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Association of EVI5 rs11808092, CD58 rs2300747, and CIITA rs3087456 polymorphisms with multiple sclerosis risk: A meta-analysis

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ABSTRACT

Purpose: Multiple sclerosis (MS) is a major demyelinating disease of the central nervous system with a strong genetic component. Previous studies have reported that the association of EVI5 rs11808092, CD58 rs2300747, and CIITA rs3087456 polymorphisms with the susceptibility to MS. However, the results were inconsistent. Thus, we conducted this meta-analysis to provide a more accurate estimation of the association between any of these polymorphisms and MS risk.

Methods: The PubMed, Embase, Chinese National Knowledge Infrastructure, Wan Fang databases and MSGene were used to search all potentially relevant studies. The odds ratio (OR) with 95% confidence interval (CI) was used to investigate the associations between these three polymorphisms and MS risk.

Results: 16 independent case–control studies from 12 publications were finally included into this meta-analysis. The results showed that EVI5 rs11808092 polymorphism was related with increasing the development of MS under five genetic models (allelic: OR = 1.17, 95% CI = 1.10–1.24, $P < 0.01$; homozygous: OR = 1.37, 95% CI = 1.18–1.59, $P < 0.01$; heterozygous: OR = 1.16, 95% CI = 1.07–1.26, $P < 0.01$; recessive: OR = 1.28, 95% CI = 1.11–1.48, $P < 0.01$; and dominant: OR = 1.19, 95% CI = 1.11–1.48, $P < 0.01$). CD58 rs2300747 polymorphism was found to be associated with decreasing MS risk in three genetic models (allelic: OR = 0.86, 95% CI = 0.78–0.94, $P < 0.01$; heterozygous: OR = 0.85, 95% CI = 0.76–0.94, $P < 0.01$, and dominant: OR = 0.84, 95% CI = 0.76–0.93, $P < 0.01$). However, this meta-analysis indicated that CIITA rs3087456 polymorphism was not related to multiple sclerosis.

Conclusions: The mutant alleles of EVI5 rs11808092 polymorphism may increase the susceptibility to MS while those of CD58 rs2300747 polymorphism may decrease MS risk. In addition, CIITA rs3087456 polymorphism might not be associated with MS.

1. Introduction

Multiple sclerosis (MS), the most common neurological disorder affecting young adults, is a chronic inflammatory, autoimmune disease of the central nervous system (CNS) characterized by demyelination, axonal loss, and progressive neurological dysfunction (Ramagopalan et al., 2007; Compston and Coles, 2008). The incidence rate of MS varies between 2 and 160 per 100,000 individuals in different areas (Pugliatti et al., 2002). As a result, about one million persons have suffered from MS all over the world, and the majority of those people are middle-aged women (Wingerchuk, 2005). Although the causes of MS are not completely clarified, it is believed that the complex interactions of genetic mutations and environmental risk factors play important roles in the pathologic process of MS (Zuvich et al., 2009; Lvovs et al., 2012).

Although the prevalence rates of MS vary substantially throughout the world, the relatives of MS patients are at greater risk for developing the disease than the general population (Ebers et al., 1995), which suggests that genetic factors might influence the development of MS. The human leukocyte antigen (HLA) on chromosome 6p21 is an extremely important genetic element for MS risk. It has been repeatedly demonstrated that the HLA-DR2 or DRB1*15 haplotype was associated with susceptibility to MS (Barcellos et al., 2003; Lincoln et al., 2005; Ramagopalan et al., 2009). Nevertheless, the

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HLA gene polymorphisms only make up 20–60% of the genetic predisposition to MS, which means a possible role of non-HLA genetic factors in disease development (Isik et al., 2013). In the past decade, several reports including some from independent genome wide association studies (GWAS), have identified the association between MS risk and the single nucleotide polymorphisms (SNPs) of several non-HLA genetic loci, including C4A, CD58, CRM7, EVI5 and CIITA. (Hoppenbrouwers et al., 2008; Rubio et al., 2008; Weber et al., 2008; Alcina et al., 2010; Bronson et al., 2010). Among these genetic risk loci, the EVI5, CD58, and CIITA genes and their correlation with the development of Multiple sclerosis are the center of our attention in this paper.

EVI5, a common location of retroviral integration and an oncogene impacted in T cell lymphomas (Liao et al., 1995), expedites cell septation during mitosis (Faitar et al., 2006). Allelic mutations in EVI5 may alter the role of RAB11 and formation of the immunological synapse, thus contributing to MS risk (Johnson et al., 2010). CD58 is found to stimulate and enhance T cell receptor signaling by engaging CD2 (Davis and van der Merwe, 1996). Because the control of activated T cells by normal regulatory $CD4^+$ T cells is damaged in MS patients (Viglietta et al., 2004), the CD58 gene polymorphisms have been an appealing target when considering the function of genetic mutation in immune system dysfunction related with MS. CIITA, also named as MHC2TA (the MHC class II transactivator gene), is a 42-kb gene locating on chromosome 16p13 and encodes the non-DNA-binding coactivator (Ting and Trowsdale, 2002). As one of MHCII molecules, CIITA plays a vital role in inflammatory response and in T cell-dependent immunity. Thus, it could contribute to many diseases including multiple sclerosis (Lincoln et al., 2005).

Several genetic polymorphism loci have been identified in these three genes such as rs10735781 and rs11808092 in EVI5, rs2300747 and rs1335532 in CD58, and rs3087456 and rs7447 in CIITA. In this paper, we focused only on rs11808092 in EVI5, rs2300747 in CD58, and rs3087456 in CIITA. We did not include other polymorphisms, because they either have been investigated by a meta-analysis (Hoppenbrouwers et al., 2009; Bronson et al., 2011; Didonna et al., 2015) or they lack enough case–control studies for a retrospective analysis.

Several publications (Rasmussen et al., 2001; Swanberg et al., 2005; Akkad et al., 2006; Martínez et al., 2007; O'Doherty et al., 2007; Bahlo et al., 2009; De Jager et al., 2009; Alcina et al., 2010; Bronson et al., 2010; Garcia-Montojo et al., 2011; Pandit et al., 2011; Bashinskaya et al., 2015) have reported the association of these three SNPs with the risk of MS, but small size of each study, minor genetic efforts and the likelihood of random errors lead to inconsistent conclusions. In addition, no meta-analysis has been carried out to detect the association between any of these three polymorphisms and MS susceptibility so far. Thus, we conducted this meta-analysis to provide a more accurate estimation of the potential association between these polymorphisms and MS development.

2. Materials and methods

2.1. Identification and eligibility of relevant studies

All potentially relevant publications up to February 14, 2016 have been searched from PubMed, Embase, Chinese National Knowledge Infrastructure (CNKI), and Wan Fang databases by using the keywords including "(MS or multiple sclerosis) and (CD58 or EVI5 or CIITA or MHC2TA) and (polymorphism or polymorphisms or variant or mutation)". In addition, we scanned the MSGene (http://www.msgene.org/) to obtain additional relevant articles which might have been missed in the initial search. This process was performed repeatedly until no additional articles could be identified.

2.2. Inclusion and exclusion criteria

Literatures were selected in our meta-analysis if they met all the following inclusion criteria: (1) on the association of CD58 rs2300747, EVI5 rs11808092, or CIITA rs3087456 polymorphisms with the risk of MS; (2) in a case–control design; (3) with complete genotype frequency data. The exclusion criteria were: (1) studies with other diseases, genes or polymorphisms; (2) animal researches or reviews; (3) studies without sufficient genotype frequency data. We selected only one if the duplicate publications were met.

2.3. Data extraction

Two reviewers extracted data independently from each eligible publication and discussed to reach a consensus when disagreements occurred. The following information was extracted from each study: first author's name, published year, area, the number of cases and controls, the frequency of genotypes in cases and controls, Hardy–Weinberg equilibrium (HWE). The studies from the same article that provided separate analyses of different area groups were classified as the independent studies.

2.4. Statistical analysis

In this meta-analysis, the strength of association between any of EVI5 rs11808092, CD58 rs2300747, or CIITA rs3087456 polymorphisms and MS risk was assessed by the odds ratio (OR) with the corresponding 95% confidence interval (CI) (DerSimonian and Laird, 1986). We used five or six genetic models including the allelic, homozygous, heterozygous, dominant, recessive and over-dominant models to dissect the association patterns. Z-test determined the significant of pooled OR, and a $P < 0.05$ was considered statistically significant. We performed I^2 test to evaluate between-study heterogeneity. When I^2 was less than 25% or between 25%–50%, which means no heterogeneity or moderate heterogeneity, fixed effect model was selected to calculate the ORs and 95% CIs of any genetic model. If not, random effect model was used (Higgins et al., 2003). The Begg's and Egger's tests were employed to assess the risk of publication bias, and a $P > 0.05$ suggested no obvious publication bias (Begg and Mazumdar, 1994; Egger et al., 1997). Sensitivity analysis was applied to investigate the influence of the individual studies to the pooled results by omitting one study at a time. In case–control studies, HWE was used for quality assessment of genotype data. Low-quality studies deviated from HWE were excluded in the sensitivity analysis. Newcastle–Ottawa Scale (NOS) criteria (Bent et al., 2006) were used to evaluate the overall quality of the included studies. The evaluation of content in the NOS was classified into three independent aspects: object selection, comparability and exposure assessment. A study of high quality should get at least five points in the NOS quality assessment. Data analysis was performed using the professional software STATA 14.0 (Stata Corporation College Station, Texas, USA) and Review manager 5.3 (Cochrane Informatics & Knowledge Management Department).

3. Results

3.1. Characteristics of published studies

Through literature search and collection based on inclusion and exclusion criteria, we found 12 qualified publications after checking possibly relevant articles (Jiang et al., 2016). Fig. 1 shows a diagram to describe the selection procedure of the eligible studies included in this meta-analysis. A total of 596 articles were identified up to February 14, 2016 from the databases. After removing 62 duplications, 534 articles remained. Among them, 440 publications were

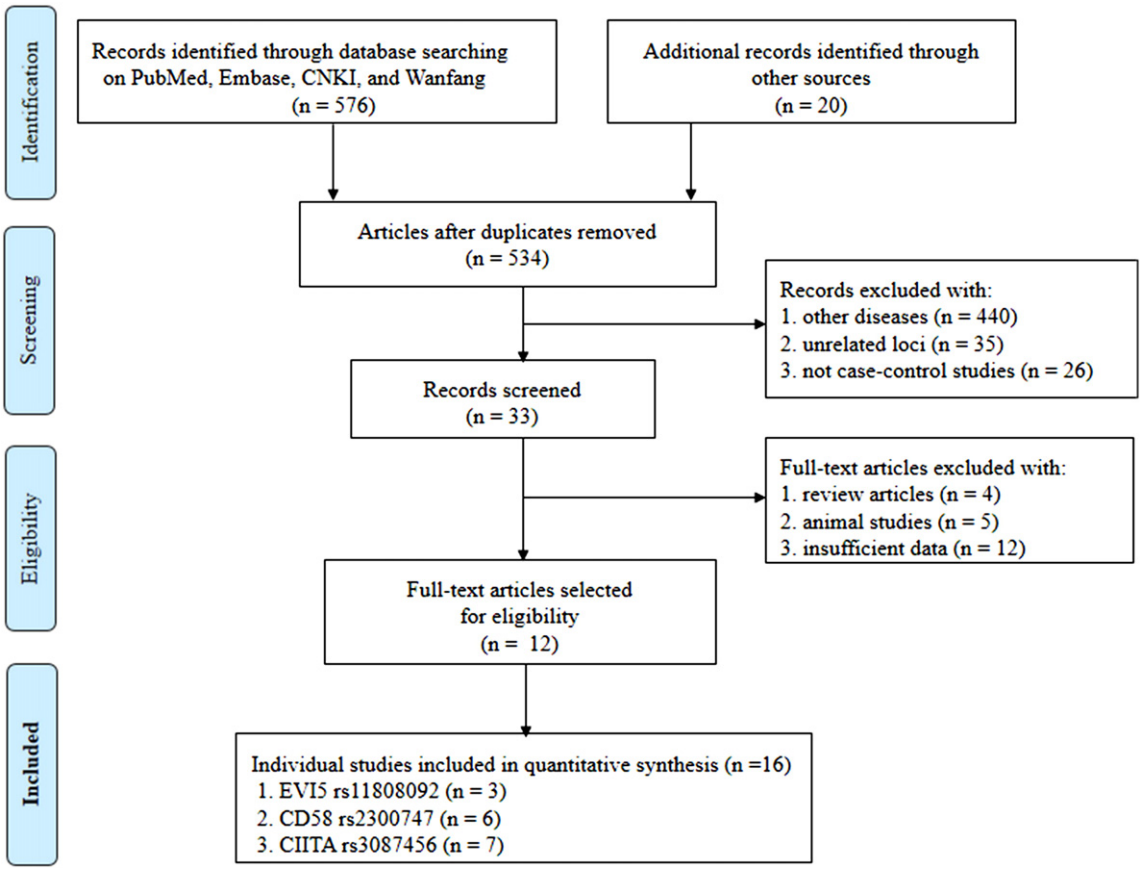

Fig. 1. A flow diagram of the process used to select eligible studies.

not linked to MS, 35 were unrelated to these loci, and 26 were not in case–control design. Therefore, we discarded them and kept 33 articles. After that, we removed another 21 publications including reviews (n = 4), animal studies (n = 5), and studies without complete genotype data (n = 12). Finally we got 12 articles which contained 16 independent studies to meet the eligibility criteria for this meta-analysis. Among these 16 eligible studies, three studies were related to EVI5 rs11808092 polymorphism, six were connected to CD58 rs2300747 polymorphism, and seven were linked to CIITA rs3087456 polymorphism. The main characteristics of all these studies are listed in Table 1. All the included studies were conformed to HWE. In addition, the NOS results showed that the quality score of each study reached six points or more (See Table 2). Therefore, all these studies in our meta-analysis were of high quality.

Table 1
The baseline characteristics of all included studies in this meta-analysis.

Gene & position	First author (ref.)	Year	Area	No. of cases	No. of controls	Genotype						HWE *P*
						Cases			Controls			
						AA	AC	CC	AA	AC	CC	
EVI5 rs11808092	ANZqene (1)	2009	Aus & NZ & UK & USA	1618	3413	138	669	811	224	1300	1889	0.999
	ANZqene (2)	2009	Australia & NZ	2256	2310	178	912	1166	156	889	1265	0.878
	Alcina	2010	Spain	726	889	80	319	327	71	364	454	0.868
						GG	GA	AA	GG	GA	AA	
	De Jaqer (1)	2009	USA	1557	855	13	263	1281	12	181	662	0.926
	De Jaqer (2)	2009	UK	961	2466	12	188	761	36	521	1909	0.919
CD58 rs2300747	De Jaqer (3)	2009	Finland	692	728	20	195	477	24	215	489	0.990
	De Jaqer (4)	2009	Belgium	348	372	3	63	282	6	84	282	0.801
	Pandit	2010	India	197	197	23	89	85	25	90	82	1.000
	Bashinskaya	2015	Russia	509	276	6	97	406	3	66	207	0.939
						GG	GA	AA	GG	GA	AA	
	Rasmussen	2001	UK	110	104	9	45	56	8	40	56	0.805
CIITA rs3087456	Swanberg	2005	Scandinavia	520	508	34	191	295	27	177	304	0.899
	Akkad	2006	Germany	646	463	30	246	370	31	183	249	0.812
	O'Doherty	2007	UK (Northern Ireland)	440	316	21	187	232	18	121	177	0.763
	Martinez	2007	Spain	396	519	25	168	203	31	192	296	1.000
	Bronson	2010	USA/UK	1320	1363	87	493	740	108	519	736	0.216
	Garcia-Montojo	2011	Spain	109	195	6	49	54	12	72	111	1.000

Table 2
Quality assessment scheme for included literatures (Newcastle–Ottawa Scale).

Literature	Selection				Comparability	Exposure			Total
	I	II	III	IV	V	VI	VII	VII	
De Jaqer	*	*	*	*	*		*	*	********
Pandit	*	*	*	*	*		*	*	********
Bashinskaya	*	*		*	*		*	*	*******
Alcina	*	*	*	*	*		*	*	********
ANZqene	*	*	*	*	*		*	*	********
Rasmussen	*	*	*	*	*		*	*	********
Swanberg	*	*		*	*		*	*	*******
Akkad	*	*	*	*	*		*	*	********
O'Doherty	*	*		*	*		*	*	*******
Martinez	*	*	*	*			*	*	*******
Bronson	*	*	*	*	*		*	*	********
Garcia-Montojo	*	*	*	*	*		*	*	********

Note: I: is the case definition adequate. II: representativeness of the cases. III: selection of controls. IV: definition of controls. V: comparability of cases and controls on the basis of the design or analysis. VI: ascertainment of exposure. VII: same method of ascertainment for cases and controls. VII: non-response rate.

3.2. Meta-analysis results

3.2.1. A meta-analysis of EVI5 rs11808092 polymorphism with the risk of MS

In our meta-analysis, a total of three studies from two publications (Bahlo et al., 2009; Alcina et al., 2010) including 4600 cases and 6612 controls were included to assess the association between EVI5 rs11808092 polymorphism and MS risk. We used the fixed effect model to calculate the pooled OR under all genetic models due to no heterogeneity among included studies. The results were shown in Fig. 2. EVI5 rs11808092 polymorphism was statistically significant related with increasing MS risk in five genetic models (allelic A *vs.* C: OR = 1.17, 95% CI = 1.10–1.24, $P < 0.01$; homozygous AA *vs.* CC: OR = 1.37, 95% CI = 1.18–1.59, $P < 0.01$; heterozygous AC *vs.* CC: OR = 1.16, 95% CI = 1.07–1.26, $P < 0.01$; recessive AA *vs.* AC + CC: OR = 1.28, 95% CI = 1.11–1.48, $P < 0.01$; and dominant AA + AC *vs.* CC: OR = 1.19, 95% CI = 1.11–1.48, $P < 0.01$) (as also shown in Table 3). Thus, EVI5 rs11808092 polymorphism was a risk factor to MS disease.

3.2.2. A meta-analysis between CD58 rs2300747 polymorphism and the susceptibility to MS

In this meta-analysis, a total of six studies from three publications (De Jager et al., 2009; Pandit et al., 2011; Bashinskaya et al., 2015) involving 4264 cases and 4894 controls were included to investigate a potential role of CD58 rs2300747 polymorphism in the risk of MS. According to the results of I^2-test, there was no between-study heterogeneity in all genetic models. Thus, the fixed effect model was also used to calculate their pooled ORs. The combined results indicated that CD58 rs2300747 polymorphism was statistically significantly associated with decreasing MS risk under three genetic models (allelic G *vs.* A: OR = 0.86, 95% CI = 0.78–0.94, $P < 0.01$; heterozygous GA *vs.* AA: OR = 0.85, 95% CI = 0.76–0.94, $P = 0.01$; dominant GG + GA *vs.* AA: OR = 0.84, 95% CI = 0.76–0.93, $P < 0.01$) (as shown in Table 3 and Fig. S1 of Supporting information). Though no association was observed in the rest two genetic models (homozygous GG *vs.* AA: OR = 0.79, 95% CI = 0.58–1.08, $P = 0.14$; recessive GG *vs.* GA + AA: OR = 0.82, 95% CI = 0.60–1.11, $P = 0.20$), their pooler ORs did not show statistical significance. Thus, we considered that CD58 rs2300747 polymorphism was a protective factor to MS susceptibility.

3.2.3. A meta-analysis of CIITA rs3087456 polymorphism on MS risk

In order to investigate the association between CIITA rs3087456 variant and MS risk, a total of seven studies (Rasmussen et al., 2001; Swanberg et al., 2005; Akkad et al., 2006; Martínez et al., 2007; O'Doherty et al., 2007; Bronson et al., 2010; Garcia-Montojo et al., 2011) involving 3541 cases and 3468 controls were included in our study. The meta-analysis showed no significant heterogeneity among studies in five genetic models ($I^2 < 50\%$), therefore we selected fixed effect model to assess the pooled ORs. The result showed that CIITA rs3087456 polymorphism was unrelated to MS susceptibility in any of five genetic models (allelic G *vs.* A: OR = 1.00, 95% CI = 0.92–1.08, $P = 0.94$; homozygous GG *vs.* AA: OR = 0.90, 95% CI = 0.74–1.10, $P = 0.30$; heterozygous GA *vs.* AA, OR = 1.05, 95% CI = 0.95–1.16, $P = 0.37$; recessive GG *vs.* GA + AA: OR = 0.89, 95% CI = 0.73–1.08, $P = 0.22$; and dominant GG + GA *vs.* AA: OR = 1.02, 95% CI = 0.93–1.13, $P = 0.61$) (Table 3 and Fig. S2 of Supporting information).

3.2.4. Heterogeneity, sensitivity analysis and publication bias

In our meta-analysis, I^2 test was performed to evaluate between-study heterogeneity and the results indicated no obvious or low heterogeneity among individual studies in all genetic models on three SNPs (Fig. 2, Figs. S1–S2 of Supporting information and Table 3). At the same time, sensitivity analysis indicated that no single study influenced the pooled OR qualitatively. We did not find the risk of publication bias

Table 3
Meta-analysis of the association between EVI5 rs11808092, CD58 rs2300747 or CIITA rs3087456 polymorphism and MS risk.

Genetic comparison	I^2 (%)	Effect model	OR [95% CI]	P_{OR}	Begg's test (z, p)	Egger's test (t, p)
EVI5 rs11808092						
A *vs.* C	0	Fixed	1.17 [1.10, 1.24]	<0.01	1.24, 0.296	0.78, 0.577
AA *vs.* CC	0	Fixed	1.37 [1.18, 1.59]	<0.01	0.00, 1.000	0.88, 0.524
AC *vs.* CC	0	Fixed	1.16 [1.07, 1.26]	<0.01	0.00, 1.000	0.60, 0.655
AA *vs.* AC + CC	0	Fixed	1.28 [1.11, 1.48]	<0.01	0.00, 1.000	0.90, 0.523
AA + AC *vs.* CC	0	Fixed	1.19 [1.11, 1.29]	<0.01	0.00, 1.000	0.74, 0.595
CD58 rs2300747						
G *vs.* A	0	Fixed	0.86 [0.78, 0.94]	<0.01	0.75, 0.452	−0.55, 0.604
GG *vs.* AA	0	Fixed	0.79 [0.58, 1.08]	0.14	0.38, 0.707	−0.77, 0.487
GA *vs.* AA	0	Fixed	0.85 [0.76, 0.94]	<0.01	0.00, 1.000	−0.43, 0.692
GG *vs.* GA + AA	0	Fixed	0.82 [0.60, 1.11]	0.20	0.00, 1.000	−0.71, 0.516
GG + GA *vs.* AA	0	Fixed	0.84 [0.76, 0.93]	<0.01	0.00, 1.000	−0.44, 0.680
GA *vs.* GG + AA	0	Fixed	0.85 [0.77, 0.95]	<0.01	0.00, 1.000	−0.38, 0.723
CIITA rs3087456						
G *vs.* A	33	Fixed	1.00 [0.92, 1.08]	0.94	0.60, 0.548	1.72, 0.147
GG *vs.* AA	0	Fixed	0.90 [0.74, 1.10]	0.30	0.73, 0.764	1.04, 0.347
GA *vs.* AA	16	Fixed	1.05 [0.95, 1.16]	0.37	1.20, 0.230	1.99, 0.103
GG *vs.* GA + AA	0	Fixed	0.89 [0.73, 1.08]	0.22	0.30, 0.764	0.71, 0.511
GG + GA *vs.* AA	32	Fixed	1.02 [0.93, 1.13]	0.61	0.90, 0.368	1.90, 0.116

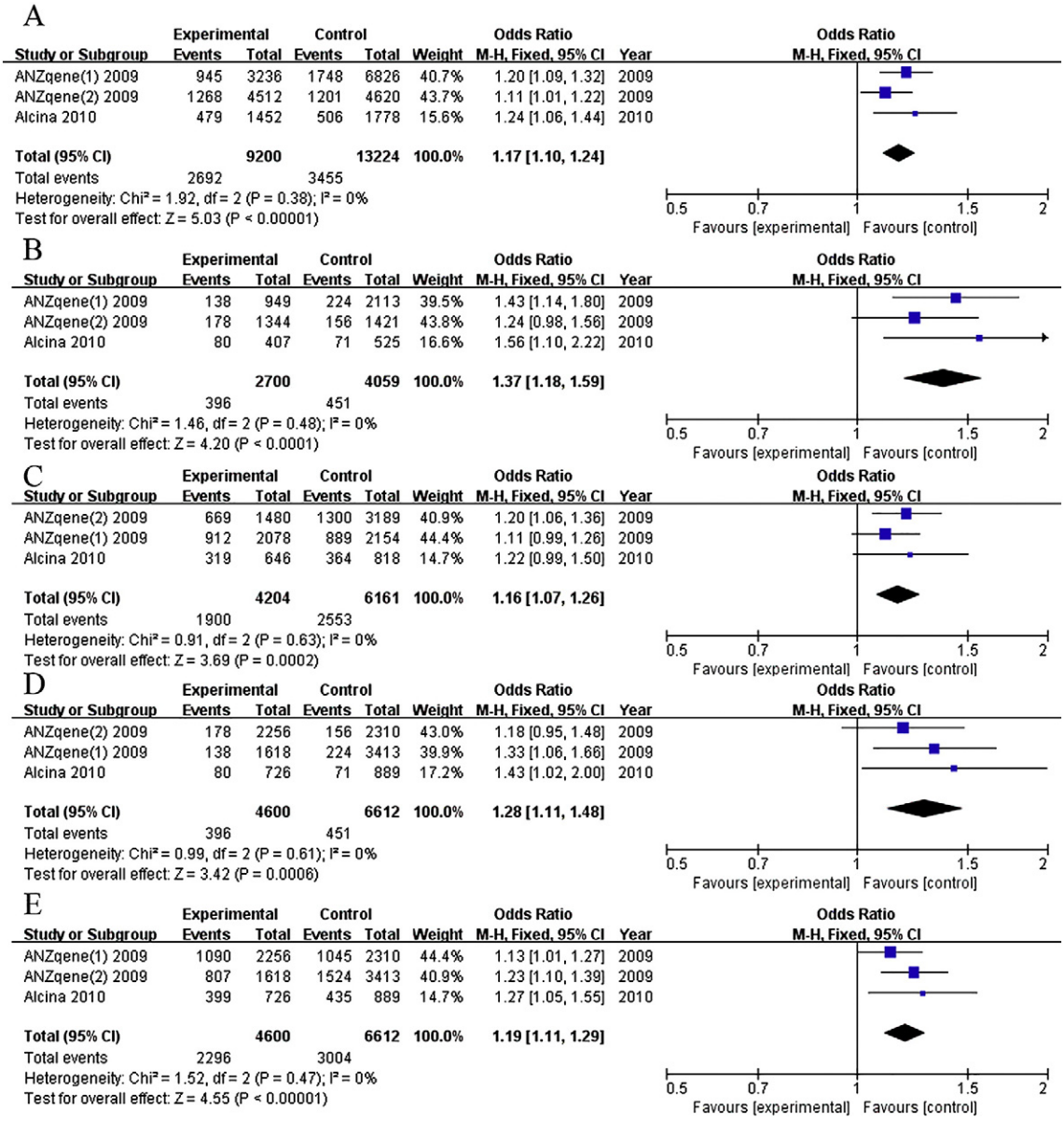

Fig. 2. Forest plots of EVI5 rs11808092 polymorphism and MS susceptibility in five genetic models. A: the allelic model (A *vs.* C); B: the homozygous model (AA *vs.* CC); C: the heterozygous model (AC *vs.* CC); D: the recessive model (AA *vs.* AC + CC); E: the dominant model (AA + AC *vs.* CC).

due to the observed *P*-values larger than 0.1 from the Begg's and Egger's test (Table 3, Figs. S3–S5 of Supporting information). Thus, the results of our meta-analysis are reliable.

4. Discussion

Multiple sclerosis, a T cell-mediated autoimmune disorder, is an inflammatory demyelinating disease affecting the CNS (McFarland and Martin, 2007). MS is probably caused by a combination of environmental and genetic risk factors (Compston and Coles, 2008; Ascherio et al., 2012). It was reported that the twins and siblings of MS patients had higher susceptibility to the disease than the general population (Willer et al., 2003; Hansen et al., 2005), indicating that the genetic rather than environmental factors triggered the clustering of MS within families (Ascherio et al., 2012). Previous studies have investigated the potential influences of the three SNPs we studied in EVI5, CD58 and CIITA genes on the susceptibility to MS (Rasmussen et al., 2001; Swanberg et al., 2005; Akkad et al., 2006; Martínez et al., 2007; O'Doherty et al., 2007; Bahlo et al., 2009; De Jager et al., 2009; Alcina et al., 2010; Bronson et al., 2010; Garcia-Montojo et al., 2011; Pandit et al., 2011; Bashinskaya et al., 2015). However, no consensus has been reached because of the relatively small sample size of each case–control study. Therefore, we performed this meta-analysis in order to provide a more precise estimation of the association between these three SNPs and multiple sclerosis risk.

Up to now, only three case–control studies from two publications (Bahlo et al., 2009; Alcina et al., 2010) have assessed the association of EVI5 rs11808092 polymorphism with MS risk. Though these studies indicated this polymorphism was a risk factor for MS, none of them further investigated the potentially different impact of the mutated genotypes of this genetic risk locus on the susceptibility to the disease (Bahlo et al., 2009; Alcina et al., 2010). Our meta-analysis showed that EVI5 rs11808092 polymorphism was statistically significant associated with the risk of MS (Fig. 2). People with the minor genotype (AA or AC) would have a higher risk of developing MS than those with the genotype CC. In addition, the homozygous mutant (AA) should be much more powerful than the heterozygous

genotype (AC) in increasing MS risk through a comparison of the pooled ORs under all five genetic models.

To date, six case–control studies from three articles (De Jager et al., 2009; Pandit et al., 2011; Bashinskaya et al., 2015) have investigated the influence of CD58 rs2300747 polymorphism on the risk of MS. De Jager et al. (2009) showed that this polymorphism was a marker for a protective effect on MS susceptibility, since the minor allele rs2300747G was found in the protective haplotype containing the CD58 gene. Bashinskaya et al. (2015) reported that though CD58 rs2300747 polymorphism didn't link to the risk of MS in a Russian population, it is a protective factor in Russia men since their carriage of rs2300747*A/A genotype in CD58 gene was associated with the development of MS. However, Pandit et al. (2011) indicated that this polymorphism was not associated with the susceptibility to MS in an Indian population. In this retrospective analysis, the heterozygous genotype (GA) was statistically significant associated with decreasing MS, while the homozygous mutant (GG) didn't seem to be related with MS (Table 3 and Fig. S1 of Supporting information). However, we would like to infer that the genotype (GG) might also be a protective variant for two reasons. First, although the confidence interval of OR was across 1 in the homozygous model, it had an obvious bias toward the protective side and the odds ratio was the minimum in all genetic models. In our opinion, the small sample size of GG genotype collected in this meta-analysis lead to a wide interval for the CI of OR across 1. Second, through a comparison among heterozygous, dominant and over-dominant models, we found that the pooled odds ratio and confidence interval in dominant model were less than those in heterozygous model. Meanwhile, the pooled OR and CI in over-dominant model were higher than the heterozygous model. Therefore, our meta-analysis supported that CD58 rs2300747 polymorphism could play a protective role in the risk of MS. Nevertheless, additional studies with larger sample sizes need to be further performed for drawing a more accurate and credible conclusion, especially with regard to the influence of CD58 rs2300747 GG genotype on the risk of MS.

So far, seven articles have studied the relationship of CIITA rs3087456 polymorphism with the risk of MS. Among them, five studies showed no evidence of association of this CIITA variant with MS (Rasmussen et al., 2001; Akkad et al., 2006; O'Doherty et al., 2007; Bronson et al., 2010; Garcia-Montojo et al., 2011), while the other two studies (Swanberg et al., 2005; Martínez et al., 2007) provided the association results a little more complex. Martínez et al. (2007) demonstrated that though no independent association was found between CIITA rs3087456 polymorphism and multiple sclerosis, the rs3087456A/G allele conferred protection for MS when haplotypes were compared between patients with the disease and controls in a northern European population. However, Swanberg et al. (2005) indicated this −168A/G polymorphism in CIITA was associated with increasing susceptibility to multiple sclerosis, though they also found the result was discordant when the samples from individuals with MS were compared with controls from healthy blood donors which were based on a number of exclusion criteria such as certain medications and chronic illness (Swanberg et al., 2005). Our meta-analysis showed that CIITA rs3087456 polymorphism was not related to either increasing or decreasing MS risk, which is quite reasonable based on the observations from all seven case–control studies. Nonetheless, The studies of Martínez et al. (2007) and Swanberg et al. (2005) denoted that the result of lacking association between CIITA rs3087456 allele and MS could be reversed when the interactions of gene–gene and gene–environment were considered, which should be the center of the attention in the future research.

In recent years, several GWAS (Bahlo et al., 2009; Sawcer et al., 2011; Bashinskaya et al., 2015; Lill et al., 2015; Lin et al., 2015) have identified multiple sclerosis risk loci involved in immune response. Though we were interested in investigating the impact of the gene–gene interactions on MS by using stratification analysis and other techniques (Shahbazi et al., 2011; Wagner et al., 2014) among these loci such as the three SNPs we studied in this meta-analysis, we were unable to do so due to the limited data and resources available from the literatures.

Four advantages could be found in this meta-analysis. Firstly, this study is the first meta-analysis to investigate the association of EVI5 rs11808092, CD58 rs23007474, and CIITA rs3087456 with MS susceptibility. Secondly, five or six genetic models were used in this meta-analysis. As a result, our study not only demonstrated which of the three SNPs was associated with MS or not, but also clarified that the potentially distinctive roles of the different genotypes of this polymorphism might play in MS risk. Thirdly, both Begg's and Egger's test results showed low risk of publication bias in our meta-analysis. Lastly, NOS analysis was also performed and its result showed that all the case–control studies included in our study were of high quality.

We should also recognize that several limitations existed in this retrospective analysis. Firstly, the relatively small sample size of each study resulted in limited statistical power to detect a potential association in this meta-analysis. Secondly, all samples are Caucasian, which indicated the results of this meta-analysis may not be applicable to other ethnic groups. Further studies in other ethnic populations are required to verify our conclusions. Thirdly, a subgroup analysis based on any environmental factor such as area, gender, or age may help clarify the potential risk factor of developing MS, but we could not perform such an analysis because of the limited data.

5. Conclusion

This meta-analysis indicated that EVI5 rs11808092 polymorphism was connected to increasing the risk of multiple sclerosis while CD58 rs2300747 polymorphism was correlated with decreasing MS susceptibility. However, CIITA rs3087456 polymorphism may not have the association with MS risk. More studies with large sample sizes, gene–gene, gene–environment interactions and well-designs are necessary to provide a reliable estimation of this association between these three polymorphisms and MS risk in the future.

Conflict of interest

The authors have declared that no competing interests exist.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.mgene.2016.04.005.

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