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Association between HLA rs3129882 polymorphism and Parkinson's disease: a meta-analysis

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Abstract. – OBJECTIVE: As one of potential candidate genes for the risk of Parkinson's disease (PD), the HLA-DRA/PARK18 (rs3129882, A > G) gene has been studied extensively. However, direct evidence for the genetic association studies between PD and rs3129882 remains inconclusive. The aim of our meta-analysis was to determine a more reliable association between the rs3129882 and PD.

MATERIALS AND METHODS: Comprehensive search strategy was used for electronic searches through PubMed, Elsevier, Springer Link, CNKI (Chinese National Knowledge Infrastructure) and WanFang (Chinese) databases to evaluate the association between rs3129882 and PD risk. Data were extracted and the odd ratios (ORs) and 95% confidence intervals (95% CIs) were calculated. Finally, we performed a meta-analysis of 13 appropriate papers by using a total of 11951 patients and 11902 controls.

RESULTS: The meta-analysis showed no significant association between rs3129882 and PD risk in all four models (the allele model, dominant model, homozygote model and the recessive model). In allele model, the result was OR = 1.043 (95% CI = 0.978, 1.113). Moreover, this association remained no significant in the subgroup analysis stratified by ethnicity.

CONCLUSIONS: In current meta-analysis, no significant association was found for rs3129882 and PD risk. And more well-designed primary researches will be needed to further evaluate the interaction of rs3129882 polymorphism and the susceptibility of PD.

Key Words:
Parkinson's disease, HLA-DRA, rs3129882, Polymorphism.

Introduction

Parkinson's disease (PD) is one of the most common neurodegenerative diseases and its clinical manifestation is characterized by resting tremor, bradykinesia, stiffness of movement, and postural instability[1]. As a chronic condition of old age, despite effective symptomatic therapies is progressive, PD affects over 1% of the elderly populations[2]. Over the past decades, a number of researchers performed lots of studies to identify the etiology of PD. These possible etiologies of PD may include the formation of free radicals and oxidative stress, age excitotoxicity, dysfunction of the mitochondrial, apoptosis, calcium cytotoxicity, trophic factor deficiency, the inflammatory process, genetic factors, environmental factors, and toxic action of nitricoxide[3-8]. Recently, among these factors, the influence of the genetic factors have been raised much attention. In 2009, Hardy et al[7] demonstrated the loci which might lead to parkinsonism as pathogenic mutations including PARK1/4, PARK8, PARK6, and these loci might contribute to the formation of the Lewy bodies in the process of PD.

The HLA gene displays a close relationship with the human immune response which has long been a focus of research as a potential role in both the risk and pathogenesis of PD[8]. The HLA complex plays an important role in human body immune surveillance and is related with many autoimmune disorders. So, an attractive hypothesis created by Ouchi et al[11] is forming that variation within the HLA genes may be important in determining risk of PD by regulating the immune responses. In 2010, Hamza et al[12] identified a common genetic variation (rs3129882, A>G) in the HLA region which was associated with late-onset sporadic PD through a genome-wide association study (GWAS). The HLA variant which displays the strongest statistical association with PD is a non-coding polymorphism in intron-1 of HLA-DRA gene. Then, many researches have been taken to assess the association between rs3129882

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and PD in different regions. Some studies[13-19] replicated Hamza et al finding, while some negative or conflicting results were also reported. Therefore, we aimed to perform a meta-analysis to derive a more precise estimation of the association between rs3129882 variant and the susceptibility of PD in a single study may have a weak power to provide reliable conclusions owing to relatively small sample size.

Materials and Methods

Search Strategy and Selection Criteria

In order to find appropriate studies for this meta-analysis, the comprehensive search strategy was carried out for electronic searches through PubMed, Elsevier, Springer Link, CNKI (Chinese National Knowledge Infrastructure) and WanFang (Chinese) databases by using the following terms: "HLA", "HLA-DRA" and "Parkinson's disease", "PD", "Parkinson disease" in combination with "variant", "mutation", "rs3129882", or "polymorphisms". Moreover, additional eligible studies were searched through selecting reference lists of all relevant articles. The languages for all researches were limited to English or Chinese and papers published up to June 2014.

Inclusion and Exclusion Criteria

The included studies should meet the following inclusion criteria: (1) concerning the association between HLA-DRA/PARK18 rs3129882 polymorphism and PD risk; (2) case-control or cohort study; (3) concluding sufficient data on genotype frequencies or allele frequencies of the rs3129882 polymorphisms for calculating the odd ratio (OR) with 95% confidence interval (CI). The exclusion criteria include: (1) review articles, case reports, comments and meta-analysis; (2) a duplicated publication. Moreover, if studies contained overlapping cases and/or controls, the largest study was preferred. If one paper consisted of more than one study group, each group was treated separately. There were no need for the written consent given by the subjects and approval acquired by Ethics Committee in our study as the data included in this meta-analysis was selected from literatures.

Data Extraction

The data was extracted independently from each study which met the inclusion and exclusion criteria by two investigators (Zhu and Lu), and the consensus was approved for all data. The following information extracted from each study was included: the first author's name, year of publication, ethnicity of the study population, research region, single gene frequency, number of cases and controls for each genotype.

Statistical Analysis

The strength of relation between rs3129882 polymorphism and PD was assessed by ORs with 95% CIs. The allele model (G vs. A), the dominant model (GG + AG vs. AA), the homozygote model (GG vs. AA) and the recessive model (GG vs. AG + AA) were used to assess the risk**.** The frequencies observed of the genotypes in the control group was detected by using a chi-square test whether conformed to HWE expectations and a *p*-value less than 0.05 was considered statistically significant. I^2 statistics were used to assess the possible between-study heterogeneity. $I^2 > 50\%$ indicated obvious between-study heterogeneity[20], and OR (95% CI) was calculated by the random effects model[21]; otherwise, the fixed effects model was selected[22]. By ways of omitting a single study included in our meta-analysis each time, sensitivity analyses were conducted to assess the stability of the meta-analysis results. Subgroup analyses were mainly performed by ethnicity (Caucasians and Asians). Asymmetry of the funnel plot was used to indicate the possible publication bias. Moreover, the Begg's and Egger's test was performed to estimate evidence for potential publication bias[23]. Data management and analysis were conducted by using Stata 11.0 (Stata Crop, College Station, TX, USA). A *p* value less than 0.05 was considered statistically significant.

Results

Characteristics of Eligible Studies

According to the search strategy, a total of 111 studies were preliminarily included. Of which, 71 papers were excluded after reading the title and abstract; 23 papers were not relevant to rs3129882; 4 papers lacked the detail data about the genotype or allele frequencies about rs3129882[24-27], and 2 papers included the same data about rs3129882[10,26]. Detailed process for selecting eligible studies was shown in Figure 1. Among the final papers included, 4 papers contained the allele frequencies[12,14,15,19], and 9 papers included the genotype frequencies[13,16-18,29-33]. 2 articles included three

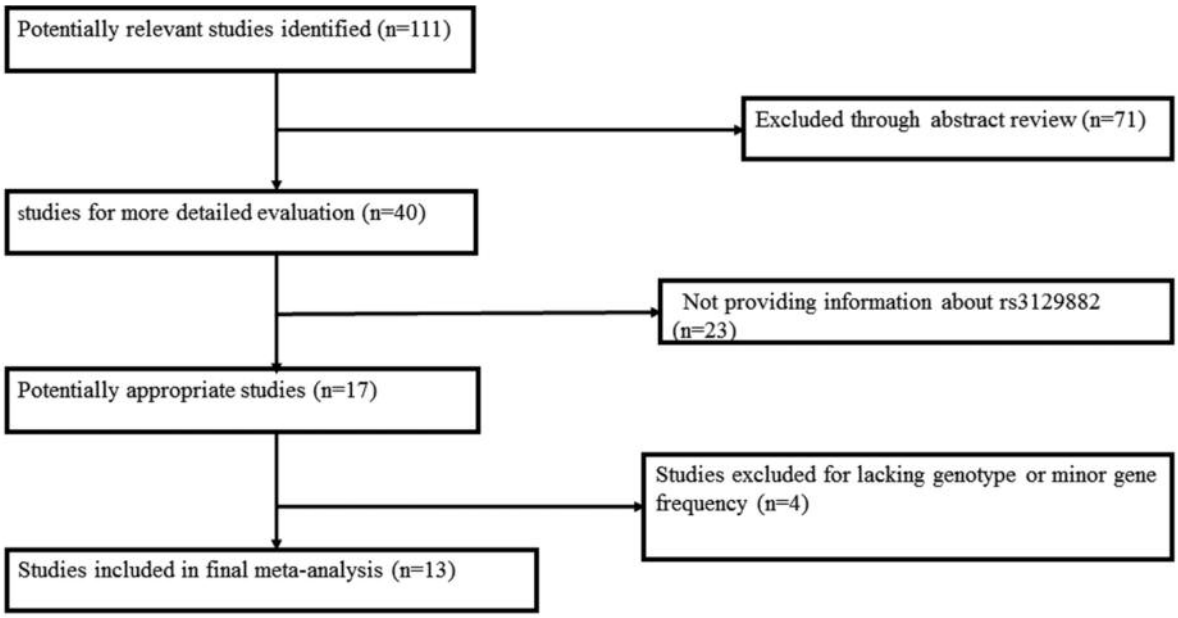

Figure 1. Study selection procedures for a meta-analysis of rs3129882 polymorphism and risk of PD.

studies respectively[12,31], which were treated as separated studies. Thus, a total of 17 studies involving 23853 subjects were eligible for the present meta-analysis. Among these 17 studies, 8 studies investigated Asian populations and 9 studies reported Caucasians. The control individuals of these studies conformed HWE (p-value of HWE > 0.05) except 2 studies[11,29]. The detailed characteristics of included studies were summarized in Table I.

Main Results

The results of this meta-analysis were listed in Table II. No significant association between PD and rs3129882 variant was observed in these 4 models when pooling overall populations (G vs A: OR = 1.043, 95% CI = 0.978, 1.113, p = 0.198; GG vs AA: OR = 0.961, 95% CI = 0.810, 1.141, p = 0.652; GA+GG vs AA: OR = 1.036, 95% CI = 0.938, 1.143, p = 0.484; GG vs AG+AA: OR = 0.950, 95% CI = 0.809, 1.115, p = 0.529). Moreover, similar results were shown in the subgroup analysis stratified by ethnicity analysis stratified by ethnicity, and the forest plot of rs3129882 polymorphism in PD in allele model was shown in Figure 2. According to the chi-squared statistic and I^2, heterogeneity was found to be a concern in allele model (p = 0.000, I^2 = 65.2%), condominant model and recessive model (p = 0.002, I^2 = 64.7%), thus a random effect model was selected.

Sensitivity Analysis

The influence of a single study on the overall meta-analysis estimation was investigated by omitting one study each time, and the deletion of one study[12] made significant difference on the association between rs3129882 and PD risk (G vs A: OR = 1.043, 95% CI = 0.978, 1.113, p = 0.198, and OR = 1.058, 95% CI = 0.990, 1.131, p = 0.097 after excluding). Moreover, sensitivity analysis was performed under allelic genetic model (shown in Figure 3), and the same analysis under other two genetic models (dominant and recessive models) observed similar results (data not shown). When excluding 2 studies which deviated from HWE, the results did not altered.

Cumulative Meta-Analysis

Cumulative meta-analysis of HLA rs3129882 association was conducted through the assortment of studies by publication time. Figure 4 showed results of the cumulative meta-analysis for the association of rs3129882 and PD in chronological order. The pooled OR tended to be stable, while the association remained non-significant with accumulation of data over time.

Assessment of Publication Bias

The publication bias of the selected studies was assessed by Funnel plot and Egger's test. Ev-

Table I. Characteristics of 17 case–control studies included in this meta-analysis.

First author	Year	Ethnicity	Region	Genotyping method	case	control	Distribution of rs3129882 genotype						Allele			
							cases			controls			cases		controls	
							AA	AG	GG	AA	AG	GG	A	G	A	G
Guo	2011	Asians	China	PCR	284	258	30	114	110	16	118	124	174	334	150	366
Zhou	2013	Asians	China	PCR	323	345	45	126	152	34	125	186	216	430	193	497
Puschmann	2011	Caucasians	US	Taqman	616	633	213	299	104	228	295	110	725	507	751	515
Puschmann	2011	Caucasians	Polish	Taqman	343	312	87	196	60	96	136	80	370	316	328	296
Puschmann	2011	Caucasians	Irish	Taqman	354	360	132	184	38	136	162	62	448	260	434	286
Chiang	2012	Asians	China Taiwan	PCR-RFLP	538	532	66	248	224	76	240	216	380	696	392	672
Lin	2013	Asians	China Taiwan	TaqMan	448	452	55	195	198	69	196	187	305	591	334	570
Zhao	2013	Asians	Singapore	TaqMan	637	675	73	260	304	76	321	278	406	868	473	877
Tian	2012	Asians	China	PCR	919	1030	157	470	392	162	481	387	784	1254	805	1255
Zhou	2011	Asians	China	PCR	224	309	37	96	91	50	112	147	170	278	212	406
Jamshidi	2014	Asians	Iran	PCR-RFLP	520	520	110	238	172	112	281	127	458	582	507	533
Pihlstrom	2013	Caucasians	Norway and Sweden	GWAS	1345	1225							1614	1076	1470	980
Ran	2013	Caucasians	Sweden	PCR	508	636							601	415	750	522
Hamza	2010	Caucasians	US	GWAS	2000	1986							2160	1840	2383	1589
Hamza	2010	Caucasians	US	GWAS	843	856							927	759	1010	702
Hamza	2010	Caucasians	US	GWAS	604	612							676	532	734	490
Mata	2011	Caucasians	Spain	TaqMan	1445	1161							1647	1243	1347	975

Abbreviation: PCR, Polymerase Chain Reaction; PCR-RFLP, Restriction Fragment Length Polymorphism of PCR; GWAS, Genome-Wide Association Study.

Table II. Meta-analysis of rs3129882 polymorphism and PD susceptibility.

Genetic models	Polymorphism	Ethnicity	No. of studies	Test for association			Test for heterogeneity		
				OR (95% CI)	Model	*p*	X^2	*p*	I^2 (%)
Allele model	G vs A	Over all	17	1.043 (0.978, 1.113)	R	0.198	44.93	0.000	64.4
		Asians	8	1.010 (0.907, 1.125)	R	0.851	18.22	0.011	61.6
		Caucasians	9	1.067 (0.982, 1.158)	R	0.126	24.58	0.002	67.5
		All in HWE	15	1.058 (0.990, 1.131)	R	0.097	40.15	0.000	65.1
Dominant model	GA+GG vs AA	Over all	11	1.036 (0.938, 1.143)	F	0.484	12.27	0.267	18.5
		Asians	8	0.999 (0.882, 1.131)	F	0.984	10.13	0.182	30.9
		Caucasians	3	1.102 (0.937,1.296)	F	0.240	1.29	0.525	0.0
		All in HWE	9	1.016 (0.914, 1.130)	F	0.766	10.31	0.244	22.4
Recessive model	GG vs AG+AA	Over all	11	0.950 (0.809, 1.115)	R	0.529	35.51	0.000	71.8
		Asians	8	1.038 (0.885, 1.219)	R	0.644	20.98	0.004	66.6
		Caucasians	3	0.719 (0.510, 1.012)	R	0.059	5.28	0.071	62.1
		All in HWE	9	1.015 (0.865, 1.190)	R	0.857	25.19	0.001	68.2
Codominant model	GG vs AA	Over all	11	0.961 (0.810, 1.141)	R	0.652	20.07	0.029	50.2
		Asians	8	1.012 (0.821, 1.246)	R	0.913	15.12	0.035	53.7
		Caucasian	3	0.856 (0.681, 1.076)	F	0.182	2.64	0.267	24.4
		All in HWE	9	0.982 (0.805, 1.198)	R	0.858	18.73	0.016	57.3

*R: Random model, F: Fixed model

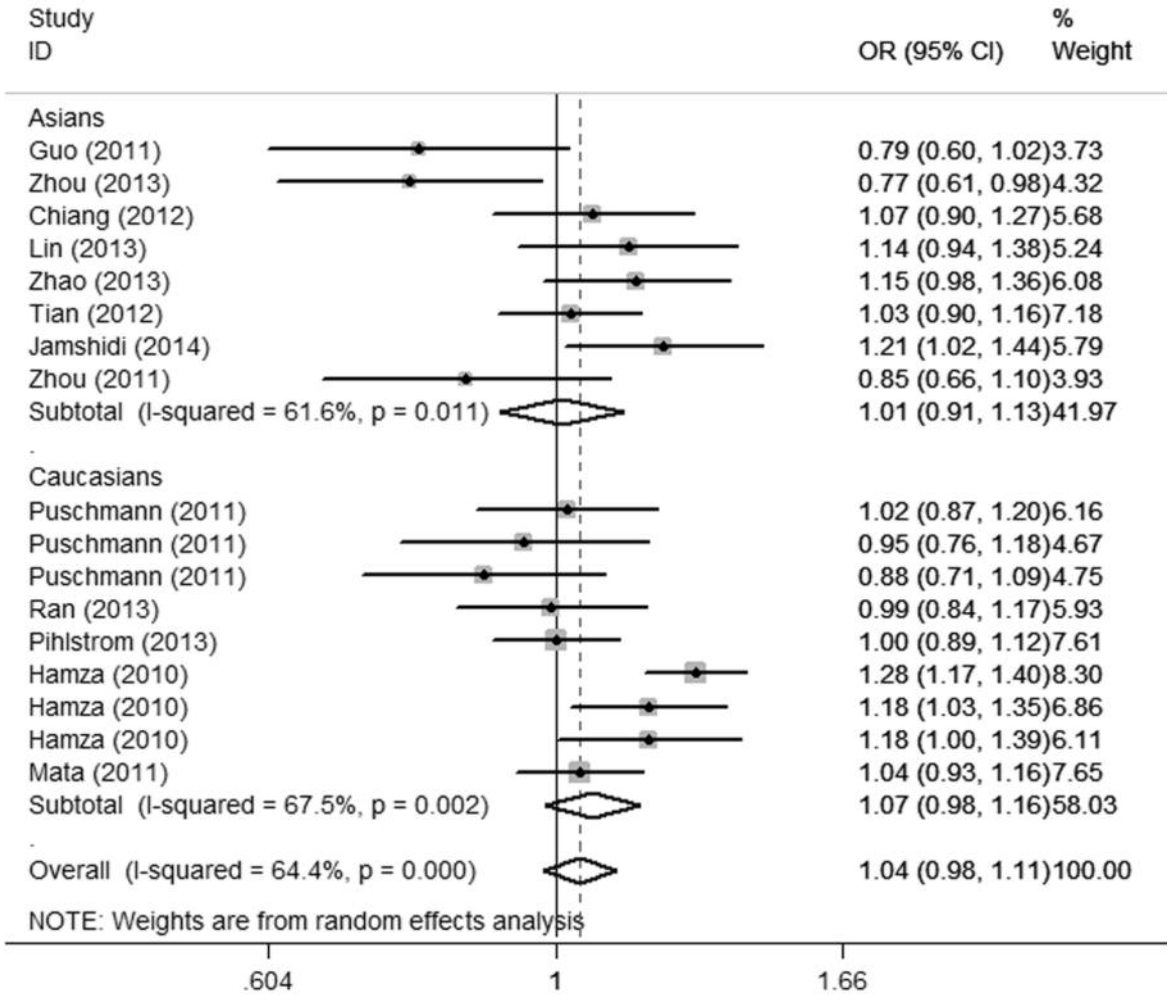

Figure 2. Forest plot of rs3129882 polymorphism in PD in Allele model in overall population and subgroup analysis stratified by ethnicity,

idence of potential publication bias was observed when using all samples under allelic genetic model. Funnel plot for meta-analysis of rs3129882 in the included studies under allelic genetic model seemed asymmetrical, and the funnel plot was shown in Figure 5.

Discussion

As an age-related progressive and heterogeneous neurodegenerative disorder, the etiology of PD is remaining obscure. As the possible mechanism, involvement of the neuroinflammation has been identified in the PD pathogenesis[34]. As one of the most important components in the process of neuroinflammation, microglia, which is featured by HLA-DR-positive in the substantial nigra (SN) of PD patients, increases levels of various pro-inflammatory cytokines in the SN including tumor necrosis factor (TNF) and interleukin-1-beta (IL-1b)[35,36].

Recently, the genetic loci like PARK1-18 have been linked to PD and 9 loci in the PARK have been identified as genetic causes and linked to monogenic PD[37]. HLA-DRA, a major histocompatibility complex, plays an important role in immune responses and inflammation. The association between HLA-DRA-PARK18 (HLA gene cluster on chromosome 6p) and PD was found in Caucasian populations[12]. In that study, the author found out that the identification of HLA rs3129882 highlighted the relationship between PD and human immunity. Rs3129882, which locates in the intron-1 of HLA-DRA gene, is a

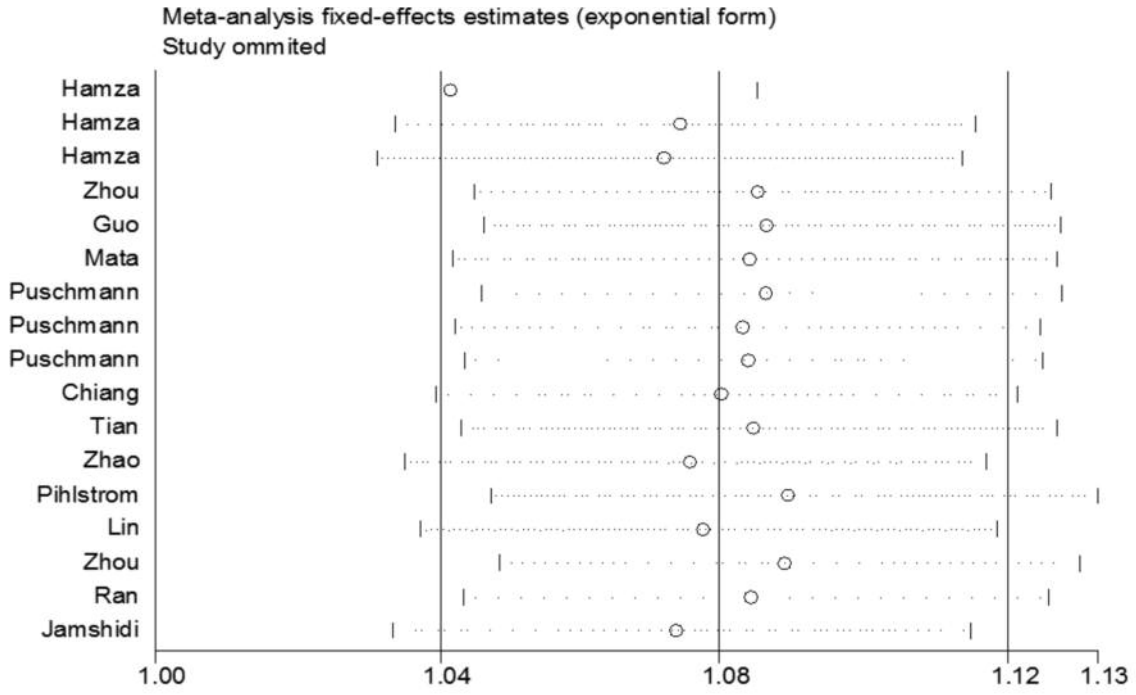

Figure 3. Sensitivity analysis of the summary odds ratio coefficients on the association between rs3129882 polymorphism with PD.

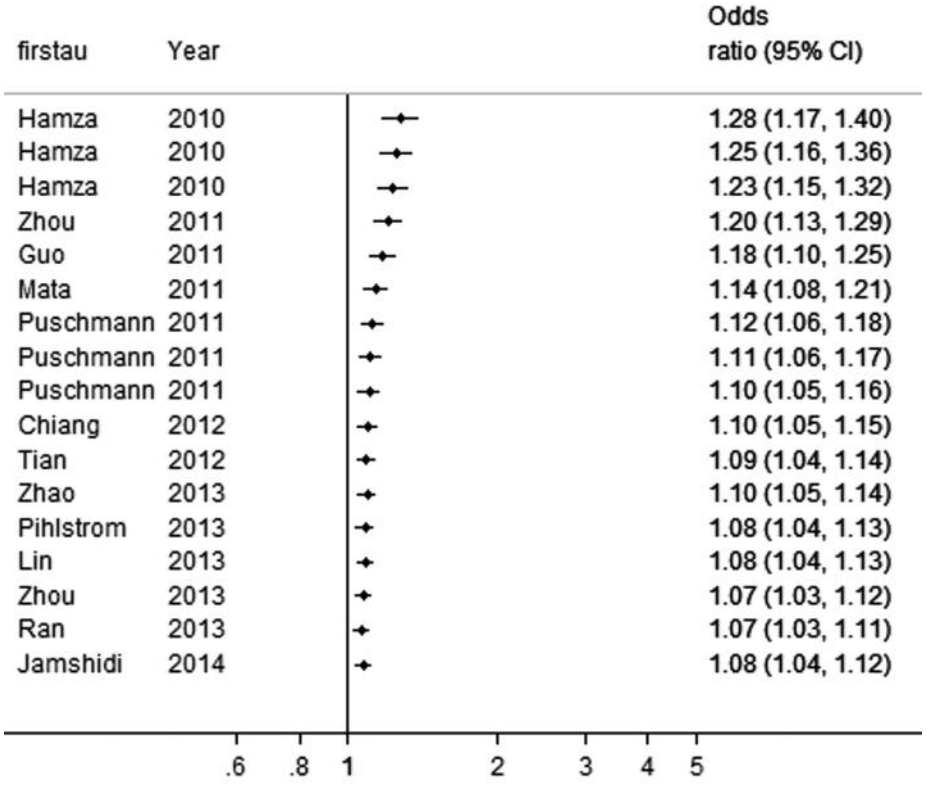

Figure 4. Cumulative meta-analysis: pooled OR with the corresponding 95% CI at the end of each year information step is shown for rs3129882 polymorphism (allelic model).

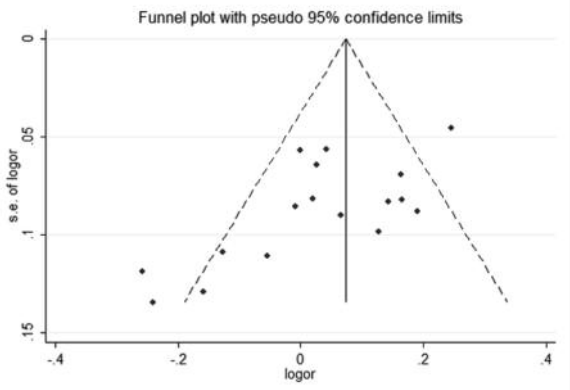

Figure 5. Funnel plot of the publication bias for rs3129882 polymorphism (allelic model).

non-coding polymorphism. The class II HLA-DRA antigens, which are expressed by antigen presenting cells and interact with T-cell receptors, are consisted of the protein chains which are encoded by the closely linked HLA-DRA and HLA-DRB. HLA-DRB chains have been observed for the linkage to lots of disorders and are characterized by highly variable. However, HLA-DRA has not been studied for its disease-relation as the monomorphic. The association between the variant in the intronic DRA and PD may indicate involvement of regulatory elements, which conforms to PD-specific over-expression of DR antigens in SN[35]. Thus, rs3129882 polymorphism may contribute to the PD process through different class II HLA-DR antigens.

In 2014, Ma et al[38] performed a meta-analysis about the relation between rs3129882 and PD in Chinese-based population and did not identify the rs3129882 as a risk for PD. In this updated and refined meta-analysis, we systematically investigated the association between SNP genotypes and alleles between rs3129882 and PD in general population. Thirteen articles about rs3129882 met the inclusion criteria in this meta-analysis, reporting on 11951 patients and 11902 controls. Among these papers, 7 articles[13-19] seemed to fail to find any association between rs3129882 polymorphism and PD risk in all subjects. However, four studies demonstrated the association for rs3129882 polymorphism and PD risk[12,29,30,32,33], and the GG genotype might be a protective factor in the Irish (OR: 0.55, P¼ 0.008), Polish (OR: 0.67, P¼ 0.040) and combined (OR: 0.75, P¼ 0.006) patient-control series while evaluated under the recessive model in one study[31]. Finally, the meta-analysis did not detect a significantly statical relation between rs3129882 polymorphism and PD whether in Allele model (OR = 1.043, 95% CI = 0.978, 1.113, p = 0.198), Dominant model (OR = 1.036, 95% CI = 0.938, 1.143, p = 0.484), Recessive model (OR = 0.950, 95% CI = 0.809, 1.115, p = 0.529) or in Codominant model (OR = 0.961, 95% CI = 0.810, 1.141, p = 0.652). The subgroup analysis stratified by race also failed to found significantly statical association for rs3129882 polymorphism and PD. Two reasons may contribute to this result. Firstly, as HLA gene is featured by highly polymorphic, the ethnic-specific effect or environmental factors may alter the effect of GWAS-linked locus in impacting the risk of PD. Another possibility is that the etiology of PD has always been described as multifactorial, and the interaction of genetic-environmental factors may act as important roles in the process of PD.

Concerning the heterogeneity, they were observed evidently in Allele model, Recessive model and Codominant model. The source of heterogeneity might come from diversities in terms of subject ethnicity, living geography and recruitment of participants. Consequently, the heterogeneity which was demonstrated in most of all pooled outcomes would not make the results conclusive and decrease the strength of evidence provided by the present meta-analysis.

And, on the other hand, the sensitivity analysis indicated that the deletion of one study made significant difference on the association between rs3129882 and PD risk[12]. In that study, subjects were selected from eight NGRC-affiliated neurology clinics in Oregon, Washington, Georgia and New York. The population structure of that study might different from others and patients were late-onset sporadic PD. Even though, our results were statistically reliable as the number of the analysis was large.

For this meta-analysis, there were also some limitations. First, due to the insufficient of the data, some important factors, such as age of onset and smoking for the association between rs3129882 and PD were not able to assess. Further, the sample size and the number of study were relatively small for some outcomes, especially in the subgroup of Caucasians, only three studies concluded. So the power used to detect true difference between cases and controls was not strong. The heterogeneity found in most analysis was another limitation.

Conclusions

In current meta-analysis, the association between rs3129882 polymorphism and PD risk was not observed in overall population or in Caucasians and Asians, even though these limitations. Future well designed case-control studies may be needed to provide more precise information to better understand the contribution of this gene variant to PD susceptibility.

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Conflict of Interest

The Authors declare that there are no conflicts of interest.

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