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Lack of Association Between *PLA2G6* Genetic Variation and Parkinson's Disease: A Systematic Review

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Background: The phospholipase A2 Group 6 (*PLA2G6*, also known as *PLA2, PARK14*, and *iPLA2*) gene encodes a group VIA calcium-independent phospholipase A2. Genetic polymorphism of *PLA2G6* has been indicated to be involved in conferring susceptibility for Parkinson's disease (PD), whereas conclusive results have not been obtained. Thus, we intended to conduct a systematic review to determine if *PLA2G6* genetic variation confers a greater susceptibility to PD.

Methods: All case-control studies that investigated the association of the *PLA2G6* polymorphisms with the risk of PD published before 15 July 2018 were included. The literature was comprehensively searched and identified in five English databases (EBSCO, Pubmed, OVID, EMBASE and ISI Web of Knowledge) and four Chinese databases (Wanfang database, Chinese Biomedical Literature Database, China Academic Journals Database and VIP database). We performed analyses of study characteristics, heterogeneity, and forest plot in analyses analogous to dominant, codominant and additive models with the pooled odds ratio (OR) in fixed- or random-effects models as the measure of association.

Results: A total of 664 potentially relevant studies were retrieved with the initial search, of which eight studies fulfilled the inclusion criteria, and included 2,779 PD patients and 3,291 control participants,. Among all the reported 27 genetic variants, 15 single nucleotide polymorphisms (SNPs) were present only in patients, and only five available SNPs (rs2267369, rs140758033, c.1959T>A (Gly653Gly), rs76718524, rs199935023) were pooled in the meta-analysis. However, there was no evidence for a significant association between the five SNPs and PD risk in dominant, codominant and allele models, suggesting a lack of association between *PLA2G6* genetic variation and PD susceptibility.

Conclusion: The present study assessed the association of *PLA2G6* genetic polymorphism with the risk PD, and the result strongly demonstrates that *PLA2G6* polymorphism is not associated with PD susceptibility.

Keywords: Parkinson's disease, PD, *PLA2G6*, systematic review

Introduction

Parkinson's disease (PD), one of the most disabling disorders of the central nervous system, frequently develops in elderly patients affecting 1% of the population above 60 years and up to 4% of the population above 85 years.[1] In addition to mental symptoms, patients with PD display typical motor symptoms such as postural instability, muscle rigidity, static tremors and difficulty with walking and gait.[2] PD is a complex multifactor disease characterized by the extensive presence of α-synuclein-containing Lewy

bodies in the substantia nigra (SN), in the pars compacta of which loss of dopaminergic neurons leads to reduced facilitation of voluntary movements.[3] Literature in the past decade has suggested that genetic factors might play an important role in the development of PD.[4] Thus far, researches related to genetic mutation or variation such as candidate-gene analyses, whole-genome linkage scans as well as family-based studies have clarified 14 chromosomal loci (*PARK1-PARK14*) in which mutations are unequivocally linked to rare forms of PD.[5]

The gene of phospholipase A2 Group 6 (*PLA2G6*, also known as *PARK14, iPLA2* and *PLA2*), consisting of 17 exons, locates on chromosome 22q12-13.[6] The protein encoded by the *PLA2G6* gene is an 85-kDa group VI calcium-independent phospholipase A2 beta (iPLA2 β, also known as PLA2G6), which selectively hydrolyses glycerophospholipids to release free fatty acids.[7] The PLA2G6 protein may play an indispensable role in transmembrane ion flux, fas-mediated apoptosis and leukotriene and prostaglandin synthesis.

PLA2G6 genetic mutation has previously been considered to cause autosomal recessive inheritance of infantile neuroaxonal dystrophy (INAD) in 2006,[8] and was also characterized as a causative gene of neurodegeneration with brain iron accumulation (NBIA).[6] Lately, the *PLA2G6* gene mutation has been identified as a locus for parkinsonism.[9–11] The neuropathological finding revealed widespread α-synuclein-containing Lewy body pathology and loss of dopaminergic neurons in the SN, supporting an association between *PLA2G6* gene mutation and PD.[9] The finding reported by Kauther et al[12] displayed that the nonsynonymous single nucleotide polymorphisms (SNPs) rs139093920 (Ala781Thr) and 2339A>G (Asn780Ser) was only present in patients of L-dopa-responsive sporadic early-onset PD (EOPD), while not in any of the control participants yet,[12] implying a possible association between *PLA2G6* and the EOPD pathogenesis. More recently, Tan et al[13] in Singapore distinguish a Pro806Arg substitution (rs140758033, c.2417C>G) in exon 17 in one of 96 PD EOPD patients, while this mutation was not found in any other 100 healthy controls.[13] This specific finding emphasized the potential role of *PLA2G6* gene mutation acting as a possible pathogenic risk factor for PD, and this is confirmed by other studies from Taiwan,[14] Germany,[12] India,[15] Japan,[11,16] Iran,[10] and China,[17–20] implying that *PLA2G6* mutations may be widely distributed in parkinsonian patients of various populations. In addition, Gui et al[19] identified four rare *PLA2G6* mutations in 4 of 250 PD patients and in none of 550 controls, and they further revealed in subsequent experiments that the catalytic activity of phospholipids-hydrolyzing function was impaired by the four mutations they reported (c.1791delC (P.His597fx69), c.1959T>A (Gly653Gly), c.2077C>G (Leu693Val), c.1966C>G (Leu656Val)), supporting a possible role of *PLA2G6* gene mutations played in the pathogenesis of PD-causing in Chinese Han populations.[19]

However, controversial results have been obtained and whether *PLA2G6* gene mutation is a risk factor for PD remains conflicting. The reported mutations such as rs140758033 which was reported to be associated with PD susceptibility[13] have also been found in control participants (10/310) as well as in PD patients (12/379),[16] leading to the speculation that *PLA2G6* gene possibly does not play an important role in PD.[16,18] Whether *PLA2G6* genetic mutation could contribute to PD, and whether single heterozygous mutations in *PLA2G6* gene is also a risk factor for PD remains intriguing.[13] Thus, this systematic review was conducted to address the possible association between *PLA2G6* genetic variation and PD susceptibility.

Methods

Literature Search and Collection

The systematic review and meta-analysis was conducted according to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) statement[21] including literature search strategy, study selection criteria, raw data extraction, and data analysis. The literature were comprehensively searched and identified in five English databases (OVID, Pubmed, EBSCO, EMBASE, and Web of Knowledge,) and four Chinese databases (Wanfang database, Chinese Biomedical Literature Database, China Academic Journals Database, and VIP database). All case-control studies that investigated the association between *PLA2G6* polymorphisms and the risk of PD published before July 15, 2018 were included. The search term we used in this study was ("Parkinsonism" or "Parkinson's disease" or PD or "Parkinsons disease") and ("phospholipase A2 group VI" or *GVI* or *PLA2* or *INAD1* or *NBIA2* or *iPLA2* or *NBIA2A* or *NBIA2B* or *PARK14* or *PNPLA9* or *CaI-PLA2* or *IPLA2-VIA* or *iPLA2beta* or *PLA2G6*) and (mutation or variation or variant or polymorphisms or polymorphism). An available literature search, reference lists as well as supplemental materials were performed independently, or subsequently identified manually to

recognize potentially relevant studies by two investigators. In addition, the website PDGene (http://www.pdgene.org) was also consulted in this study.

Inclusion and Exclusion Criteria

All the available studies had to meet the following inclusion criteria: 1) a case-control design that was conducted to evaluate the association between *PLA2G6* gene mutation and PD risk; 2) sufficient original data such as genotype frequency or number could be obtained directly in the published paper, be calculated from the text, or provided by the authors after request to calculate the odds ratio (OR) with its 95% confidence interval (CI) and *P*-value; 3) raw data not being the same as other studies; 4) be published in an English or Chinese peer-reviewed journal. Studies were excluded if they met the following exclusion criteria: 1) animal studies; 2) without case-control design; 3) contained overlapping data with another study; 4) cases only or without controls; 5) editorials, comments, reviews and abstracts; and 6) sufficient data could not be obtained in the published version nor provided, even after requesting from authors.

The included studies were determined by two reviewers working independently to identify by title, key words, abstract, and full-text. Relevant to recommendations for the genetic association reports, the scientific quality of the included studies was evaluated according to the HuGENET guidelines[22] and study quality was assessed using the Reporting of Observational Studies in Epidemiology (STROBE) tool.[23] The STROBE statement, a 22-item tool specifically designed to evaluate observational studies quality, does not provide ways to clearly define a score allowing one to rate the quality of the study. As a general rule, the higher the score, the higher the quality of the study. According to the reports of Masini et al[24] and Biagi et al,[25] the cut-offs for three levels of score was adopted: 0–14 as poor quality, 15–25 as intermediate quality and 26–33 as good quality of the study in this report.

Data Extraction

For all the included studies we pooled to in the systematic review, the following information was collected from each of all eligible studies, including the first author, year of publication, ethnicity, number of PD cases and controls, number of the EOPD and LOPD patients, gender and sex ratio, age at onset and examination, and disease duration, gene scanning area, genotyping methods, genotype counts among cases and controls, and Hardy-Weinberg equilibrium (HWE) in controls (*P*-value). If overlapped samples were used in more than one paper, the one that contained the largest sample size and the most detailed were kept. If key data was missing from the published paper or only expressed graphically, we tried to contact the first author or the corresponding author to inquire for further information or to calculate it by ourselves if feasible. Two authors worked independently to evaluate all the trials and evaluate all the data. If the two participants could not reach a consensus, another specialized investigator was consulted to resolve the disagreement.

Statistical Analysis

An estimate of the combined effect sizes utilizing OR with a random effects model or a fixed effects model was used to calculate the frequency of genotype and alleles of *PLA2G6* and estimate the risks of the genotypes on PD. Codominant model of heterozygote comparison (Aa vs AA), dominant model (aa+Aa vs AA), and additive model (allele a vs allele A) was adopted respectively to estimate the risks of the genotypes on PD, in which "A" and "a" represented the major and the minor allele, respectively. Heterogeneity across individual studies was assessed with the value of I^2 or a chi-square-based Q-test.[26] A random-effects model was used when *P*-value of the Q-test <0.1 or $I^2 > 50\%$, otherwise, a fixed-effects model was applied.[27] Sensitivity analysis was performed by deleting one individual study in turn from the total and reanalyzing the remainder to evaluate the stability of the results. Egger's regression test[28] was applied to investigate the potential publication bias. The Review Manger 5 Version 5.0 and Comprehensive Meta-Analysis Version 2.2 were used to perform all the statistical analyses. Pooled OR with 95% CI was adopted to measure the strength of the association between *PLA2G6* genetic variation and PD risk. Probability of *P*-value less than 0.05 was considered statistically significant.

Results

Characteristics of the Study

The flow chart of literature collection and selection is shown in Figure 1. A total of 664 potentially relevant articles were identified from nine databases according to the search strategy. After removing 186 duplicated articles, 478 potentially relevant studies were further identified after going through the titles and abstracts. After reading through the full text articles, 83 studies were preliminarily selected

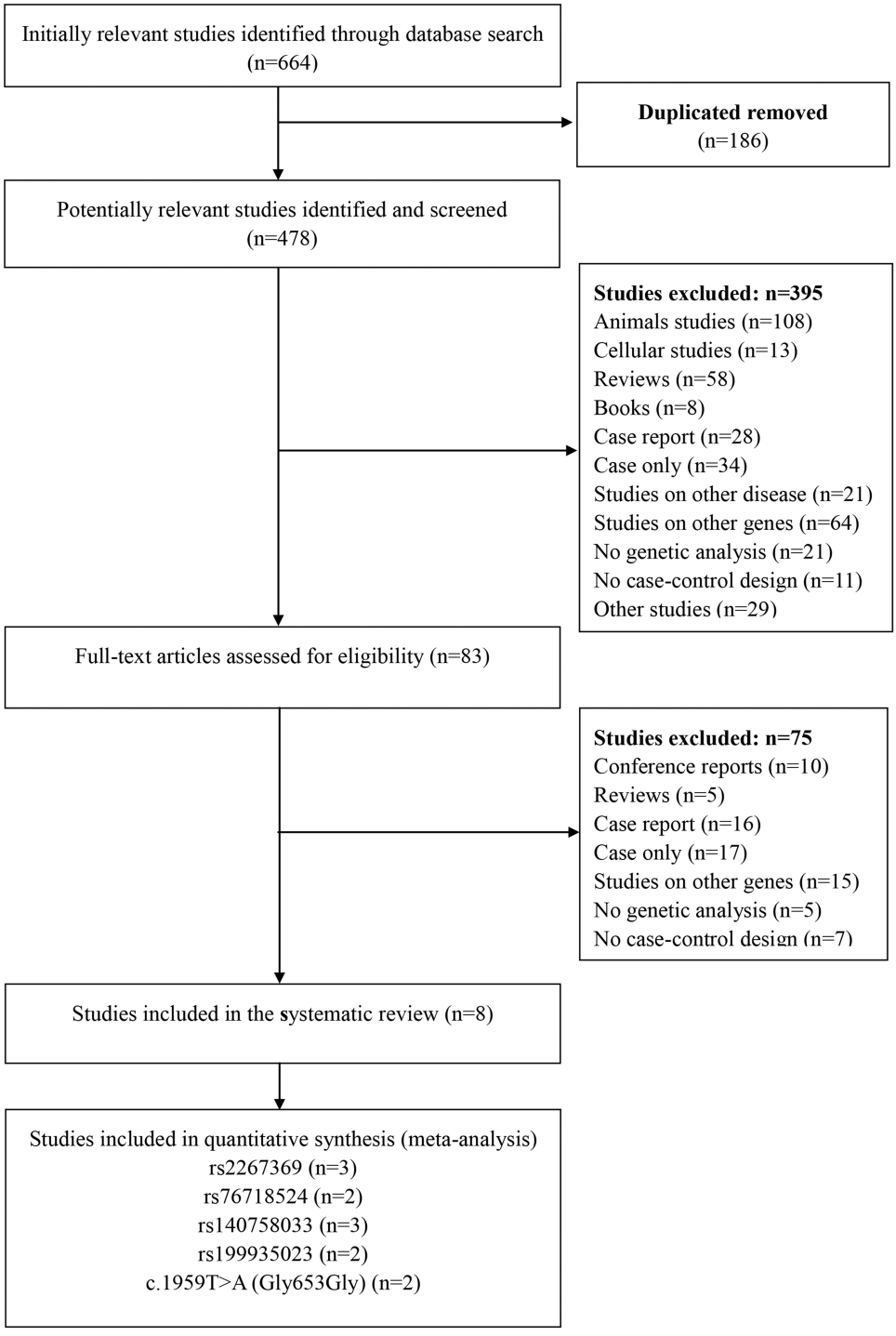

Figure 1 Flow diagram of the study selection process.

for further assessment for eligibility, and 5 reviews, 16 case reports and 10 academic proceedings were excluded. Also, another 44 studies were abandoned because they were without case-control design (n=7), not related to *PLA2G6* gene (n=15), without proper control subjects (n=17) and insufficient published genotype data (n=5). Thus, eight eligible studies[12–14,16–20] fulfilling the inclusion criteria included 2,779 PD patients and 3,291 controls.

In Table 1, we provide the main characteristics, and summarize the quality of all the included studies in Supplementary Table 1. For detailed literature evaluation and scoring methods, please refer to the Supplementary Table 2 excerpted from

Table 1 Characteristics of the Eligible Studies Included in the Systematic Review

Study	Genotyping Method	Scanning Area	Ethnicity	Cases						Controls		
				n	Male (%)	fPD (%)	Age at Onset (Range)	Age at Examination (Range)	Disease Duration	n	Male (%)	Age at Examination (Range)
Gui, Y. X. et al 2013[19]	PCR and DNA sequencing	All exons	Chinese	250	145 (58.0)	NA	55.4±10.2	60.6±10.5	60.6±10.5	550	324 (58.9)	61.4±11.3
Zhou, Y. et al 2012[20]	PCR–RFLP	SNP specific	Chinese	202	106 (52.5)	NA	57.3±11.1 (27–83)	62.7±10.7 (24–84)	3.9±3.3	212	125 (59.0)	62.7±10.4 (34–86)
Tian, J. Y. et al 2012[17]	PCR and DNA sequencing	All the exons and exon-intron boundaries	Chinese	72	42 (58.3)	72(100)	32.7±6.4 (13–40)	NA	4.2±3.8 (1–16)	500	NA	NA
Lv, Z.Y. et al 2012[18]	PCR and DNA sequencing	SNP specific	Chinese	531	302 (56.9)	0(0)	55.0±11.7 (19–81)	NA	NA	561	280 (50.0)	53.3±16.4
Lu, C. S. et al 2012[14]	DNA sequencing, TaqMan and MLPA analysis	All the exons and exon-intron boundaries	Taiwanese	981	582 (59.3)	25 (0.25)	56.8±11.6 (31–91)	NA	NA	802	569 (70.9)	59.0±16.2 (22–91)
Tomiyama, H. et al 2011[16]	PCR and DNA sequencing	A the exons	Japanese	379	181 (47.8)	0(0)	52.7±14.3 (7–88)	60.2±14.0 (12–92)	7.4±5.6 (0–40)	310	122 (39.3)	58.5±13.2 (23–98)
Kauther, K. M. et al 2011[12]	PCR and DNA sequencing	All the exons and exon-intron boundaries	German	268	110 (41.0)	41 (15.3)	42.4 (18–50)	NA	NA	256	119 (46.4)	47.6 (19–83)
Tan, E. K. et al 2010[13]	PCR and DNA sequencing	All the exons and exon-intron boundaries	Singaporean	96	NA	NA	NA	NA	NA	100	NA	NA

Abbreviations: NA, not available; fPD, familial Parkinson's disease; PCR-RFLP, polymerase chain reaction-restriction fragment length polymorphism; MLPA, multiple-ligation probe amplification; SNP, single nucleotide polymorphism.

relevant literature.[23] In this report, we included five intermediate quality studies[14,17-20] and three poor quality studies.[12,13,16] The year of publication was distributed from 2010 to 2013. In terms of the sample sizes of all the studies, it ranged from 72 to 981 cases and 100 to 802 controls. The participants in those included studies were from different countries or areas, specifically four studies from China,[17–20] one from Taiwan,[14] and the other three from Japan,[16] Germany[12] and Singapore,[13] respectively. PD patients including sPD patients as well as fPD patients were mainly diagnosed based on the United Kingdom Parkinson's Disease Brain Bank criteria. Among all those included studies, one study[17] included fPD patients, five studies[13,16,18-20] included only sPD patients, and the other two[12,14] included both sPD patients and fPD patients. Polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP),[20] PCR and DNA direct sequencing,[12,13,16-19] and DNA sequencing combined with TaqMan together with multiple-ligation probe amplification (MLPA) analysis[14] were the main genotyping methods adopted in these included studies. The scanning areas were determined mainly by SNP specific,[20] the exons[16,19] or the exons and exon-intron boundaries.[12–14,17,18] The age distribution showed no significant difference between PD patients and controls in all the included eight studies (Table 1). Finally, all the control subjects showed no deviation from HWE with all *P*-values > 0.05 (Supplementary Table 3).

The Summary of *PLA2G6* Gene SNPs and Quantitative Synthesis

The study comprehensively summarized the genotype and allele frequencies of a total of 27 SNPs in *PLA2G6* gene that have been reported by case-control studies meeting the inclusion criteria to date, among which, seven SNPs (rs4375, rs132985, rs2284063,[18] rs11570597 (−130C>T), rs11570680 (1027G>A, Ala343Thr), −20C>A and rs138683183 (2340C>T, Asn780Asn)[12]) exist in PD patients as well as in control participants, the other 15 SNPs were only found in PD patients (Supplementary Table 3), and only five SNPs (rs2267369, rs76718524, rs140758033, c.1959T>A (Gly653Gly) and rs199935023) reported by two or more studies were available for meta-analysis.

Related to the five SNPs available for quantitative synthesis, three papers with 660 PD patients and 758 control participants concerning rs2267369,[12–14,16,18] three studies with 675 patients of PD and 610 control participants concerning rs140758033,[13,14,16] two studies with 470 patients of PD and 468 control participants concerning rs76718524,[12,20] two studies with 346 patients and 650 controls concerning c.1959T>A,[13,19] and two studies with 1361 PD patients and 1112 control participants concerning rs199935023,[14,16] respectively, were pooled in the meta-analysis (Table 2 and Supplementary Table 3).

The genotype frequency is presented in Supplementary Table 3. The meta-analyses between rs2267369, rs140758033, rs76718524, c.1959T>A, rs199935023 and PD have been conducted, and the main results of meta-analysis are shown in Table 2. Generally, a fixed-effects model was used under the allele model, dominant model and codominant model of heterozygote comparison due to the absence of heterogeneity among the individual studies included in this meta-analysis. The pooled meta-analysis results showed that no significant associations existed between all the five single SNPs and PD susceptibility under all the three genetic models (Table 2 and Supplementary Figure 1).

Sensitivity Analysis and Potential Bias

Sensitive analyses on rs2267369 and rs140758033, the only two SNPs which were included in three or more studies available for meta-analysis, was conducted by sequentially excluding each case-control study, and the results of all the three genetic models were consistent, suggesting the credibility and stability of this meta-analysis of the overall population and subgroup. Besides, publication bias was evaluated by the Egger's test, and no significant results were observed (data not shown).

Discussions

Main Findings

The existing study lacks pooled assessments on the association between *PLA2G6* genic variation and PD susceptibility, even though numerous studies on the impact of *PLA2G6* gene mutation on PD risk have been reported.[19,29-31] This specific study consequently has been designed to uncover whether this relationship is warranted. In this study, a comprehensive study search was conducted and eight articles with a total of 6,070 PD patients and control participants were included to investigate the relationship between *PLA2G6* genetic variants and the risk of PD. The genotype distribution of a total of 27 *PLA2G6* genetic variants were summarized, and five available variants (rs2267369, rs140758033, rs76718524, rs199935023, and c.1959T>A) were pooled in the meta-analysis. Overall, our quantitative analysis

Table 2 Summary of the Meta-Analysis Results Related to the Pooled *PLA2G6* Variants and Parkinson's Disease

Variant	No. of Studies	Total Participants (Cases/Controls)	Genetic Model	Pooled OR (95% CI)	P-value	I^2
rs2267369	3	1418 (660/758)	A	1.21 (0.93–1.56)	0.15	0%
			D	1.28 (0.97–1.69)	0.08	0%
			C	1.32 (0.99–1.75)	0.06	0%
rs76718524	2	938 (470/468)	A	0.96 (0.06–15.31)	0.97	NA
			D	0.96 (0.06–15.31)	0.97	NA
			C	0.96 (0.06–15.31)	0.97	NA
rs140758033	3	1285 (675/610)	A	0.99 (0.46–2.12)	0.97	0%
			D	0.99 (0.46–2.13)	0.97	0%
			C	0.99 (0.46–2.13)	0.97	0%
rs199935023	2	2473 (1361/1112)	A	1.73 (0.56–5.31)	0.34	NA
			D	1.55 (0.49–4.86)	0.46	NA
			C	1.36 (0.42–4.40)	0.60	NA
c.1959T>A (Gly653Gly)	2	996 (346/650)	A	4.50 0.46–43.57)	0.19	NA
			D	4.51 (0.46–43.85)	0.19	NA
			C	4.51 (0.46–43.85)	0.19	NA

Note: I^2 represents the variation in OR attributable to heterogeneity.
Abbreviations: CI, confidence interval; OR, odds ratio; A, allele model; D, dominant model; C, codominant model of heterozygote comparison; NA: not available.

failed to reveal significant association between *PLA2G6* genetic variation and susceptibility of PD depending on the available academic evidence so far.

According to the available literature, apart from INAD[8] and NBIA,[6] *PLA2G6* genetic variation is indicated to be related with Type 2 diabetes risk (rs132984 and rs2284060)[32] and it has also been reported to be associated with some other brain diseases such as bipolar disorder (rs3788533)[33] and Alzheimer's disease.[34] *PLA2G6* gene variation was considered to be relevant with the underlying risk for PD,[19] which disrupted cell membrane structure, promoted apoptosis,[6,18] destroyed in lipid and glucose metabolism[35] and thus probably led to PD. Besides, patients with *PLA2G6*-related dystonia-parkinsonism typically show prominent parkinsonism with other signs such as dystonia, severe cognitive decline, pyramidal signs, and psychiatric features.[9] Thus, to some extent, *PLA2G6* has been termed as one of the risk factors for both fPD patients,[36] which consist of about 10% of PD patients, as well as idiopathic PD.[14,31]

On the contrary, our meta-analysis results obtained from this study did not reach any clear consensus, and also did not reveal any significant association between all the five available SNPs of *PLA2G6* and PD risk (Table 2, Supplementary Figure 1), even though 15 SNPs were present only in PD patients (Supplementary Table 2). Besides, the literature on the relationship between all the total 27 SNPs reported by case-control studies up to now and PD is replete with small studies that report controversial findings. Furthermore, it is worth noting that seven SNPs were present both in PD patients and controls (Supplementary Table 2), suggesting them to be physiological genetic variants rather than causal mutations. To sum up, our present study failed to reveal significant association between *PLA2G6* polymorphism and susceptibility of PD. Through this present study, to elucidate the etiology of PD, instead of this specific kind of research related to a single genetic mutation which may be not prospective in terms of elucidating the pathological mechanism of PD directly, more studies with larger sample size are warranted to be conducted in future.

Limitations

Some limitations to this study should be discussed. Firstly, the genetic background of ethnic groups was not categorized due to the limited number of the included feasible

studies, and a gene-environment or gene-gene interaction which may potentially exert an effect on the statistical results was not investigated. Secondly, the published literature was not sufficiently large for a meta-analysis on most of the reported variants, especially for the five SNPs pooled to the meta-analysis. Finally, the limitations of the observational nature of the original data and the lack of uniformity among studies could not be overlooked, for example, the negative results were less often published compared with positive results, and some studies lacked some of the detailed clinical presentation information such as treatment medication, duration of disease, co-morbid conditions, which may cause serious confounding bias.

Conclusions

The present systematic review and meta-analysis assessed the association of *PLA2G6* genetic polymorphism with the risk PD. We found 15 variants were present only in PD patients, but failed to detect a significant association between the available five SNPs of *PLA2G6* and the risk of PD. The results strongly demonstrate that *PLA2G6* polymorphism is not associated with susceptibility to PD.

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Disclosure

The authors report no conflicts of interest in this work.

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