63
rs2537706	G/G	475 (77.5%)	315 (77.2%)	Codominant	0.96	0.70–1.32	0.62
	G/A	122 (19.9%)	78 (19.1%)		1.41	0.68–2.89	
	A/A	16 (2.6%)	15 (3.7%)	Dominant	1.01	0.75–1.37	0.93
				Recessive	1.42	0.69–2.91	0.34
				Over-dominant	0.95	0.69–1.30	0.75
				Additive	1.05	0.82–1.35	0.69
rs534561	C/C	314 (50.4%)	193 (46.6%)	Codominant	1.19	0.91–1.54	0.42
	C/G	253 (40.6%)	186 (44.9%)		1.02	0.64–1.61	
	G/G	56 (9.0%)	35 (8.4%)	Dominant	1.16	0.90–1.48	0.25
				Recessive	0.94	0.60–1.46	0.78
				Over-dominant	1.18	0.92–1.52	0.19
				Additive	1.08	0.89–1.31	0.45
rs2072446	C/C	497 (80.7%)	324 (78.5%)	Codominant	1.14	0.84–1.57	0.68
	C/T	114 (18.5%)	85 (20.6%)		1.21	0.32–4.54	
	T/T	5 (0.8%)	4 (1.0%)	Dominant	1.15	0.84–1.56	0.39
				Recessive	1.18	0.31–4.41	0.81
				Over-dominant	1.14	0.83–1.56	0.41
				Additive	1.14	0.85–1.52	0.39
rs7219709	C/C	491 (79.6%)	333 (80.6%)	Codominant	0.94	0.69–1.30	0.82
	C/T	118 (19.1%)	76 (18.4%)		0.72	0.21–2.42	
	T/T	8 (1.3%)	4 (1.0%)	Dominant	0.93	0.68–1.27	0.65
				Recessive	0.73	0.22–2.44	0.60
				Over-dominant	0.95	0.69–1.31	0.75
				Additive	0.92	0.69–1.23	0.59
rs1804011	C/C	443 (73.7%)	327 (80.3%)	Codominant	0.69	0.50–0.95	*0.049*
	C/A	145 (24.1%)	74 (18.2%)		0.62	0.23–1.64	
	A/A	13 (2.2%)	6 (1.5%)	Dominant	0.69	0.50–0.93	*0.014*

Table 3 (continued)

tag-SNP	Genotypes	Control group	PD group	Genetic models[a]	OR value	95% CI	*P* value[b]
				Recessive	0.67	0.25–1.78	0.41
				Over-dominant	0.70	0.51–0.96	*0.025*
				Additive	0.72	0.54–0.94	*0.016*
rs734194	T/T	302 (49.0%)	211 (51.5%)	Codominant	0.88	0.67–1.14	0.52
	T/G	266 (43.1%)	162 (39.5%)		1.08	0.68–1.72	
	G/G	49 (7.9%)	37 (9.0%)	Dominant	0.91	0.71–1.17	0.46
				Recessive	1.15	0.74–1.80	0.54
				Over-dominant	0.87	0.67–1.12	0.27
				Additive	0.97	0.80–1.18	0.76
rs741072	C/C	251 (40.6%)	162 (39.2%)	Codominant	1.00	0.77–1.31	0.38
	C/T	290 (46.9%)	187 (45.3%)		1.29	0.88–1.90	
	T/T	77 (12.5%)	64 (15.5%)	Dominant	1.06	0.82–1.37	0.63
				Recessive	1.29	0.90–1.85	0.16
				Over-dominant	0.94	0.73–1.21	0.62
				Additive	1.10	0.92–1.32	0.30
rs741073	G/G	365 (58.6%)	269 (65.0%)	Codominant	0.71	0.54–0.93	*0.037*
	G/A	226 (36.3%)	119 (28.7%)		1.08	0.63–1.86	
	A/A	32 (5.1%)	26 (6.3%)	Dominant	0.76	0.58–0.98	*0.033*
				Recessive	1.22	0.71–2.08	0.47
				Over-dominant	0.71	0.54–0.92	*0.010*
				Additive	0.86	0.69–1.06	0.15
rs1049610	A/A	525 (84.3%)	342 (82.6%)	Codominant	1.09	0.78–1.53	0.32
	A/G	97 (15.6%)	69 (16.7%)		4.55	0.47–43.98	
	G/G	1 (0.2%)	3 (0.7%)	Dominant	1.33	0.81–1.57	0.49
				Recessive	4.48	0.46–43.35	0.16
				Over-dominant	1.08	0.77–1.52	0.64
				Additive	1.16	0.84–1.60	0.37

OR, odds ratio; *CI*, confidence interval

[a] Assuming M represents major allele and m represents minor allele, each genetic model can be described as follows: codominant: M/m vs M/M and m/m vs M/M, two OR values were listed from top to bottom in corresponding rows; dominant: (m/m + M/m) vs M/M; recessive: m/m vs (M/M +M/m); over-dominant: M/m vs (M/M +m/m); additive: m/m and M/m were weighed 2 and 1 respectively to M/M. The analyses of all models were adjusted by age and sex

[b] The given *P* values were not corrected by Bonferroni correction and Italic numbers indicate *P* values <0.05

In the present study, at a type I error rate of 0.05, the statistical power to detect a relative risk of 1.8 or more compared with the control group was above 81% for all selected tag-SNPs, suggesting that our study has enough power to detect the statistical significance of the association. However, although rs741073 and rs1804011 were associated with the reduced risk of PD after adjustment for confounding factors (age and sex), these associations did not retain after Bonferroni correction.

The p75NTR is a pan-receptor for nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), neurotrophin-3 (NT3), and neurotrophin-4/5 (NT4/5). It belongs to the tumor necrosis factor receptor superfamily and plays diverse roles in regulating cell survival, neuronal degeneration, and cell death. It is mainly expressed in cholinergic neurons of basal forebrain, striatum, and spinal cord. Chen et.al (Wang et al. 2008) first reported that p75NTR was also expressed in the dopamine neurons of substantia nigra in adult rats, and the expression of p75NTR was up-regulated by excitotoxic kainic acid (KA) insult using reverse transcription polymerase chain reaction (RT-PCR). The double immunofluorescence further revealed p75NTR-positive immunoreactivity in the substantia nigra, and co-localizations of p75NTR and tyrosine hydroxylase (TH) were found in a large amount of substantia nigra neurons. Consistently, cell count data indicated that about 47% of TH-positive neurons showing p75NTR-immunoreactivity in control animals, which increased to 98% in the KA-insulted animals (Wang et al. 2008). Recently, they discovered that the expressions of proNGF and sortilin were abundantly and selectively identified in TH-positive dopamine neurons in the substantia nigra. Dynamic proNGF and sortilin changes along with dopamine

neuronal loss were demonstrated in the substantia nigra of both the lactacystin and 6-OHDA rat models of PD (Xia et al. 2013). Additionally, pro-neurotrophins preferentially bind to p75NTR-sortillin complex inducing cell apoptosis, growth cone collapse, and synaptic weakening. Therefore, p75NTR may play an important role in the neuronal death of dopamine neurons in the substantia nigra. Moreover, the selective vulnerability of this neuronal population was demonstrated to be impacted by mitochondrial dysfunction (Abou-Sleiman et al. 2006). It was found that p75NTR also acts as a negative modulate factor for the cell survival and sensitivity to mitochondrial insult of mesencephalic dopaminergic neurons, and altered levels of p75NTR expression may contribute to the susceptibility to PD (Alavian et al. 2009). The function of p75NTR in the pathogenesis and development of PD still needs to be further studied.

As two age-related, progressive, and genetically complex diseases, AD and PD are the two most common neurodegenerative diseases affecting the elderly worldwide. Although they are clinically distinct, these two diseases have several features in common. Pathologically, as a hallmark of AD, amyloid-β (Aβ) was observed in the brain of PD patients (Compta et al. 2011; Kalaitzakis et al. 2008); meanwhile, Lewy body deposition also presented in AD cases (Lippa et al. 1997). Genetically, AD and PD share some overlapping genetic background, such as *APOE* and *MAPT* genetic variants were successively reported to confer the risk for both diseases (Goris et al. 2007; Laws et al. 2007; Polvikoski et al. 1995; Williams-Gray et al. 2009). Our previous studies demonstrated that p75NTR plays diverse roles in the metabolism of Aβ, neuronal death, neurite degeneration, and tau hyperphosphorylation in AD (Yao et al. 2015). The expression of p75NTR was increased with aging and further activated by Aβ, and the activated p75NTR in turn promotes Aβ production, thus forming a vicious cycle and finally resulting in Aβ over-production (Zeng et al. 2011). Coincidently, the level of p75NTR expression was also up-regulated in the dopamine neurons of PD animal models. Based on these findings, along with the neurotoxic signaling via the binding of pro-neurotrophins to p75NTR-sortillin complex, p75NTR may mediate the cell death and neurite degeneration of both cholinergic and dopaminergic neurons. Therefore, it is reasonable to propose that p75NTR may be another link between the pathogenesis of AD and PD, rendering it interesting to explore whether genetic variants within *NGFR* contribute to both diseases as well. It was reported that rs2072446 and rs734194 within *NGFR* were closely associated with AD susceptibility in a French cohort, while no association were found between the SNPs in the promoter region of *ADAM17* and AD (Cheng et al. 2012; Cozza et al. 2008; Wang et al. 2010). Our study also found that rs2072446 was significantly associated with an increased risk of AD, which is probably due to the influence of this missense variant on the physiological shedding of p75ECD (unpublished data). Notwithstanding *NGFR* and *ADAM17* tend to be promising candidate genes for PD, our findings did not support the relationship between the included tag-SNPs within them and PD in Chinese Han population. However, given the important role of p75NTR in the pathogenesis of PD, the relationship between other common or rare genetic variants beyond the scope of this study and the susceptibility of PD needs to be further validated.

Conclusions

Despite of the important role of p75NTR in the selective neuronal death of dopamine neurons and the pathogenesis of PD, our study failed to reveal the association between the selected tag-SNPs within *NGFR*, *ADAM17*, and the risk of PD in Chinese Han population. Future studies with a larger sample size in Chinese and different ethnics are warrant to confirm the effect of *NGFR*, *ADAM17* gene polymorphism on the genetic mechanism of PD.

Funding Information This study was supported by the National Natural Science Foundation of China (Grant no. 81870860 and 81571239) and the Ministry of Science and Technology of China (Grant no.2016YFC1306401).

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

References

Abou-Sleiman PM, Muqit MM, Wood NW (2006) Expanding insights of mitochondrial dysfunction in Parkinson's disease. Nat Rev Neurosci 7:207–219. https://doi.org/10.1038/nrn1868

Alavian KN, Sgado P, Alberi L, Subramaniam S, Simon HH (2009) Elevated P75NTR expression causes death of engrailed-deficient midbrain dopaminergic neurons by Erk1/2 suppression. Neural Dev 4:11. https://doi.org/10.1186/1749-8104-4-11

Al-Shawi R, Hafner A, Chun S, Raza S, Crutcher K et al (2007) ProNGF, sortilin, and age-related neurodegeneration. Ann N Y Acad Sci 1119:208–215. https://doi.org/10.1196/annals.1404.024

Barrett GL (2000) The p75 neurotrophin receptor and neuronal apoptosis. Prog Neurobiol 61:205–229

Barrett JC, Fry B, Maller J, Daly MJ (2005) Haploview: analysis and visualization of LD and haplotype maps. Bioinformatics 21:263–265. https://doi.org/10.1093/bioinformatics/bth457

Bian GL, Wei LC, Shi M, Wang YQ, Cao R, Chen LW (2007) Fluoro-Jade C can specifically stain the degenerative neurons in the substantia nigra of the 1-methyl-4-phenyl-1,2,3,6-tetrahydro pyridine-treated C57BL/6 mice. Brain Res 1150:55–61. https://doi.org/10.1016/j.brainres.2007.02.078

Chen LW, Wang YQ, Bian GL, Wei LC, Yung KL (2008a) Neurokinin-3 peptide instead of neurokinin-1 synergistically exacerbates kainic

acid-inducing degeneration of neurons in the substantia nigra of mice. J Neurochem 105:203–216. https://doi.org/10.1111/j.1471-4159.2007.05132.x

Chen LW, Yung KK, Chan YS, Shum DK, Bolam JP (2008b) The proNGF-p75NTR-sortilin signalling complex as new target for the therapeutic treatment of Parkinson's disease. CNS Neurol Disord Drug Targets 7:512–523

Cheng HC, Sun Y, Lai LC, Chen SY, Lee WC, Chen JH, Chen TF, Chen HH, Wen LL, Yip PK, Chu YM, Chen WJ, Chen YC (2012) Genetic polymorphisms of nerve growth factor receptor (NGFR) and the risk of Alzheimer's disease. J Negat Results Biomed 11:5. https://doi.org/10.1186/1477-5751-11-5

Compta Y, Parkkinen L, O'Sullivan SS, Vandrovcova J, Holton JL, Collins C, Lashley T, Kallis C, Williams DR, de Silva R, Lees AJ, Revesz T (2011) Lewy- and Alzheimer-type pathologies in Parkinson's disease dementia: which is more important? Brain J Neurol 134:1493–1505. https://doi.org/10.1093/brain/awr031

Cozza A, Melissari E, Iacopetti P, Mariotti V, Tedde A, Nacmias B, Conte A, Sorbi S, Pellegrini S (2008) SNPs in neurotrophin system genes and Alzheimer's disease in an Italian population. J Alzheimers Dis: JAD 15:61–70

Esler WP, Wolfe MS (2001) A portrait of Alzheimer secretases–new features and familiar faces. Science 293:1449–1454. https://doi.org/10.1126/science.1064638

Fernandez-Espejo E (2004) Pathogenesis of Parkinson's disease: prospects of neuroprotective and restorative therapies. Mol Neurobiol 29:15–30. https://doi.org/10.1385/MN:29:1:15

Fujii T, Yamamoto N, Hori H, Hattori K, Sasayama D, Teraishi T, Hashikura M, Tatsumi M, Okamoto N, Higuchi T, Kunugi H (2011) Support for association between the Ser205Leu polymorphism of p75(NTR) and major depressive disorder. J Hum Genet 56:806–809. https://doi.org/10.1038/jhg.2011.107

Gau YT, Liou YJ, Yu YW, Chen TJ, Lin MW et al (2008) Evidence for association between genetic variants of p75 neurotrophin receptor (p75NTR) gene and antidepressant treatment response in Chinese major depressive disorder. Am J Med Genet Part B, Neuropsychiatr Genet:Off Publ Int Soc Psychiatr Genet 147B:594–599. https://doi.org/10.1002/ajmg.b.30646

Gibson TM, Wang SS, Cerhan JR, Maurer MJ, Hartge P, Habermann TM, Davis S, Cozen W, Lynch CF, Severson RK, Rothman N, Chanock SJ, Morton LM (2012) Inherited genetic variation and overall survival following follicular lymphoma. Am J Hematol 87:724–726. https://doi.org/10.1002/ajh.23184

Goris A, Williams-Gray CH, Clark GR, Foltynie T, Lewis SJ et al (2007) Tau and alpha-synuclein in susceptibility to, and dementia in, Parkinson's disease. Ann Neurol 62:145–153. https://doi.org/10.1002/ana.21192

Hamza TH, Zabetian CP, Tenesa A, Laederach A, Montimurro J, Yearout D, Kay DM, Doheny KF, Paschall J, Pugh E, Kusel VI, Collura R, Roberts J, Griffith A, Samii A, Scott WK, Nutt J, Factor SA, Payami H (2010) Common genetic variation in the HLA region is associated with late-onset sporadic Parkinson's disease. Nat Genet 42:781–785. https://doi.org/10.1038/ng.642

Junyent M, Parnell LD, Lai CQ, Arnett DK, Tsai MY et al (2010) ADAM17_i33708A>G polymorphism interacts with dietary n-6 polyunsaturated fatty acids to modulate obesity risk in the Genetics of Lipid Lowering Drugs and Diet Network study nutrition, metabolism, and cardiovascular diseases. NMCD 20:698–705

Kalaitzakis ME, Graeber MB, Gentleman SM, Pearce RK (2008) Striatal beta-amyloid deposition in Parkinson disease with dementia. J Neuropathol Exp Neurol 67:155–161. https://doi.org/10.1097/NEN.0b013e31816362aa

Kunugi H, Hashimoto R, Yoshida M, Tatsumi M, Kamijima K (2004) A missense polymorphism (S205L) of the low-affinity neurotrophin receptor p75NTR gene is associated with depressive disorder and attempted suicide. Am J Med Genet Part B, Neuropsychiatric Genet : Off Publ Int Soc Psychiatr Genet 129B:44–46. https://doi.org/10.1002/ajmg.b.30062

Laws SM, Friedrich P, Diehl-Schmid J, Muller J, Eisele T et al (2007) Fine mapping of the MAPT locus using quantitative trait analysis identifies possible causal variants in Alzheimer's disease. Mol Psychiatry 12:510–517. https://doi.org/10.1038/sj.mp.4001935

Lippa CF, Pulaski-Salo D, Dickson DW, Smith TW (1997) Alzheimer's disease, Lewy body disease and aging: a comparative study of the perforant pathway. J Neurol Sci 147:161–166

Lorraine VK, Anthony EL (2015) Parkinson's disease. Lancet 386:896–912. https://doi.org/10.1016/S0140-6736(14)61393-3

Luo Y (1999) Chinese diagnostic criteria of Parkinson's disease. Chin J Prac Intern Med 19:325–328

Maraganore DM, de Andrade M, Elbaz A, Farrer MJ, Ioannidis JP et al (2006) Collaborative analysis of alpha-synuclein gene promoter variability and Parkinson disease. Jama 296:661–670. https://doi.org/10.1001/jama.296.6.661

Nalls MA, Plagnol V, Hernandez DG, Sharma M, Sheerin UM et al (2011) Imputation of sequence variants for identification of genetic risks for Parkinson's disease: a meta-analysis of genome-wide association studies. Lancet 377:641–649. https://doi.org/10.1016/s0140-6736(10)62345-8

Nalls MA, Pankratz N, Lill CM, Do CB, Hernandez DG et al (2014) Large-scale meta-analysis of genome-wide association data identifies six new risk loci for Parkinson's disease. Nat Genet 46:989–993. https://doi.org/10.1038/ng.3043

Olanow CW, Tatton WG (1999) Etiology and pathogenesis of Parkinson's disease. Annu Rev Neurosci 22:123–144. https://doi.org/10.1146/annurev.neuro.22.1.123

Polvikoski T, Sulkava R, Haltia M, Kainulainen K, Vuorio A, Verkkoniemi A, Niinistö L, Halonen P, Kontula K (1995) Apolipoprotein E, dementia, and cortical deposition of beta-amyloid protein. N Engl J Med 333:1242–1247. https://doi.org/10.1056/NEJM199511093331902

Satake W, Nakabayashi Y, Mizuta I, Hirota Y, Ito C, Kubo M, Kawaguchi T, Tsunoda T, Watanabe M, Takeda A, Tomiyama H, Nakashima K, Hasegawa K, Obata F, Yoshikawa T, Kawakami H, Sakoda S, Yamamoto M, Hattori N, Murata M, Nakamura Y, Toda T (2009) Genome-wide association study identifies common variants at four loci as genetic risk factors for Parkinson's disease. Nat Genet 41:1303–1307. https://doi.org/10.1038/ng.485

Shen LL, Manucat-Tan NB, Gao SH, Li WW, Zeng F et al (2018) The ProNGF/p75NTR pathway induces tau pathology and is a therapeutic target for FTLD-tau. Mol Psychiatry 23:1813–1824. https://doi.org/10.1038/s41380-018-0071-z

Sidransky E, Nalls MA, Aasly JO, Aharon-Peretz J, Annesi G, Barbosa ER, Bar-Shira A, Berg D, Bras J, Brice A, Chen CM, Clark LN, Condroyer C, de Marco EV, Dürr A, Eblan MJ, Fahn S, Farrer MJ, Fung HC, Gan-Or Z, Gasser T, Gershoni-Baruch R, Giladi N, Griffith A, Gurevich T, Januario C, Kropp P, Lang AE, Lee-Chen GJ, Lesage S, Marder K, Mata IF, Mirelman A, Mitsui J, Mizuta I, Nicoletti G, Oliveira C, Ottman R, Orr-Urtreger A, Pereira LV, Quattrone A, Rogaeva E, Rolfs A, Rosenbaum H, Rozenberg R, Samii A, Samaddar T, Schulte C, Sharma M, Singleton A, Spitz M, Tan EK, Tayebi N, Toda T, Troiano AR, Tsuji S, Wittstock M, Wolfsberg TG, Wu YR, Zabetian CP, Zhao Y, Ziegler SG (2009) Multicenter analysis of glucocerebrosidase mutations in Parkinson's disease. N Engl J Med 361:1651–1661. https://doi.org/10.1056/NEJMoa0901281

Simon-Sanchez J, Schulte C, Bras JM, Sharma M, Gibbs JR et al (2009) Genome-wide association study reveals genetic risk underlying Parkinson's disease. Nat Genet 41:1308–1312. https://doi.org/10.1038/ng.487

Sole X, Guino E, Valls J, Iniesta R, Moreno V (2006) SNPStats: a web tool for the analysis of association studies. Bioinformatics 22:1928–1929. https://doi.org/10.1093/bioinformatics/btl268

Szczepankiewicz A, Sobkowiak P, Rachel M, Breborowicz A, Schoneich N et al (2012) Multilocus analysis of candidate genes involved in neurogenic inflammation in pediatric asthma and related phenotypes: a case-control study. J Asthma 49:329–335. https://doi.org/10.3109/02770903.2012.669442

Wang YQ, Bian GL, Bai Y, Cao R, Chen LW (2008) Identification and kainic acid-induced up-regulation of low-affinity p75 neurotrophin receptor (p75NTR) in the nigral dopamine neurons of adult rats. Neurochem Int 53:56–62. https://doi.org/10.1016/j.neuint.2008.06.007

Wang M, Li Y, Lu Y, Zuo X, Wang F, Zhang Z, Jia J (2010) The relationship between ADAM17 promoter polymorphisms and sporadic Alzheimer's disease in a Northern Chinese Han population. J Clin Neurosci: Off J Neurosurg Soc Australasia 17:1276–1279. https://doi.org/10.1016/j.jocn.2010.01.008

Weskamp G, Schlondorff J, Lum L, Becherer JD, Kim TW et al (2004) Evidence for a critical role of the tumor necrosis factor alpha convertase (TACE) in ectodomain shedding of the p75 neurotrophin receptor (p75NTR). J Biol Chem 279:4241–4249. https://doi.org/10.1074/jbc.M307974200

Williams-Gray CH, Goris A, Saiki M, Foltynie T, Compston DA et al (2009) Apolipoprotein E genotype as a risk factor for susceptibility to and dementia in Parkinson's disease. J Neurol 256:493–498. https://doi.org/10.1007/s00415-009-0119-8

Xia Y, Chen BY, Sun XL, Duan L, Gao GD, Wang JJ, Yung K, Chen LW (2013) Presence of proNGF-sortilin signaling complex in nigral dopamine neurons and its variation in relation to aging, lactacystin and 6-OHDA insults. Int J Mol Sci 14:14085–14104. https://doi.org/10.3390/ijms140714085

Xu Z, Taylor JA (2009) SNPinfo: integrating GWAS and candidate gene information into functional SNP selection for genetic association studies. Nucleic Acids Res 37:W600–W605

Yao XQ, Jiao SS, Saadipour K, Zeng F, Wang QH, Zhu C, Shen LL, Zeng GH, Liang CR, Wang J, Liu YH, Hou HY, Xu X, Su YP, Fan XT, Xiao HL, Lue LF, Zeng YQ, Giunta B, Zhong JH, Walker DG, Zhou HD, Tan J, Zhou XF, Wang YJ (2015) p75NTR ectodomain is a physiological neuroprotective molecule against amyloid-beta toxicity in the brain of Alzheimer's disease. Mol Psychiatry 20:1301–1310. https://doi.org/10.1038/mp.2015.49

Yuan HY, Chiou JJ, Tseng WH, Liu CH, Liu CK, Lin YJ, Wang HH, Yao A, Chen YT, Hsu CN (2006) FASTSNP: an always up-to-date and extendable service for SNP function analysis and prioritization. Nucleic Acids Res 34:W635–W641

Zeng F, Lu JJ, Zhou XF, Wang YJ (2011) Roles of p75NTR in the pathogenesis of Alzheimer's disease: a novel therapeutic target. Biochem Pharmacol 82:1500–1509. https://doi.org/10.1016/j.bcp.2011.06.040

Zeng F, Zou HQ, Zhou HD, Li J, Wang L, Cao HY, Yi X, Wang X, Liang CR, Wang YR, Zhang AQ, Tan XL, Peng KR, Zhang LL, Gao CY, Xu ZQ, Wen AQ, Lian Y, Zhou XF, Wang YJ (2013) The relationship between single nucleotide polymorphisms of the NTRK2 gene and sporadic Alzheimer's disease in the Chinese Han population. Neurosci Lett 550:55–59. https://doi.org/10.1016/j.neulet.2013.06.061