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Association between the IL7R T244I polymorphism and multiple sclerosis: a meta-analysis

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Abstract Previously published analyses of the association between the interleukin 7 receptor (*IL7R*) T244I polymorphism (rs6897932) and multiple sclerosis (MS) have yielded conflicting results. We performed a meta-analysis to assess whether the combined data showed this association, and to investigate its effect size. We analyzed 10 studies identified from PubMed (12,185 MS patients and 15,855 controls) and calculated the odds ratios (ORs) and 95% confidence intervals (CIs) for the C-allele, the C/C genotype (recessive effect) and the C/C + C/T (dominant effect) genotype. Heterogeneity within and between studies was observed: allele C: $Q = 30.86$, $P = 0.002$; genotype C/C: $Q = 30.28$, $P = 0.003$. Using a random-effects model, the C-allele and the C/C genotype were associated with MS (OR = 1.11, 95% CI = 1.04–1.19, $P = 0.001$ for the C-allele; OR = 1.15, 95% CI = 1.06–1.24, $P = 0.0009$ for the C/C genotype). The C/C + C/T genotype was also associated with MS using a fixed-effects model (OR = 1.15, 95% CI = 1.05–1.26, $P = 0.003$). There was no significant publication bias among the selected studies according to the funnel plot. We also performed the analysis on a European subgroup. This revealed an association between *IL7R* T244I and MS ($P < 0.00001$ for the C-allele and the C/C genotype; $P = 0.0004$ for the C/C + C/T genotype), no heterogeneity was observed (allele C: $P = 0.07$; genotype C/C: $P = 0.10$). In conclusion, the meta-analysis demonstrated that the *IL7R* T244I polymorphism was associated with susceptibility to MS.

Keywords Multiple sclerosis · IL7R · Polymorphism · Meta-analysis

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Introduction

MS is an autoimmune-mediated demyelinating disorder characterized by multiple lesions of the central nervous system [1]. The worldwide prevalence of MS is 0.1–0.2%. Generally speaking, the incidence rate among women is more than twice that among men [2]. MS is a complex disease caused by multiple genetic and environmental factors [3, 4]. Although the pathogenesis of MS is not completely understood, a genetic contribution to MS susceptibility has been shown in studies of twins and families, and in genome-wide linkage and association screens [3, 5–9]. Many studies have indicated that the HLA-DRB1 locus on chromosome 6p21 confers susceptibility to MS [10–12]. However, this does not fully explain the genetic basis. Large-scale linkage and association studies have

suggested that other loci outside the HLA region have small but non-negligible effects [13].

The association between the *IL7R* T244I polymorphism and multiple sclerosis is the first non-HLA association widely replicated [14, 15]. The *IL7R* gene maps to chromosome 5p13 and encodes the interleukin 7 receptor α chain (IL7Rα; also known as CD127) [16]. IL7Rα is a member of the type I cytokine receptor family and forms a receptor complex with the cytokine receptor gamma chain (CD132), for which IL7 is the ligand [17]. It is expressed by cells of the lymphoid lineage, in which it has essential functions in the proliferation and survival of T and B lymphocytes [18]. In MS, the *IL7R* T244I (rs6897932) single nucleotide polymorphism (SNP) is most likely the causative variant. T244I is located within exon 6 of *IL7R*, within a transmembrane domain of the encoded protein. *IL7R* T244I influences the levels of soluble and membrane-bound isoforms of IL7Rα by putatively disrupting an exonic splicing silencer [19]. Some studies have indicated that the 'C' allele of *IL7R* T244I results in an approximately two-fold increase in the skipping of exon 6 compared with transcripts containing the 'T' allele, and that this is strongly associated with increased risk of MS [13, 19, 20]. However, others studies have shown a weak or no association between *IL7R* T244I and susceptibility to MS [21, 22].

We have carried out a meta-analysis of published studies to assess whether the combined evidence demonstrates an association between the *IL7R* T244I polymorphism and MS, and to perform a preliminary investigation on its effect size.

Materials and methods

Identification of eligible studies and data extraction

Using PubMed, we performed an exhaustive search for all the studies that have examined the association of *IL7R* T244I with MS. We used the following key words: 'T244I', 'rs6897932', 'interleukin 7 receptor', 'IL7R', 'polymorphism' and 'multiple sclerosis'. No restrictions were placed on language, race, ethnicity or geographic area. The following criteria were used to identify relevant published studies: (i) the date of publication was before March 2010; (ii) the data were original (independent studies); (iii) enough information was provided to calculate the odds ratio (OR); (iv) the distribution of genotypes in the control group was in Hardy–Weinberg equilibrium; and (v) the study followed a case–control design and all the controls were healthy individuals. We excluded the following: (i) studies that contained overlapping data; (ii) studies in which the number of wild-type genotypes could not be ascertained; and (iii) studies in which family members had been studied. The following information was extracted from each study: the first author, year of publication, demographics, the number of cases and controls, the *P* value, the OR or relative risk, the 95% confidence interval (CI) of the OR and the C-allele frequency of the *IL7R* T244I polymorphism.

Evaluation of the statistical association

We contrasted the effect of the C versus T alleles, the C/C versus the C/T + T/T genotypes (recessive effect) and the C/C + C/T versus the T/T genotypes (dominant effect). The OR and its 95% CI were calculated for each study. In this study, we assessed the within- and between-study variation or heterogeneity by testing Cochran's *Q*-statistics [23]. The null hypothesis was that all studies were evaluating the same effect. Not rejecting the above hypothesis usually leads a meta-analysis to adopt a fixed-effects model. The fixed-effects model assumes that the estimated effect sizes only differ by the sampling error. In contrast, if a significant *Q*-statistic ($P < 0.1$) indicates heterogeneity across studies, a random-effects model should be adopted [24]. The random-effects model assumes that different studies are measuring different underlying effects and considers both within- and between-study variation.

We measured the degree of inconsistency across studies by calculating the percentage of total between-study variation, because of heterogeneity rather than random variation, as an I^2 metric using the formula: $I^2 = Q - d.f./Q$, considering $I^2 = 1$–24% as low heterogeneity; $I^2 = 25$–49% as moderate heterogeneity, $I^2 = 50$–74% as large heterogeneity and $I^2 > 75\%$ as extreme heterogeneity [25]. Statistical manipulations were performed using the program Review Manager 5.0 (Oxford, UK). We considered the power of each study as the probability of detecting an association between the *IL7R* T244I polymorphism and MS, and calculated it at the 0.05 level of significance, assuming a small effect size (0.1). The power analysis was performed using G*power (http://www.psycho.uni-duesseldorf.de/aap/projects/gpower).

Results

Studies included in the meta-analysis

Fourteen association studies related to the *IL7R* T244I polymorphism and susceptibility to MS were identified through PubMed searches (the most recent article was dated March 2010) [3, 4, 13, 18–22, 26–30]. Four association studies were excluded for overlapping data (the removed studies were [3, 6, 29, 30]). All studies were

published in English. Ultimately, ten studies remained for our meta-analysis. A total of 12,185 MS patients and 15,855 controls were investigated (Table 1).

Meta-analysis of available data

In this study we have calculated the combined OR and its 95% CI of the risk C-allele, the C/C and C/C + C/T genotypes. The weighting factors (weight%) used to calculate the combined OR were calculated from the inverse of the variance for each study. Cochran's Q-statistics and I^2 were used to evaluate heterogeneity between studies. The results of the meta-analysis are shown in Table 2.

Heterogeneity was found among the individual estimates of the ORs for the C-allele and MS ($Q = 30.86$, $P = 0.002$, $I^2 = 61$. Three studies [13, 19, 22] showed that the T-allele was the risk allele, whereas the other studies showed that the C-allele was the risk allele. The risk allele was not consistent across all studies). We therefore adopted the random-effects model to test the association between the *IL7R* T244I polymorphism C-allele and MS. The overall OR for the C-allele was 1.11, its 95% CI was 1.04–1.19 and the P value was 0.001 (Fig. 1). In other words, the meta-analysis demonstrated that the *IL7R* T244I C-allele does confer susceptibility to MS.

Heterogeneity was also identified between studies for the C/C genotype and MS ($Q = 30.28$, $P = 0.003$, $I^2 = 60$). We therefore tested the association of the *IL7R* T244I C/C genotype with MS using a random-effects model. Figure 2 shows that the overall OR was 1.15, its 95% CI was 1.06–1.24 and the P value was 0.0009. This demonstrates that there is an association between the *IL7R* T244I C/C genotype and susceptibility to MS.

In contrast, there was only a small heterogeneity between studies for the C/C + C/T genotype and MS ($Q = 15.73$, $P = 0.20$, $I^2 = 24$). We therefore adopted the fixed-effects model to test the association between the *IL7R* T244I polymorphism C/C + T/T genotype and MS. The overall OR was 1.15, its 95% CI was 1.05–1.26 and the P value was 0.003 (Fig. 3). Therefore, the *IL7R* T244I C/C + C/T genotype was associated with MS in our meta-analysis.

The funnel plot for MS studies showed significant symmetry. It indicated that there was no significant publication bias among the selected studies (Fig. 4).

Table 1 Study-specific association tests for SNP *IL7R* T224I

Study [Reference]	Population	Risk allele	Case (counts)			Control (C)			Power[a]	Major findings
			CC	CT	TT	CC	CT	TT		
F Weber et al. 2008 [4]	Germany	C	115	78	13	337	229	39	81.27	OR = 1.14; $P = 0.17$
JP Rubio et al. 2008 [22]	Australia	T	640	424	70	727	464	74	99.83	OR = 0.96; $P = 0.58$
Ramagopalan SV et al. 2007 [27]	Canada	C	602	491	100	783	639	131	99.95	OR = 1.28; $P = 0.002$
O'Doherty C et al. 2008 [21]	USA	C	124	72	11	201	174	38	70.2	$P = 0.005$
O'Doherty C-1 et al. 2008 [21]	UK	C	257	176	30	287	206	37	88.32	$P = 0.638$
Simon G Gregory et al. 2007 [19]	USA	T	265	156	17	256	192	31	85.73	OR = 1.34; $P = 0.05$
Simon G Gregory-1 et al. 2007 [19]	UK and Belgium	T	622	396	59	1412	1087	226	99.99	OR = 1.24; $P = 0.003$
Hafler DA et al. 2007 [20]	UK and US	C	1306	871	145	1680	1120	187	100	OR = 1.18; $P = 2.75 \times 10^{-5}$
D. A. Akkad et al. 2009 [18]	Germany	C	719	465	83	456	346	66	99.61	$P = 0.0539$
Suvi P. Kallio et al. 2009 [26]	Finland	C	439	394	89	588	633	171	99.78	OR = 1.24; $P = 0.002$
A. Alcina et al. 2008 [13]	Spain	T	356	202	32	304	254	36	93.24	OR = 0.75; $P = 0.003$
A. Alcina-1 et al. 2008 [13]	Sweden	T	593	508	109	605	518	111	99.86	OR = 0.8; $P = 0.0005$
Arne Svejgaard et al. 2008 [28]	Nordic	C	642	423	83	595	500	115	99.81	

OR odds ratio

[a] Power calculations assume $\alpha = 0.05$ and small effect size (0.1)

Table 2 Meta-analysis of the *IL7R* T244I polymorphism in MS

Comparison	Combined OR	95% CI	Heterogeneity test			Meta-analysis statistics	
			Q	P	I^2 (%)	Z	P
C-allele versus T-allele	1.11	1.04–1.19	30.86	0.002	61	3.21	0.0010
C/C versus C/T + T/T	1.15	1.06–1.24	30.28	0.003	60	3.31	0.0009
C/T + C/C versus T/T	1.15	1.05–1.26	15.73	0.200	24	3.00	0.0030

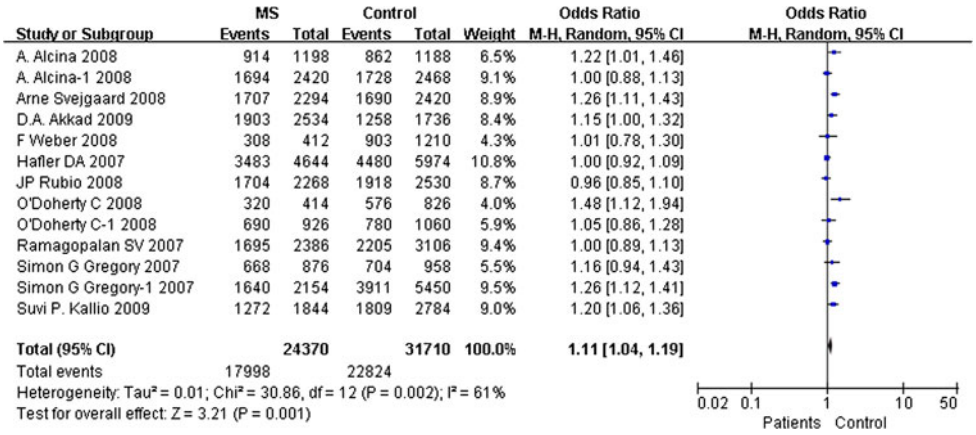

Fig. 1 ORs and 95% CIs of individual studies and pooled data for the association between the *IL7R* T244I polymorphism C allele and MS, across all studies

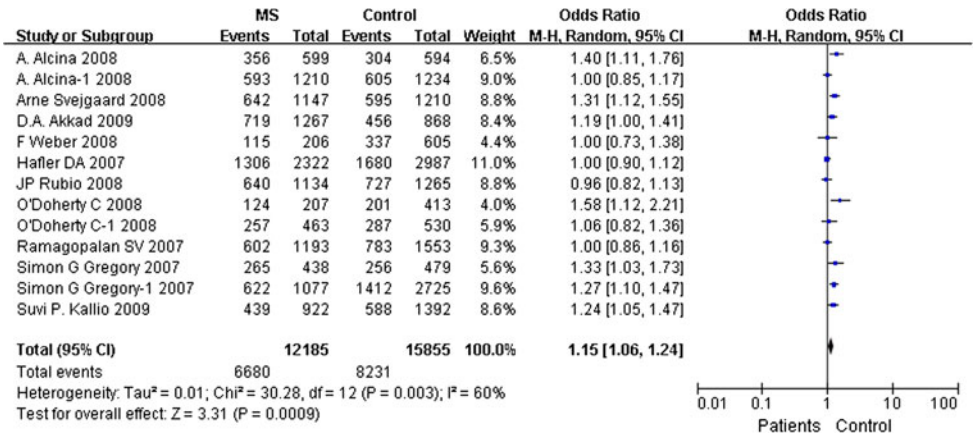

Fig. 2 ORs and 95% CIs of individual studies and pooled data for the association between the *IL7R* T244I polymorphism C/C genotype and MS, across all studies

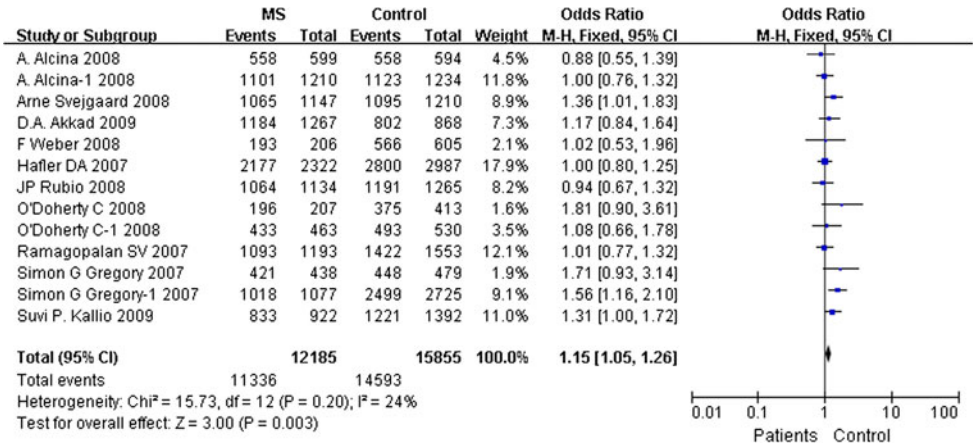

Fig. 3 ORs and 95% CIs of individual studies and pooled data for the association between the *IL7R* T244I polymorphism C/C + C/T genotype and MS, across all studies

We have included in the meta-analysis only the studies performed on European population [4, 13, 18, 19, 21, 26, 28]. Under fixed-effects models, the overall OR for the risk C-allele was 1.17 (95% CI = 1.11–1.23, $P < 0.00001$) (Supplementary Fig. 1), for the recessive effect (C/C genotype) the OR was 1.21 (95% CI = 1.13–1.29, $P < 0.00001$) (Supplementary Fig. 2), and for the dominant effect (C/C + C/T genotype) the OR was 1.24 (95% CI = 1.10–1.39, $P = 0.0004$) (Supplementary Fig. 3) (Table 3). In this subgroup, no heterogeneity was observed. However, there was high heterogeneity among all studies. Further studies are required to identify heterogeneity.

Discussion

Since the first association between the *IL7R* T244I polymorphism and MS was reported in 2003 [14], many studies have attempted to replicate the association. However, these analyses have yielded conflicting results. We performed a

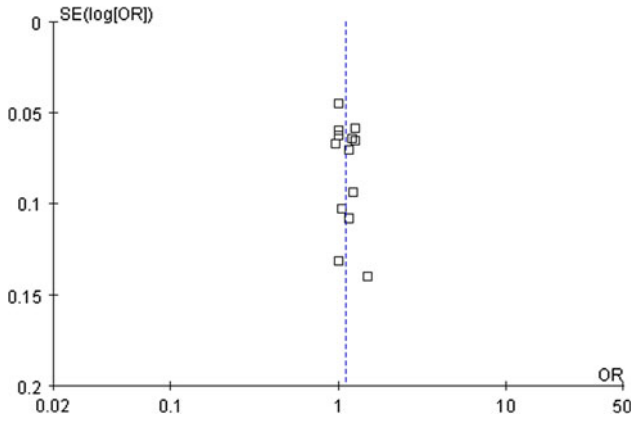

Fig. 4 Funnel plot with ORs of all studies on the association between the *IL7R* T244I polymorphism and MS

Table 3 Subgroup (Europe) meta-analysis of the *IL7R* T244I polymorphism in MS

Comparison	Combined OR	95% CI	Heterogeneity test			Meta-analysis statistics	
			Q	*P*	I^2 (%)	*Z*	*P*
C-allele versus T-allele	1.17	1.11–1.23	14.63	0.07	45	6.09	<0.00001
C/C versus C/T + T/T	1.21	1.13–1.29	13.49	0.10	41	5.82	<0.00001
C/T + C/C versus T/T	1.24	1.10–1.39	9.21	0.33	13	3.53	0.00040

meta-analysis to establish the relationship between the *IL7R* T244I polymorphism and susceptibility to MS. In our meta-analysis, we found a high heterogeneity for the C-allele and the C/C genotype ($Q = 30.86$, $P = 0.002$ and $Q = 30.28$, $P = 0.003$, respectively) between studies. The common OR for the risk C-allele was 1.11 (95% CI = 1.04–1.19, $P = 0.001$), for the recessive effect (C/C genotype) it was 1.15 (95% CI = 1.06–1.24, $P = 0.0009$) and for the dominant effect (C/C + C/T genotype) it was 1.15 (95% CI = 1.05–1.26, $P = 0.003$). The overall data showed that there is an association between the *IL7R* T244I polymorphism and MS.

In vitro experiments have shown that T244I affects alternative splicing of exon 6. Transcripts that include exon 6 encode a membrane-bound IL7Rα, whereas transcripts that skip exon 6 produce a predicted soluble form of the protein. Carriers of the 'C' allele at T244I have been shown to produce less membrane-bound IL7Rα protein than carriers of the 'T' allele, leading to a further increase in the soluble form of IL7Rα. These changes might affect IL7 signaling and enhance the antigenic T cell response to myelin basic protein and myelin oligodendrocyte glycoprotein, both of which have been implicated in the development of MS [19]. Expression of the IL-7–IL7Rα ligand-receptor complex in the cerebrospinal fluid is increased, which supports the simplistic interpretation that increased IL7 signaling induces immune cell proliferation and survival [15]. In summary, the T244I C-allele has been identified as a risk allele for MS in many studies, and this is consistent with our meta-analysis.

The main purpose of performing a meta-analysis is to improve the statistical power and obtain more compelling results by increasing the sample size. However, there are still some limitations. Meta-analyses may be distorted by publication bias and heterogeneity. Our funnel plots showed significant symmetry (Fig. 4), indicating no significant publication bias. Heterogeneity was observed when all studies were included in the meta-analysis, but not within the European subgroup. This suggests that regional differences might be an important reason for the heterogeneity.

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