Meta-analysis of the IL23R and IL12B polymorphisms in multiple sclerosis

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<td>Huang, Jian; Zhongshan School of Medicine, Sun Yat-sen University, Yang, Yaqi; Zhongshan School of Medicine, Sun Yat-sen University, Department of Anatomy and Neurobiology Zhou, Fengmei; The First Affiliated Hospital, Sun Yat-sen University, Department of Surgery Liang, Zibin; Zhongshan School of Medicine, Sun Yat-sen University, Department of Anatomy and Neurobiology Kang, Miaomiao; Zhongshan School of Medicine, Sun Yat-sen University, Department of Anatomy and Neurobiology Kuang, Ying; Zhongshan School of Medicine, Sun Yat-sen University, Department of Anatomy and Neurobiology Li, Feng; Zhongshan School of Medicine, Sun Yat-sen University, Department of Anatomy and Neurobiology</td>
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<td>IL12B, IL23R, meta-analysis, multiple sclerosis, polymorphism</td>
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</table>
Meta-analysis of the \textit{IL23R} and \textit{IL12B} polymorphisms in multiple sclerosis

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Abstract

Purpose: Polymorphisms in the genes encoding interleukin-23 receptor (*IL23R*) and the p40 subunit of IL-12/23 (*IL12B*) have been implicated in multiple sclerosis (MS) risk. However, results of different studies are inconsistent. Our aim was to perform a meta-analysis on this topic.

Methods: We assessed two variants (rs10889677 and rs7517847) of *IL23R* and the A1188C polymorphism (rs3212227) of *IL12B*. Electronic databases (PubMed, Web of Science and Scopus) were searched for eligible studies published until September 2014. Odds ratio (OR) and 95% confidence interval (95% CI) were used to investigate the strength of the association in dominant, recessive, homozygote and allelic comparison models.

Results: Seven case-control studies with 2250 MS patients and 2320 controls were included in this meta-analysis. The pooled analysis showed no association of rs10889677, rs7517847 and rs3212227 with MS risk in any of the genetic model. The pooled OR was 0.97 (95% CI: 0.86-1.08) for rs10889677, 1.01 (95% CI: 0.90-1.12) for rs7517847, and 0.93 (95% CI: 0.79-1.09) for rs3212227 in allelic comparison model. Similar ORs were obtained in other genetic models. The pooled results from sensitivity analyses by removing each of the involved study in turn were unchanged.

Conclusions: The *IL23R* polymorphisms rs10889677, rs7517847 and the *IL12B* polymorphism rs3212227 are not associated with MS risk.

Key words: *IL12B*, *IL23R*, meta-analysis, multiple sclerosis, polymorphism
Introduction

Multiple sclerosis (MS) is a chronic inflammatory demyelinating disease of the central nervous system (CNS) characterized by inflammation, demyelination, varying degrees of axonal loss, and progressive neurological dysfunction [1]. It is the most common neurological disease affecting young Caucasian adults. Although aetiologic mechanisms remain largely unknown, epidemiological studies indicate that MS risk is determined by an interplay of genetic and environmental factors. The human leukocyte antigen (HLA) region on chromosome 6p21 is the most important genetic element for MS susceptibility. The HLA-DR2 or DRB1*15 haplotype (DQB1*0602, DQA1*0102, DRB1*1501, DRB5*0101) has been consistently associated with MS in populations of European ancestry [2]. However, the HLA locus only accounts for 20-60% of the genetic susceptibility in MS, implying that non-HLA genetic factors may also play a role in disease susceptibility [3]. Recently, non-HLA associations have been reported with the interleukin 2 receptor alpha (IL2RA) [4], interleukin 7 receptor alpha (IL7RA) [5], and interferon regulatory factor 5 (IRF5) genes [6]. Identifying non-HLA genes that contribute to MS susceptibility will not only help unravel mechanisms of disease but also provide insight for the development of targeted preventive therapies.

Interleukin-23 (IL-23) is a key pro-inflammatory cytokine which contributes to the development of T cell-dependent inflammation and is critical in the induction of autoimmunity [7]. It consists of the shared IL-12/23 p40 subunit and a unique p19 subunit, which are respectively encoded by the IL12B on chromosome 5 and IL23A on chromosome 12 [8]. IL-23 is mainly produced by activated dendritic cells (DCs) and macrophages, and signals through its heterodimeric IL-23R complex, which is composed by two subunits encoded by the IL12RB1 gene on chromosome 19 and IL23R on chromosome 1 [9]. IL-23/IL-23R signaling plays an important role in favouring terminal differentiation, maintenance and pathogenicity of a highly pathogenic T cell population expressing IL-17 and granulocyte-macrophage...
colony-stimulating factor (GM-CSF) [7]. These cytokines have been linked to numerous autoimmune diseases, including MS, type 1 diabetes (T1D), and inflammatory bowel disease (IBD). Given the critical role of the IL-23/IL-23R signaling in autoimmunity, the IL23R and IL12B genes are considered to be candidate genes for MS. Several common polymorphisms have been identified in the IL23R and IL12B genes, including two single nucleotide polymorphisms (SNPs) in the 3’ untranslated region (rs10889677) and intron 6 (rs7517847) of IL23R, and a SNP located at position +1188 (rs3212227) in the IL12B gene. Several genetic association studies have been undertaken to investigate the relationship of these polymorphisms with MS, but small sample size and minor genetic effects lead to inconsistent results. To validate the potential association of the IL23R and IL12B polymorphisms with MS, we performed a meta-analysis of data reported in seven case-control studies including 4570 subjects (2250 cases and 2320 controls).

Materials and methods

Information sources and search strategy

We followed the guidelines for systematic reviews of genetic association studies. We conducted a systematic computerized literature search updated to September 2014 using PubMed, Web of Science and Scopus databases without language restrictions. Search terms included “multiple sclerosis”, “MS”, “interleukin-23”, “IL-23”, “interleukin-23 receptor”, “IL-23R”, “interleukin-12”, “IL-12”, “polymorphism”, “genetics” and “association”. We also checked the references from retrieved publications to identify any additional relevant study. Although the initial search was without language restrictions, we only included publications written in English at final.

Inclusion and exclusion criteria

Genetic association studies were included in this meta-analysis if they met the
following criteria: (1) case-control design; (2) evaluating the relationship of the \textit{IL23R} and/or \textit{IL12B} polymorphism with MS; and (3) sufficient data for calculating an odds ratio (OR) with 95% confidence interval (95% CI). The major exclusion criteria were as follows: (1) case reports, abstract, review, comment and editorial; (2) insufficient data; and (3) duplicate data.

Data extraction
Publications were reviewed and data were extracted by two investigators. Any disagreement was resolved by consensus among the two. The following data were collected from each study: first author’s name, year of publication, country, ethnicity, total number of cases and controls, genotypic frequencies, and genotyping method. Where there were multiple publications from the same study group, data were extracted from each report and only the most complete and up-to-date data were selected. We did not contact the authors to collect further information.

Statistical analyses
All analyses were performed using STATA 11.0. Raw data of genotypic distribution without adjustment were used for calculation of the study-specific estimates of OR and 95% CI. ORs were calculated for dominant, recessive, homozygote and allelic comparison models. The significance of the pooled effect size was determined using a Z test, with significance level set at 0.05. The presence of heterogeneity between studies was explored with the Cochran’s Q statistic; \(P<0.10\) indicated significant heterogeneity. In case of no significant heterogeneity, summary estimates were calculated using the standard Mantel-Haenszel fixed-effects model [10]. Otherwise, the DerSimonian Laird random-effects model was fitted [11]. We conducted sensitivity analyses to determine whether the results were considerably influenced by any single study by systematically excluding each study and recalculating the significance of the result. Potential publication bias was evaluated visually by examining for possible skewness in funnel plots and statistically with the methods described by Begg [12] and Egger [13]. For publication bias, \(P<0.05\) was considered
Results

Study characteristics

Figure 1 describes the literature selection process. We identified a total of 493 reports in the initial search and removed 483 non-relevant or duplicate publications based on screens of titles and abstracts. Three studies were excluded after evaluating the remaining ten publications in their entirety. Overall, we identified seven papers published in English that met the inclusion criteria and included these in the meta-analysis [14-20]. No existing systematic or meta-analytic reviews on this topic were found. In terms of ethnicity, six studies containing 2072 cases and 2099 controls were undertaken in Caucasians [14-19], whereas one study with 178 cases and 221 controls was performed in Asians [20]. In terms of polymorphism, three studies investigated rs10889677 [17,18,20], two studies assessed rs7517847 [18,20], and five studies evaluated rs3212227 [14-16,19,20]. Table 1 presents the characteristics of the individual studies. Table 2 showed genotypic distribution of each polymorphism in cases and controls.

Quantitative data synthesis

Table 3 provides the main results of this meta-analysis. For rs10889677, two studies were conducted in Caucasians [17,18], while one study was performed in Asians [20]. Pooling the data from these studies showed no association between rs10889677 and MS in all study subjects under dominant model (OR=0.95, 95% CI: 0.81-1.10, \( P_h=0.872, P_z=0.482 \)) (Table 3), recessive model (OR=1.05, 95% CI: 0.70-1.57, \( P_h=0.084, P_z=0.818 \)) (Table 3), homozygote model (OR=1.05, 95% CI: 0.80-1.38, \( P_h=0.282, P_z=0.726 \)) (Table 3) and allelic comparison model (OR=0.97, 95% CI: 0.86-1.08, \( P_h=0.678, P_z=0.564 \)) (Table 3 and Fig.2). In subgroup analysis stratified by ethnicity, no association between rs10889637 and MS was found in Caucasians in
dominant model (OR=0.94, 95% CI: 0.81-1.10, \(P_h=0.839\), \(P_z=0.437\)) (Table 3),
recessive model (OR=1.31, 95% CI: 0.64-2.71, \(P_h=0.064\), \(P_z=0.461\)) (Table 3),
homozygote model (OR=1.05, 95% CI: 0.79-1.25, \(P_h=0.112\), \(P_z=0.736\)) (Table 3) and
allelic comparison model (OR=0.98, 95% CI: 0.87-1.11, \(P_h=0.523\), \(P_z=0.740\)) (Table 3 and Fig.2). We did not conduct subgroup analysis in Asians since there was only one study [20].

Two studies provided results on association of rs7517847 with MS risk. Among them, one study was undertaken in Caucasians [18], while one study was conducted in Asians [20]. Pooling data from these showed no association between this polymorphism and MS in all study subjects under dominant model (OR=1.03, 95% CI: 0.87-1.23, \(P_h=0.351\), \(P_z=0.703\)) (Table 3), recessive model (OR=0.97, 95% CI: 0.80-1.18, \(P_h=0.411\), \(P_z=0.765\)) (Table 3), homozygote model (OR=1.00, 95% CI: 0.79-1.25, \(P_h=0.295\), \(P_z=0.979\)) (Table 3) and allelic comparison model (OR=1.01, 95% CI: 0.90-1.12, \(P_h=0.279\), \(P_z=0.934\)) (Table 3 and Fig.3). We did not perform subgroup analysis according to ethnicity because of limited availability of published data.

The \textit{IL12B} polymorphism rs3212227 was evaluated in five studies. Among which, four studies were conducted in Caucasians [14-16,19], whereas one study was performed in Asians [20]. The pooled analysis showed no association between this polymorphism and MS in all study subjects under dominant model (OR=0.86, 95% CI: 0.70-1.05, \(P_h=0.255\), \(P_z=0.139\)) (Table 3), recessive model (OR=1.21, 95% CI: 0.55-2.69, \(P_h=0.012\), \(P_z=0.639\)) (Table 3), homozygote model (OR=1.14, 95% CI: 0.52-2.46, \(P_h=0.024\), \(P_z=0.747\)) (Table 3) and allelic comparison model (OR=0.93, 95% CI: 0.79-1.09, \(P_h=0.338\), \(P_z=0.365\)) (Table 3 and Fig.4). In subgroup analysis based on ethnicity, we still did not find an association between rs3212227 and MS risk in Caucasians under dominant, recessive, homozygote and allelic comparison models (Table 3). We did not perform subgroup analysis in Asians in that there was only one study [20].
Sensitivity analysis, heterogeneity and publication bias

In order to reflect the influence of the individual data set to the pooled ORs, each of the involved study was excluded in turn. The corresponding pooled ORs were not significantly altered for any of the SNPs assessed in all study subjects. Between-study heterogeneity was shown in Table 3 in detail. Most pooled analyses showed no heterogeneity. Since publication bias was difficult to detect when the number of studies was small, we selected rs3212227 under allelic comparison model to evaluate publication bias (five studies included). The shape of the funnel plot seemed symmetrical (Fig. 5). Both Begg’s test and Egger’s test showed no evidence of publication bias ($P=0.462$ and $P=0.684$, respectively).

Discussion

IL-23 is a pro-inflammatory cytokine which signals through its heterodimeric IL-23R complex. IL-23 is essential for the survival and/or expansion of Th17 cells, which produce IL-17A, IL-17F, IL-22 and interferon-γ (IFN-γ) and are key mediators of inflammation and autoimmunity [7]. Accumulating evidence from clinical and experimental studies suggests a critical role of the IL-23/IL-23R signaling in the pathogenesis of MS [21]. Increased IL-23 levels, as well as Th17 cells and cytokines, are present in MS lesions [22-24]. Both IL-23 (p19)-knockout mice and IL-12/23 (p40)-deficient mice, but not those lacking IL-12 (p35), are resistant to experimental autoimmune encephalomyelitis (EAE), an animal model for human MS [25]. In addition, IL23r is required for Th17 cells to induce EAE upon adoptive transfer in vivo [26]. Therapeutic treatment with anti-IL-23p19 or anti-IL-12/23p40 antibody showed beneficial effects on the clinical and neuropathological expression of CNS inflammation of EAE [27,28]. Therefore, genes belonging to the IL-23 pathway, including IL23R and IL12B, are thought to be candidate genes for MS.
Two polymorphisms (rs10889677 and rs7517847) located in the *IL23R* gene and one polymorphism (rs3212227) located in the *IL12B* gene were most frequently evaluated in case-control association studies for MS risk. The functionality of these SNPs is currently unknown. The *IL23R* SNP rs10889677 may lead to increased mRNA stability [29], whereas the *IL12B* polymorphism rs3212227 can possibly affect production of the IL-12/23p40 subunit [15]. In this meta-analysis we analyzed the association between these three polymorphisms and MS. The main findings are as follows: (1) there is no association between rs10889677 and MS risk in all study subjects (Caucasians and Asians) and Caucasians; (2) rs7517847 is not associated with MS risk in all study subjects (Caucasians and Asians); and (3) there is no association between rs3212227 and MS risk in all study subjects (Caucasians and Asians) and Caucasians.

Begovich and coworkers evaluated the *IL23R* polymorphisms rs11209026, rs7530511 and the *IL12B* polymorphisms rs6887695 and rs3212227 in a family-based study including 910 MS-nuclear families with a total of 3132 individuals, finding no evidence of transmission distortion of any of the tested alleles [30]. Their findings support our results. It is also noteworthy that there are no genome-wide association studies (GWAS) that reports an association between these polymorphisms and MS risk. Although the present meta-analysis did not suggest an association between these polymorphisms and MS, we could not rule out that other SNPs in *IL23R* or *IL12B* contribute to risk for MS. Recently, the study by Varadé et al. reported an association of the *IL12B* SNP rs6887695 with MS in a large case-control study with 2863 cases and 2930 controls in a Spanish population (OR=1.09, 95% CI: 1.01-1.17), suggesting a modest effect of this SNP on MS risk [31]. To clearly clarify the role of the *IL23R* and *IL12B* genes in genetic predisposition to MS, further studies using large sample numbers are needed to evaluate other variants in these regions among different populations. In addition, the international multiple sclerosis genetics consortium (IMSGC) recently identified a MS-associated SNP rs4680534 in the *IL12A* gene using data from GWAS studies [32], indicating that apart from *IL23R* and *IL12B*, variants in
other genes of the IL23 pathway should also be taken into account in association studies.

In our study, most pooled analyses showed no between-study heterogeneity. However, few analyses presented low heterogeneity. Several potential factors may account for it, including sample size, ethnicity and genotyping method. Because of relatively small number of the eligible studies and the limitation of the published data, we did not further investigate the precise sources for heterogeneity. For pooled analyses showing heterogeneity, the DerSimonian Laird random-effects model was used to calculate the overall effect. Sensitivity analyses for the association between the \textit{IL23R}, \textit{IL12B} polymorphisms and MS in all study subjects did not change our results, indicating that the results of this meta-analysis were stable.

Some limitations need to be considered. First, due to the limited availability of published results, the number of studies included in each meta-analysis is relatively small. Future association studies should be performed using large sample numbers to establish a more definitive conclusion. Second, most eligible studies were conducted in Caucasians. Further studies should include larger non-Caucasian population to evaluate race-specific effects of \textit{IL23R} and \textit{IL12B} on MS risk. Third, there were not enough data available to investigate the association between the \textit{IL23R}, \textit{IL12B} polymorphisms and clinical features of MS, including the age of onset and disease severity.

**Conclusion**

In conclusion, our meta-analysis of the association of the \textit{IL23R} polymorphisms rs10889677, rs7517847 and the \textit{IL12B} polymorphism rs3212227 with MS did not detect any significant association. Further studies using large sample numbers are warranted to establish a more definitive conclusion. In addition, other polymorphisms in \textit{IL23R} and \textit{IL12B}, and variants in other genes belonging to the IL-23 pathway
should be evaluated.

Declaration of Interests

No conflict of interest declared. The authors alone are responsible for the content and writing of this paper.

Acknowledgments

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1 Brück W. The pathology of multiple sclerosis is the result of focal inflammatory demyelination with axonal damage. J Neurol. 2005;252(Suppl. 5):v3P9.


Table 1 Characteristics of eligible studies in meta-analysis.

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<th>Number</th>
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<th>Genotyping method</th>
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<td>Ethnicity</td>
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PCR-RFLP, polymerase chain reaction-restriction fragment length polymorphism; UK, united kingdom.
Table 2 Genotypic distribution of the *IL23R* and *IL12B* polymorphisms in cases and controls

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<th>Controls</th>
<th></th>
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<th>A allele</th>
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<td>C allele</td>
<td>A allele</td>
<td>CC</td>
<td>CA</td>
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<td>C allele</td>
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<td>1449</td>
<td>583</td>
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<td>472</td>
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<td>9</td>
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Table 3 Meta-analysis of the effect of the IL23R and IL12B polymorphisms on risk for multiple sclerosis

<table>
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<th>Recessive OR (95% CI)</th>
<th>P (het)</th>
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<th>Homozygote OR (95% CI)</th>
<th>P (het)</th>
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<th>Allelic comparison OR (95% CI)</th>
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<td>0.872</td>
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<td>1.05 (0.78-1.41)</td>
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<td>1.05 (0.70-1.57)</td>
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<td>0.726</td>
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<td>1.00 (0.79-1.25)</td>
<td>0.295</td>
<td>0.979</td>
<td>1.01 (0.90-1.12)</td>
<td>0.279</td>
<td>0.934</td>
</tr>
<tr>
<td>rs3121227 (IL12B)</td>
<td>0.86 (0.70-1.05)</td>
<td>0.255</td>
<td>0.139</td>
<td>1.21 (0.55-2.69)</td>
<td>0.012</td>
<td>0.639</td>
<td>1.14 (0.52-2.46)</td>
<td>0.024</td>
<td>0.747</td>
<td>0.93 (0.78-1.09)</td>
<td>0.338</td>
<td>0.365</td>
</tr>
<tr>
<td>Caucasians</td>
<td>0.86 (0.68-1.08)</td>
<td>0.149</td>
<td>0.197</td>
<td>1.37 (0.45-4.15)</td>
<td>0.030</td>
<td>0.575</td>
<td>1.30 (0.44-4.14)</td>
<td>0.037</td>
<td>0.641</td>
<td>0.96 (0.70-1.36)</td>
<td>0.338</td>
<td>0.365</td>
</tr>
</tbody>
</table>

CI, confidence interval; OR, odds ratio; P (het), P-value for heterogeneity; P (z), P-value for overall effect.
Figure legends

Figure 1    Process of study selection.

Figure 2    Meta-analysis of the association between the IL23R polymorphism rs10889677 and MS risk in allelic comparison model.

Figure 3    Meta-analysis of the association between the IL23R polymorphism rs7517847 and MS risk in allelic comparison model.

Figure 4    Meta-analysis of the association between the IL12B polymorphism rs3212227 and MS risk in allelic comparison model.

Figure 5    Begg’s funnel plot for the IL12B polymorphism rs3212227 and MS risk in allelic comparison model.
Potentially relevant records identified through database searches (N=493)

Publications excluded after initial screen of title and abstract (N=483)

Publications retained for closer scrutiny (N=10)

Publications excluded due to:
1. Family-based study (N=1)
2. Evaluation of other SNPs (N=1)
3. Duplicate data (N=1)

Studies meeting all criteria (N=7)

Process of study selection.
254x190mm (300 x 300 DPI)
Meta-analysis of the association between the IL23R polymorphism rs10889677 and MS risk in allelic comparison model.

314x225mm (300 x 300 DPI)
Meta-analysis of the association between the IL23R polymorphism rs7517847 and MS risk in allelic comparison model.

314x227mm (300 x 300 DPI)
Meta-analysis of the association between the IL12B polymorphism rs3212227 and MS risk in allelic comparison model.

316x239mm (300 x 300 DPI)
Begg’s funnel plot for the IL12B polymorphism rs3212227 and MS risk in allelic comparison model.

180x115mm (300 x 300 DPI)