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No association between *APOE* epsilon 4 allele and multiple sclerosis susceptibility: A meta-analysis from 5472 cases and 4727 controls

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ABSTRACT

Background: Apolipoprotein E (*APOE*) gene ε4, 2 alleles have been reported to be associated with multiple sclerosis (MS), but results were conflicting. In order to derive a more precise estimation of the associations, a meta-analysis was performed.
Methods: The PubMed, EBSCO and BIOSIS databases were searched to identify eligible studies published in English before March, 2011. Data were extracted using standardized forms. The association was assessed by odds ratio (OR) with 95% confidence intervals (CIs). Begg's test was used to measure publication bias.
Results: A total of 20 case–control studies, containing 5472 patients/4727 controls for ε4 allele and 4636 patients/4047 controls for ε2 allele were included. The associations between *APOE* ε4, 2 alleles and MS were not found in overall population ($OR_{\varepsilon4}=0.997$, 95% CI = 0.861–1.156; $OR_{\varepsilon2}=1.097$, 95% CI = 0.940–1.279). Subgroup analysis revealed that *APOE* ε4, 2 alleles were not associated with an increased risk of MS in Caucasian population ($OR_{c\text{-}\varepsilon4}=0.924$, 95% CI = 0.819–1.041; $OR_{c\text{-}\varepsilon2}=1.127$, 95% CI = 0.955–1.331). There was no evidence of publication bias according to Begg's regression test.
Conclusions: This meta-analysis suggests that *APOE* ε4, 2 alleles are not associated with MS susceptibility. However, large sample, representative population-based studies with homogeneous MS patients, and well matched controls are warranted to confirm this finding.

1. Introduction

Multiple sclerosis (MS) is a common inflammatory disease of the central nervous system (CNS) characterized by myelin loss, varying degrees of axonal pathology, and progressive neurological dysfunction [1]. The causes of MS are largely unknown. However, epidemiologic studies reveal a significant environmental contribution to the pathogenesis of MS [2,3]. Familial aggregation and twin studies indicate the presence of genetic factors for susceptibility to this condition [4,5]. Several genomic screens have been performed to find genetic linkage to MS. The chromosome 19q13 region showed genetic linkage to MS [6,7].

In various genes, the apolipoprotein E (*APOE*) gene, which is located in the chromosome 19q13.2 region and codes for ApoE, has been one of the most studied in the past [8,9]. ApoE is a glycoprotein synthesized in the CNS by glial cells which has a crucial role in membrane remodeling and repair, as well as an immunomodulatory effect [10]. The *APOE* gene exists in three common allelic forms (ε2, ε3, ε4) and the corresponding protein isoforms Apo E2, E3 and E4 are distinguishable by having different combinations of the amino acids arginine and cysteine at positions 112 and 158. The amino acid changes result in distinctive physical and biochemical properties [11]. Additionally, the *APOE* gene exists in two minor allelic forms (ε1, ε5) which are present in less than 0.1% of the population [12–14]. ApoE is one of the proteins associated with cholesterol haemostasis, E1 and E2 decreases the plasma level of the cholesterol but E4 and E5 increases it [13,15]. E2 and E3 activities for the clearance of the β-amyloid plaques in Alzheimer diseases are 20 times more than E4 [16]. In addition, ApoE has antioxidant activities that ranked E2 > E3 > E4 [17]. According to these associations, it seems that ε4 allele is a hazardous allelic form in comparison with ε3 and ε2 alleles, but it is noteworthy that some associations with ε2 allele were reported [18].

The relationship between the *APOE* ε4 allele and MS has been studied over the last two decades. Many studies found a positive association between *APOE* ε4 allele and the risk of disease progression [19–21]. However, several other retrospective studies found no association [22–24]. Partially, because of the *APOE* gene is a minor gene and/or the relatively small sample-size in each published

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Table 1
Characteristics of case–control studies included in meta-analysis.

First author	Year	Country (ethnicity)	Genotyping method	Sample size (case/control)	Allele carrier (n)			
					MS		Control	
					ε2+	ε4+	ε2+	ε4+
Lee et al. [35]	2010	South Korea (EA)	NA	836/680	NA	141	NA	104
Losonczi et al. [49]	2010	Hungary (M)	PCR-RFLP	90/45	26	35	17	4
Bonetti et al. [40]	2009	Finland (C)	Sequenced	737/1156	43	132	72	212
Mustafina et al. [39]	2008	Russian (C)	PCR-RFLP	120/263	12	34	34	61
Koutsis et al. [34]	2007	Greek (M)	PCR-RFLP	212/216	26	35	23	26
Ramsaransing et al. [33]	2005	Netherlands (C)	NA	82/29	11	24	6	9
Cocco et al. [31]	2005	Italy (C)	NA	871/348	59	88	18	37
Al-Shammri et al. [30]	2005	Kuwait (AR)	PCR-RFLP	39/106	1	8	10	19
Pinholt et al. [32]	2005	Denmark (C)	PCR-RFLP	385/361	63	109	48	115
Zakrzewska-Pniewska et al. [37]	2004	Poland (C)	PCR-RFLP	99/100	14	20	9	21
Zwemmer et al. [38]	2004	Netherlands (C)	Mutation Detection Kit	408/144	67	115	16	52
Niino et al. [29]	2003	Japan (EA)	PCR-RFLP	135/134	11	16	10	17
Savettieri et al. [24]	2003	Italy (C)	PCR-RFLP	428/107	53	62	15	9
Ballerini et al. [27]	2000	Italy (C)	PCR-RFLP	66/67	15	6	11	15
Hogh et al. [20]	2000	Denmark (C)	PCR-RFLP	238/361	10	76	8	115
Weatherby et al. [36]	2000	UK (C)	PCR-RFLP	370/159	65	88	20	43
Ferri et al. [28]	1999	Italy (C)	NA	161/153	18	15	16	18
Oliveri et al. [48]	1999	Italy (C)	PCR-RFLP	89/107	7	12	14	9
Gaillard et al. [41]	1998	France (C)	NA	70/100	9	14	15	22
Rubinsztein et al. [41]	1994	UK (C)	NA	36/91	2	9	7	34

NA: not available; MS: multiple sclerosis; EA: East Asian; C: Caucasian; M: mixed population; AR: Arabs.

studies. Therefore, we performed a meta-analysis of the published studies to derive a more precise estimation of the association. Concurrently, the relationship between the *APOE* ε2 allele and MS will also be analyzed.

2. Materials and methods

2.1. Search strategy

All studies reporting the association between the *APOE* ε4, 2 alleles and MS susceptibility published in English before March, 2011 were identified by comprehensive computer based on searches of Medline, EBSCO and BIOSIS. The following keywords were used for searching: ("multiple sclerosis" OR "MS") AND ("polymorphism*" OR "variant*") AND ("ApoE" OR "APOE" OR "apolipoprotein E"). The most complete and recent results were used when there were multiple publications from the same study group. We only recruited data from published papers. Hand searches for related articles were also performed.

2.2. Inclusion criteria

Two investigators reviewed all identified studies independently to determine whether an individual study was eligible for inclusion. The selection criteria for studies to be considered for this meta-analysis were as follows: 1) *APOE* polymorphisms in MS; 2) case–control studies; 3) proper MS diagnosis criteria; 4) not republished data; 5) not animal studies. The study would be excluded if the information could not be obtained.

2.3. Data extraction

Two investigators extracted the data independently, and the result was reviewed by a third investigator. The following information was extracted from a study: first author, year of publication, study population (country, ethnicity), the number of patients and controls for a study, genotyping method, and genotype information.

2.4. Statistical analysis

The number of allele carrier at ε2 and ε4 from each respective study were calculated. We examined the contrast of the ε4 carriers (ε4+) vs. ε4 non-carriers (ε4−), and ε2+ vs. ε2−. The associations between *APOE* ε2, 4 alleles and MS susceptibility were estimated by odd risk (OR) and its 95% confidence intervals (95% CIs).

Heterogeneity across the eligible studies was tested using Q-test, and it was considered statistically significant when $P<0.1$. Heterogeneity was also quantified with I^2 metric [25] ($I^2=(Q-df)/Q\times100\%$. $I^2<25\%$, no heterogeneity; $I^2=25$–50%, moderate heterogeneity; $I^2=50$–75%, large heterogeneity, $I^2>75\%$, extreme heterogeneity). When the effects were assumed to be homogeneous ($P>0.1$, $I^2<50\%$), the fixed-effects model was used; otherwise, the random-effects model was more appropriate. To evaluate the ethnicity-specific effects, subgroup analyses was performed in ethnic group. Sensitivity analysis was performed to evaluate the stability of the results. Individual studies included in the meta-analysis were deleted one at a time to determine the contribution of the individual data to the pooled ORs. Begg's test was used to measure publication bias, which

Table 2
Main results of pooled ORs in the meta-analysis.

Genetic model	Ethnicity	Sample size		Test of heterogeneity			Test of association		Test of publication bias	
		Case	Control	Q	*P*	I^2 (%)	OR	95% CI	z	*P*
ε4+ vs. ε4−	Overall	5472	4727	30.22	0.049	37.1	0.997	0.861–1.156	0.55	0.681
	Caucasian	4160	3546	15.00	0.378	6.7	0.924	0.819–1.041	0.49	0.621
ε2+ vs. ε2−	Overall	4636	4047	16.06	0.589	0.0	1.097	0.940–1.279	1.75	0.080
	Caucasian	4160	3546	12.36	0.577	0.0	1.127	0.955–1.331	0.59	0.553