Variants in the IL7RA gene confer susceptibility to multiple sclerosis in Caucasians: evidence based on 9734 cases and 10436 controls

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Recently, numerous genome wide association studies (GWAS) and other case-control association studies examining the relationship between interleukin-7 receptor α chain (IL7RA) gene rs3194051, rs987107, rs11567686, and rs11567685 variants and multiple sclerosis (MS) risk have been conducted, but the conclusions have been inconsistent. The main objective of this meta-analysis was to more precisely explore the association of these four IL7RA variants with MS development. Twenty-seven eligible studies involving 9734 cases and 10436 controls were included in the present meta-analysis. Power calculation, publication bias, sensitivity analysis and cumulative meta-analysis were performed to derive a reliable conclusion. Our study indicated three IL7RA loci were significantly associated with increasing MS risk (rs3194051: recessive model: OR = 1.22, 95% CI 1.08–1.38; rs987107: recessive model: OR = 1.44, 95% CI 1.22–1.69; and rs11567686: dominant model: OR = 1.18, 95% CI 1.01–1.37). Additionally, IL7RA rs11567685 variants might not be related to MS development. In all, IL7RA locus polymorphisms could play an important role in the predisposition to MS, which could contribute to a better understanding the pathogenesis of multiple sclerosis.

Multiple sclerosis (MS), an inflammatory autoimmune disease of the central nervous system (CNS), is characterized by lymphocytic infiltration, demyelination and axonal loss1. It is estimated that MS affects approximately 2.5 million people throughout the world2, and approximately 400,000 Americans are currently diagnosed with MS, with 200 newly diagnosed cases each week3. Patients in the advanced stages of MS may have various neurological symptoms including ataxia, gait instability and cognitive deficits4, which seriously reduces the quality of their lives. Multiple sclerosis causes a heavy economic burden on society; for example, in 2009 the annual treatment cost for each patient was more than $23,000 in the United States5.

Although the exact etiology of MS is still not completely understood, there is growing evidence that the interplay between environmental factors including Epstein-Barr virus (EBV)6, latitude7, smoking8, and vitamin D9, and genetic factors contribute to the risk of developing MS10. In addition, it has been well established that variants in the major histocompatibility complex (MHC) gene on chromosome 6p21 are an extremely important genetic factor for MS susceptibility11-13. However, recent independent genome wide association studies (GWAS) have revealed some non-MHC MS susceptibility genes, such as CXCR514, BCL1015, IL2RA16, IL7RA17 and CD8618.

The IL7RA gene is located on chromosome 5p13.2 and encodes the interleukin 7 receptor-α (namely CD127) protein, which plays a vital role in V(D)J recombination during lymphocyte development19 and controls the T lymphocyte receptor-γ loci approachability by histone acetylation and STAT520. Over the last decade it has been established that this gene influences MS risk in Caucasians21-23. For example, in 2003, Teutsch et al. first identified...
the IL7RA rs11567686 and rs11567685 polymorphisms, which were suggested to have a potential association with susceptibility to MS24. In 2005, Zhang et al. described a significant association between IL7RA rs3194051 and rs987107 variants and an increased risk of MS observed in Swedish patients23. Subsequently, multiple studies were conducted to explore the impact of these IL7RA polymorphisms on the development and pathogenesis of MS in different ancestral groups; however, these studies provided conflicting results17, 21, 22, 25–27. To the best of our knowledge, no systematic review of such association has been carried out to contend with the issue of inconsistencies from different research studies. Therefore, we synthesized available evidence from all published studies regarding the relationship between IL7RA polymorphisms and MS and performed a meta-analysis to elucidate the association between these four single nucleotide polymorphisms (SNPs) and susceptibility to MS in Caucasians.

Materials and Methods

Search strategies. Two reviewers systematically searched literature from the PubMed, Embase, Google Scholar, China National Knowledge Infrastructure (CNKI) and MS Gene (http://www.msgene.org/) databases (up to June 14, 2016). We first explored the CNKI database, but no eligible studies could be retrieved (data not shown in Fig. 1). We then performed a search of English databases using the following keywords: (interleukin 7 receptor OR IL7R OR ILRA OR IL-7R-alpha OR CDW127 OR IL7RA OR CD127) AND (polymorphism OR mutation OR variant) AND “multiple sclerosis”. Additional studies were manually examined from the references cited in the original literature. For case-control studies with overlapping data, the one with the largest sample size was included in this meta-analysis.

Study inclusion criteria. The following inclusion criteria were used for selecting suitable studies: (i) the study was on the association of IL7R rs3194051, rs987107, rs11567686 or rs11567685 polymorphisms with MS; (ii) the study used a case–control design; (iii) the study provided raw genotype data (such as GG, GA and AA genotypes) for calculating the odds ratio with 95% confidence interval. Articles that did not meet the above inclusion criteria were excluded from our meta-analysis.

Data extraction. For each eligible study, the following data were extracted: (1) first author’s name and publication year, (2) area and ethnicity of the participants, (3) the number of cases and controls or the distribution of genotypes (4) source of control and genotyping method, (5) age and gender information, and (6) type and diagnostic criteria for multiple sclerosis. Two reviewers independently completed this step and collected the data carefully. Any disagreement was resolved by a discussion with a third reviewer.

Quality assessment. The Newcastle-Ottawa Scale (NOS) criteria were used to assess the quality of retrieved studies, which included three aspects: object selection, comparability and exposure assessment28. Studies with at least six points were considered high quality studies.

Statistical analysis. The Hardy-Weinberg equilibrium (HWE) was performed for testing the genotype distribution of the control group within each included study, and a P-value greater than 0.05 meant that the study sample was representative of the population in the corresponding area. The pooled odds ratios (ORs) with 95% confidence intervals (CIs) were calculated to evaluate the strength of the relationship between each IL7RA polymorphism and MS risk. The estimated ORs were as follows:

- For rs3194051 SNP: GG vs. AA (OR1), GA vs. AA (OR2), and GG vs. GA (OR3).
The above crude ORs were then used to determine the most applicable or ideal genetic model using the following method initially described by Thakkinstian et al. 29 (Table 1):

1. If OR1 = +, OR2 = −, and OR3 = −, then a dominant model is suggested.
2. If OR1 = +, OR2 = −, and OR3 = +, then a recessive model is suggested.
3. If OR1 = −, OR2 = +, OR3 = +, and OR2 is at a lesser risk than both OR1 and OR3, then a complete overdominant model is suggested.
4. If OR1 = +, OR2 +, and OR3 = +, then a codominant model is suggested.

( + means a statistically significant result; + + means the effect size is greater than +; − means a non-significant result)

A P-value of less than 0.05 for the Z-test indicated statistical significance of the pooled ORs. We used the statistical software Power and Sample Size Calculation (PS) version 3.1.2 (http://biostat.mc.vanderbilt.edu/wiki/Main/PowerSampleSize) 30 to perform power calculations regarding the association of each IL7RA variant with MS under the appropriate model, and a power value greater than 0.8 meant high statistical power in this meta-analysis. The P test was conducted to estimate the between-study heterogeneity. The random-effect model (DerSimonian and Laird method) was used when significant heterogeneity existed among the studies (I² ≥ 50%); otherwise, the fixed-effect model (Mantel-Haenszel) was used. Sensitivity analysis was conducted by removing one study at a time, especially the one not in HWE, to evaluate the stability of the overall results. Additionally, a cumulative meta-analysis sorted upon sample size was carried out to explain precisely the association of IL7RA polymorphisms with MS risk under their special genetic models, which updated the pooled results every time a new study sample was added. Publication bias was estimated by Begg’s funnel plot and Egger’s tests among the eligible studies, and a P-value > 0.05 suggested no apparent bias. The software STATA 14.0 (Stata Corporation College Station, Texas, USA) was used for all statistical analyses.

### Results

**Literature search results.** Figure 1 describes the procedure of the literature search and the study selection in this meta-analysis. Following the initial search strategy, 303 potential publications were identified. Among them, 38 were found to be duplicates. After these duplicates were removed, we obtained 265 articles, which included 56 that were related to other diseases, 112 concerning unrelated loci and 7 articles whose studies did not utilize a case-control design. Therefore, these 175 articles were excluded and 90 articles remained. Subsequently, we further screened these remaining articles (n = 90) by removing the reviews (n = 2). Finally, 15 articles including 27 eligible studies were included in this meta-analysis 23, 25–37. Among these 27 individual studies, 8, 6, 5, and 8 studies were linked to IL7RA rs3194051, rs987107, and rs11567685 polymorphisms, respectively.

**Main characteristics of included studies.** Table 2 provides the number of cases and controls, the number of genotypes of IL7RA rs3194051, rs987107, rs11567685, and rs11567685 loci, HWE and power analysis for each included study. From this table, it can be determined that the genotypic frequency distribution of the control group was consistent with HWE in all eligible studies, except for three (one reported by Zhang et al. 25 and two by Haj et al. 23). Further, the statistical power for all included studies under the applicable model ranged from 0.05 to 0.98. Table 3 describes the main characteristics of all the studies included in this meta-analysis, which could be divided into some diverse subgroups, regardless of some studies whose data might not be available. The genotyping method was divided into three subgroups: 'PCR' 23, 'RT-PCR' 25, 26, 34, 37, 'PCR-RFLP' 21, 24, 27, 29, 31, 33, 37, and the diagnostic criteria were also classified into three subgroups: 'Poser' 25, 26, 34, 37, 'McDonald' 25, 26, 31, 'Poser & McDonald' 22, 24, 34, 35, 37, 37, the diagnostic criteria of control consisted of hospital-based (HB) 17, 23, 24 and population-based (PB) 25, 26, 31 groups. The mean age ranged from 28.8 to 45.6 years old in MS patients and from 29.4 to 54.5 years old in controls, while the percentage of females ranged from 67.5% to 71.60% in MS patients and from 49.20% to 81.90% in controls. The MS patients were mainly stratified into relapsing remitting (RR), secondary progressive (SP), and primary progressive (PP) groups, and their frequency varied from 52.9% to 91% in the RR groups, 0 to 26% in the SP

| Mode of inheritance | MM vs. WW (OR1)* | MW vs. WW (OR2) | MM vs. MW (OR3) |
|---------------------|------------------|----------------|-----------------|
| Dominant            | +                | +              | −               |
| Recessive           | +                | −              | +               |
| Complete overdominant* | −                | +              | +               |
| Codominant          | + +              | +              | +               |

Table 1. Multiple comparisons of genotype effects and possible modes of inheritance. Note: MM: homozygous mutant genotype; MW: heterozygous mutant genotype; WW: wild genotype. *ORi is pooled odds ratio; **complete overdominant model: OR2 is at a lesser risk than both OR1 and OR3. + means a significant result; + + means the effect size is greater than +; − means a non-significant result.

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22, 34, 35, 37. The source of control consisted of hospital-based (HB) 17, 23, 24 and population-based (PB)25, 26, 31 groups. The mean age ranged from 28.8 to 45.6 years old in MS patients and from 29.4 to 54.5 years old in controls, while the percentage of females ranged from 67.50% to 71.60% in MS patients and from 49.20% to 81.90% in controls. The MS patients were mainly stratified into relapsing remitting (RR), secondary progressive (SP), and primary progressive (PP) groups, and their frequency varied from 52.9% to 91% in the RR groups, 0 to 26% in the SP
In this meta-analysis, we found that the IL7RA rs3194051 polymorphism was associated with MS risk. Eight studies containing a total of 7292 MS patients and 8142 healthy controls were included in this meta-analysis to investigate the association between the rs3194051 polymorphism and MS risk. The estimated OR1, OR2, and OR3 were 1.21 (95% CI: 1.06–1.37), 0.97 (95% CI: 0.90–1.03), and 1.17 (95% CI: 1.02–1.33), respectively, suggesting a recessive genetic effect (GG vs. GA + AA) of MS risk allele G. A fixed effect model was conducted because only moderate heterogeneity ($I^2 = 43\%$) existed in the recessive model. A statistically significant association was observed between the rs3194051 SNP and the susceptibility to MS ($OR = 1.22, 95\% CI: 1.08–1.38$) (Table 4 and Fig. 2A). In addition, the statistical power calculation based on the inclusion of sample size gave a value of 0.99, which indicated powerful evidence for the conclusion of this significant association.

**IL7RA rs987107 polymorphism and MS risk.** A total of 3898 MS patients and 4858 matched-controls across six studies were genotyped for the rs987107 polymorphism and MS susceptibility in this retrospective analysis. The estimated OR1, OR2, and OR3 were 1.41 (95% CI: 1.20–1.67), 0.96 (95% CI: 0.88–1.05), and 1.48 (95% CI: 1.25–1.75), respectively. These results suggested that the recessive model was also the most appropriate to be used here. We pooled the genotype data using a fixed effect model due to no between-study heterogeneity ($I^2 = 0\%$). The combined data indicated that the rs987107 variant might contribute to the development of MS ($OR = 1.44, 95\% CI: 1.22–1.69$) (Table 4 and Fig. 2B). The sample sizes of the six studies allowed full power ($power = 1$) to detect this OR value, which showed strong evidence for the increased association between the rs987107 polymorphism and MS risk.

**IL7RA rs11567686 polymorphism and MS risk.** In this meta-analysis, we collected five related studies with a total of 1353 MS cases and 1544 controls. Pooling these studies yielded an OR1 of 1.23 (95% CI: 0.98–1.56), OR2 of 1.16 (95% CI: 0.99–1.36), and OR3 of 1.05 (95% CI: 0.85–1.30). The confidence intervals of OR1 and OR2 were slightly greater than 1 which could be considered as marginally significant. Thus, the dominant pattern was regarded as the most applicable model in this case. Due to unobserved heterogeneity among studies ($I^2 = 0\%$), we used the fixed-effect model to calculate the pooled OR under the dominant model. The result indicated that groups, and 0 to 19.8% in the PP groups. In addition, the NOS results suggested that all eligible studies in this meta-analysis were of high quality because their scores were equal to or greater than six points.

| IL7RA polymorphisms | First Author | Year | No. of Cases | No. of Controls | Cases MM | MM WW | WW MM | Power analysis* |
|----------------------|--------------|------|--------------|--------------|---------|--------|--------|----------------|
| rs3194051(8) (A>G)   | Zhang        | 2005 | 667          | 558          | 54      | 235    | 378    | 0.01, 0.98     |
|                      | Gregory      | 2007 | 438          | 478          | 46      | 157    | 235    | 0.49, 0.78     |
|                      | Lundmark     | 2007 | 1785         | 2564         | 149     | 657    | 979    | 0.33, 0.99     |
|                      | O'Doherty(1) | 2008 | 208          | 413          | 18      | 85     | 105    | 0.87, 0.15     |
|                      | O'Doherty(2) | 2008 | 463          | 531          | 31      | 178    | 254    | 1.00, 0.05     |
|                      | Akkad        | 2009 | 1279         | 857          | 102     | 511    | 666    | 0.80, 0.11     |
|                      | Bahlo        | 2009 | 2255         | 2308         | 152     | 868    | 1235   | 0.96, 0.07     |
|                      | Kallio       | 2009 | 197          | 433          | 13      | 76     | 108    | 1.00, 0.09     |
| rs987107(6) (C>T)    | Zhang        | 2005 | 528          | 563          | 53      | 186    | 289    | 0.33, 0.93     |
|                      | Gregory      | 2007 | 438          | 479          | 46      | 157    | 235    | 0.57, 0.79     |
|                      | Lundmark     | 2007 | 1779         | 2565         | 152     | 651    | 976    | 0.35, 0.99     |
|                      | O'Doherty(1) | 2008 | 207          | 413          | 17      | 83     | 107    | 1.00, 0.12     |
|                      | O'Doherty(2) | 2008 | 462          | 527          | 31      | 178    | 253    | 1.00, 0.05     |
|                      | Jäger        | 2013 | 484          | 311          | 48      | 194    | 242    | 0.77, 0.77     |
| rs11567686(5) (A>G)  | Teutsch      | 2003 | 176          | 176          | 19      | 79     | 78     | 0.86, 0.12     |
|                      | Broux        | 2010 | 65           | 33           | 8       | 29     | 28     | 1.00, 0.48     |
|                      | Hoe          | 2010 | 810          | 991          | 102     | 370    | 338    | 1.00, 0.30     |
|                      | Heidari      | 2011 | 100          | 100          | 18      | 51     | 31     | 0.84, 0.24     |
|                      | Haj          | 2015 | 202          | 244          | 49      | 99     | 54     | 0.02, 0.70     |
| rs11567685(8) (T>C)  | Teutsch      | 2003 | 101          | 90           | 7       | 37     | 57     | 0.48          |
|                      | Booth        | 2005 | 363          | 182          | 28      | 134    | 201    | 0.04          |
|                      | Akkad        | 2009 | 1304         | 889          | 103     | 507    | 694    | 0.87          |
| rs11567685(8) (T>C)  | Teutsch      | 2005 | 101          | 90           | 7       | 37     | 57     | 0.48          |
|                      | Booth        | 2005 | 363          | 182          | 28      | 134    | 201    | 0.04          |
|                      | Akkad        | 2009 | 1304         | 889          | 103     | 507    | 694    | 0.87          |

Table 2. IL7RA genotypic distribution among MS cases and controls in the included studies. Note: MM: homozygous mutant genotype; MW: heterozygous mutant genotype; WW: wild genotype; NA: not available; power analysis*: rs3194051 (recessive model); rs987107 (recessive model); rs11567686 (dominant model).
### IL7RA polymorphisms

| rs3194051(8) (A > G) | First Author | Year | Area | Ethnicity | Genotyping method | Diagnostic criteria | Source of controls | NOS score |
|----------------------|--------------|------|------|-----------|-------------------|---------------------|-------------------|-----------|
| Zhang                | 2005         | Sweden | Caucasian | PCR | Poser | HB | 7 |
| Gregory              | 2007         | USA | Caucasian | RT-PCR | NA | HB | 8 |
| Lundmark             | 2007         | Nordic countries | Caucasian | RT-PCR | Poser&McDonald | NA | 7 |
| O’Doherty(1)         | 2008         | USA | Caucasian | NA | NA | NA | 6 |
| O’Doherty(2)         | 2008         | Northern Ireland | Caucasian | NA | NA | NA | 6 |
| Akkad                | 2009         | Germany | Caucasian | PCR-RFLP | Poser | NA | 8 |
| Bahlo                | 2009         | Australia, New Zealand | Caucasian | NA | Poser&McDonald | NA | 7 |
| Kallo                | 2009         | Finland | Caucasian | RT-PCR | Poser&McDonald | NA | 8 |
| Zhang                | 2005         | Sweden | Caucasian | PCR | Poser | HB | 7 |
| Gregory              | 2007         | USA | Caucasian | RT-PCR | NA | HB | 8 |
| Lundmark             | 2007         | Nordic countries | Caucasian | RT-PCR | Poser&McDonald | NA | 7 |
| O’Doherty(1)         | 2008         | USA | Caucasian | NA | NA | NA | 6 |
| O’Doherty(2)         | 2008         | Northern Ireland | Caucasian | NA | NA | NA | 6 |
| Jager                | 2013         | Germany | Caucasian | RT-PCR | McDonald | PB | 7 |

### rs987107(6) (C > T)

| First Author | Year | Area | Ethnicity | Genotyping method | Diagnostic criteria | Source of controls | NOS score |
|--------------|------|------|-----------|-------------------|---------------------|-------------------|-----------|
| Teutsch      | 2003 | Australia | Caucasian | PCR-RFLP | Poser | HB | 6 |
| Broux        | 2010 | Belgium | Caucasian | PCR-RFLP | NA | NA | 7 |
| Hoe          | 2010 | Australia | Caucasian | PCR-RFLP | NA | NA | 6 |
| Herdari      | 2011 | Iran | Caucasian | PCR-RFLP | McDonald | PB | 6 |
| Haj          | 2015 | Iran | Caucasian | PCR-RFLP | McDonald | PB | 6 |
| Teutsch      | 2003 | Australia | Caucasian | PCR-RFLP | Poser | HB | 6 |
| Booth        | 2005 | Australia | Caucasian | RT-PCR | Poser&McDonald | NA | 7 |
| Akkad        | 2009 | Germany | Caucasian | PCR-RFLP | Poser | NA | 8 |
| Broux        | 2010 | Belgium | Caucasian | RT-PCR | NA | NA | 8 |
| Hoe          | 2010 | Australia | Caucasian | PCR-RFLP | NA | NA | 6 |
| Herdari      | 2011 | Iran | Caucasian | PCR-RFLP | McDonald | PB | 6 |
| Basyan       | 2014 | Jordan | Caucasian | PCR-RFLP | NA | NA | 7 |
| Haj          | 2015 | Iran | Caucasian | PCR-RFLP | McDonald | PB | 6 |

### rs11567686(5) (A > G)

| First Author | Year | Area | Ethnicity | Genotyping method | Diagnostic criteria | Source of controls | NOS score |
|--------------|------|------|-----------|-------------------|---------------------|-------------------|-----------|
| Teutsch      | 2003 | Australia | Caucasian | PCR-RFLP | Poser | HB | 6 |
| Booth        | 2005 | Australia | Caucasian | RT-PCR | Poser&McDonald | NA | 7 |
| Akkad        | 2009 | Germany | Caucasian | PCR-RFLP | Poser | NA | 8 |
| Broux        | 2010 | Belgium | Caucasian | PCR-RFLP | NA | NA | 7 |
| Hoe          | 2010 | Australia | Caucasian | PCR-RFLP | NA | NA | 6 |
| Herdari      | 2011 | Iran | Caucasian | PCR-RFLP | McDonald | PB | 6 |
| Haj          | 2015 | Iran | Caucasian | PCR-RFLP | McDonald | PB | 6 |
| Teutsch      | 2003 | Australia | Caucasian | PCR-RFLP | Poser | HB | 6 |
| Broux        | 2010 | Belgium | Caucasian | RT-PCR | Poser&McDonald | NA | 7 |
| Hoe          | 2010 | Australia | Caucasian | PCR-RFLP | NA | NA | 6 |
| Herdari      | 2011 | Iran | Caucasian | PCR-RFLP | McDonald | PB | 6 |
| Basyan       | 2014 | Jordan | Caucasian | PCR-RFLP | NA | NA | 7 |
| Haj          | 2015 | Iran | Caucasian | PCR-RFLP | McDonald | PB | 6 |

### rs11567685(8) (T > C)

| First Author | Year | Area | Ethnicity | Genotyping method | Diagnostic criteria | Source of controls | NOS score |
|--------------|------|------|-----------|-------------------|---------------------|-------------------|-----------|
| Teutsch      | 2003 | Australia | Caucasian | PCR-RFLP | Poser | HB | 6 |
| Broux        | 2010 | Belgium | Caucasian | PCR-RFLP | NA | NA | 7 |
| Hoe          | 2010 | Australia | Caucasian | PCR-RFLP | NA | NA | 6 |
| Herdari      | 2011 | Iran | Caucasian | PCR-RFLP | McDonald | PB | 6 |
| Basyan       | 2014 | Jordan | Caucasian | PCR-RFLP | NA | NA | 7 |
| Haj          | 2015 | Iran | Caucasian | PCR-RFLP | McDonald | PB | 6 |

| Table 3. Main characteristics of studies included in the meta-analysis. Note: HB: hospital-based; PB: population-based; NA: not available; RR: relapsing remitting; SP: secondary progressive; PP: primary progressive; PR: progressive-relapsing. |
the rs11567686 polymorphism might confer an increased risk of MS (OR = 1.18, 95% CI: 1.01–1.37) (Table 4 and Fig. 2C) with a high statistical power value of 0.87.

**IL7RA rs11567685 polymorphism and MS risk.** Eight eligible investigations with 3162 cases and 2743 normal people were included in the analysis of the association between the rs11567685 variant and susceptibility to MS. Pooling these studies generated an OR1 of 0.96 (95% CI: 0.78–1.18), OR2 of 0.90 (95% CI: 0.81–1.00), and OR3 of 1.05 (95% CI: 0.85–1.30). According to these estimates, we could not select the ideal pattern using the method of determined genetic model. Therefore, six potential genetic models were performed; and the remaining three models are allelic model (OR = 0.94, 95% CI: 0.87–1.02), dominant model (OR = 0.91, 95% CI: 0.82–1.22), and recessive model (OR = 1.00, 95% CI: 0.82–1.22), respectively. The fixed effect model was conducted for all of the above statistical analyses because of no significant heterogeneity. No evidence of significant association was found under all possible genetic models, along with low statistical power (Table 4 and Fig. 2D).

**Sensitivity analysis and cumulative meta-analysis.** A leave-one-out sensitivity analysis showed that the pooled ORs were not significantly changed for rs3194051, rs987107 and rs11567686 variants when all the included studies, containing those three studies distracted from HWE (investigated by Zhang et al. and Haj et al.), were excluded one by one. This indicated that our results were robust and reliable (data not shown).

In the cumulative meta-analysis sorted by sample size, the pooled results detected a dynamic tendency of increased association between the minor variants of these three loci and the risk of MS under their most applicable genetic models, which confirmed our earlier conclusion. As an example, Fig. 3 described a tendency of increased association between the rs987107 polymorphism and MS risk in the recessive model. The combined ORs were not significantly fluctuated from accumulating each new study sample, which was also consistent with the findings of the sensitivity analysis.

**Publication bias.** In the present meta-analysis publication bias was estimated by Begg's funnel plot and Egger's quantitative test. From the shape of funnel plots, we did not observe any asymmetric signal under all analyzed models (Fig. 4 illustrates no publication bias for the association of the rs987107 polymorphism with MS.

| Table 4. Meta-analysis of IL7RA polymorphisms on MS. Note: bold: significant P-value (<0.05); bold*: marginal association (0.05 < P-value < 0.1); #Suggested model. |
|---|
| **IL7RA variants** | **Genetic comparison** | **F(%)** | **Effect model** | **OR (95%CI)** | **P<sub>cat</sub>** | **Egger’s test** (t, p) | **Statistical Power** |
| rs3194051 (8) | GG vs. AA | 31 | Fixed | 1.21 (1.06, 1.37) | <0.01 | | |
| | GA vs. AA | 0 | Fixed | 0.97 (0.90, 1.03) | 0.32 | | |
| | GG vs. GA | 76 | Random | 1.17 (1.02, 1.33) | 0.02 | | |
| | GG vs. AA + GA* | 43 | Fixed | 1.22 (1.08, 1.38) | <0.01 | (0.61, 0.56) | 0.99 |
| rs987107 (6) | TT vs. CC | 0 | Fixed | 1.41 (1.20, 1.67) | <0.01 | | |
| | TC vs. CC | 0 | Fixed | 0.96 (0.88, 1.05) | 0.34 | | |
| | TT vs. TC | 0 | Fixed | 1.18 (1.25, 1.75) | <0.01 | | |
| | TT vs. CC + TC* | 0 | Fixed | 1.44 (1.22, 1.69) | <0.01 | (−0.21, 0.85) | 1.00 |
| rs11567686 (5) | GG vs. AA | 0 | Fixed | 1.23 (0.98, 1.56) | 0.07* | | |
| | GA vs. AA | 0 | Fixed | 1.16 (0.99, 1.36) | 0.06* | | |
| | GG vs. GA | 0 | Fixed | 1.05 (0.85, 1.30) | 0.63 | | |
| | GG vs. AA + AA* | 0 | Fixed | 1.18 (1.01, 1.37) | 0.03 | (2.47, 0.09) | 0.87 |
| rs11567685 (8) | CC vs. TT | 0 | Fixed | 0.96 (0.78, 1.18) | 0.72 | (−1.05, 0.34) | 0.09 |
| | CT vs. TT | 21 | Fixed | 0.90 (0.81, 1.00) | 0.06* | (−1.54, 0.18) | 0.77 |
| | CC vs. CT | 0 | Fixed | 1.05 (0.85, 1.30) | 0.63 | (−0.09, 0.93) | 0.08 |
| | C vs. T | 17 | Fixed | 0.94 (0.87, 1.02) | 0.15 | (−1.69, 0.14) | 0.56 |
| | CC vs. CT + TT | 22 | Fixed | 0.91 (0.82, 1.01) | 0.07* | (−1.70, 0.14) | 0.72 |
| | CC vs. TT + CT | 0 | Fixed | 1.00 (0.82, 1.22) | 1.00 | (−0.62, 0.56) | 0.05 |
The Egger's test also did not display any evidence of obvious publication bias for the association of these SNPs with MS risk (Table 4).
Discussion

Multiple sclerosis, an immune mediated disease in which T cells play an important role, is the chronic inflammatory neurologic disorder of the CNS affecting young adults, especially women. There is growing evidence that genetic factors might play vital roles in MS development. Human leukocyte antigen (HLA), for example, has been widely reported to have a strong effect on MS. IL7RA, on the other hand, serves as the first non-HLA gene that was also determined to have an association with MS susceptibility. The present study is the first meta-analysis on the relationship between IL7RA variants and development of MS.

IL7R functions as a significant pleiotropic receptor for the signaling pathway of IL7 in autoimmune disease. IL7 interacts with the IL7R common gamma chain (namely CD132) and its alpha chain (namely IL7RA or CD127), forming the signaling complex in the IL7 cascade. The IL7/IL7R interaction is vital to the survival, proliferation, and differentiation of T-cells, especially CD4+ T-cells, which exist in the inflammatory lesions of the people with multiple sclerosis. Thus, there is no doubt that an experimental investigation of the association of polymorphisms in the IL7RA gene with MS could help us to better understand the pathogenic mechanisms and develop molecularly targeted agents for MS treatment. Previous case-control studies have reported on the association between multiple IL7RA variants and the risk of MS, but the conclusions were inconsistent because of low statistical power, small sample size, or the complex gene-gene and gene-environment interactions involved in the disease. Therefore, to evaluate the function of IL7RA polymorphisms on MS more precisely, we conducted this meta-analysis, which increased statistical power by pooling the available data from individually published studies.

We collected eight studies on the rs3194051 variant and six studies on the rs987107 polymorphism; the baseline characteristics of these studies on genetic polymorphism of these two loci shared considerable similarities. The combined results from our meta-analysis indicated that both of these IL7RA polymorphisms were associated with increasing MS risk with high statistical power; this finding is well-matched with the conclusions of two individual studies investigated by Zhang et al. and Lundmark et al. Among the other studies that suggested no obvious association between these two polymorphisms and MS risk, one involving rs3194051 and two involving rs987107 conducted by Gregory et al. and Jäger et al., respectively, was actually shown to have a significant trend of developing MS since their individual confidence intervals were just slightly across 1 (Fig. 2A,B). Moreover, the studies by O'Doherty et al. on both polymorphisms and the study by Kallio on the rs3194051 minor allele only suggested no relationship with MS but had relatively small sample sizes. Further, the distinct main features of cases and controls in individual studies, such as the different degrees of disease development among cases and the dissimilar genotype distributions in different geographical regions, might explain the lack of a significant association between the rs3194051 polymorphism and MS in the other two studies by Akkad et al. and Bahlo et al. Thus, our conclusions of the association of both rs3194051 and rs987107 polymorphisms with MS risk should be reliable, especially with the high statistical power calculated in this meta-analysis.

We included five studies in this meta-analysis that investigated the relationship between the rs11567686 polymorphism and MS risk. The pooled results under the dominant model concluded that the rs11567686 minor alleles were statistically significantly associated with the susceptibility to MS. This conclusion would be reliable since it was also derived from a combined odds ratio with high statistical power. Though all the included studies individually indicated that rs11567686 polymorphism was not related with increasing MS risk, two studies, especially the one investigated by Hoe et al. with the largest sample size, showed a possibility of marginal association between this polymorphism and the disease (as shown in Fig. 2C). In addition, the association was also found in the stratified subgroup of SP + PP MS patients when compared with healthy controls (P < 0.05) from two reports. Thus, the significant finding that the combined result was different from that of any of the included studies reflected the advantage of meta-analysis, by which we might properly evaluate the real genetic effect on disease development with greater statistical power through pooling all samples or synthesizing overall data available in previous studies.

In this retrospective analysis, eight studies were included to explore the effect of the rs11567685 variant on multiple sclerosis. For this association study we could not derive its most applicable genetic model. Thus, we utilized six potential genetic models to explore the association between the rs11567685 polymorphism and the...
predisposition to MS. Our results under all models suggested no relationship between this polymorphism and MS development, which was in agreement with the results from seven studies. Only one study conducted by Ibyayan et al. indicated a association between the rs11567685 polymorphism and MS development; it is possible that the contradictory conclusion from this study might be attributed to its small sample size. Additionally, low between-study heterogeneity and a lack of publication bias obtained from this analysis further suggests the credibility of our conclusion.

There are four advantages in our study. First, meta-analysis has been recognized as an effective method to address a wide variety of clinical questions in evidence-based medicine by combining the results of multiple previously reported quantitative studies. To the best of our knowledge, this is the first meta-analysis on the issue of IL7RA variants with susceptibility to MS. Second, our meta-analysis had a relatively large sample size and strong statistical power, which helped to make the conclusion more convincing. Third, no obvious between-study heterogeneity and publication bias were observed in this retrospective analysis. Fourth, the results from both sensitivity analysis and cumulative meta-analysis confirmed the robustness of our conclusions.

The findings from the studies reviewed in this analysis should be interpreted with caution for several reasons. First, MS is a multifactorial disease and many other factors including age, gender, control of source, latitude, genotyping methods and gene-gene interactions might contribute to its susceptibility, but due to the insufficient data, we could not perform corresponding subgroup and stratified analyses to further explore in-depth reasons for MS pathogenesis. Second, our results might not be generalizable to other ethnicities because of all of the included studies involved Caucasians. Third, a language bias may have existed because this meta-analysis only included English articles due to database limitations. Despite the above limitations, the present study is the first comprehensive meta-analysis with high statistical power that helps to expand our knowledge about the molecular biology and functional significances of IL7RA polymorphisms and the relationship with MS susceptibility.

Taken together, our meta-analysis indicated that IL7RA rs3194051, rs987107 and rs11567686 variants might contribute to the genetic susceptibility of MS, while the rs11567685 polymorphism had no effect on multiple sclerosis. While these results could provide a better understanding of MS pathogenesis, future well-designed studies with large sample sizes, gene-gene and gene-environment interactions are needed to confirm our present conclusions.

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Author Contributions
H.L. and J.H. carried out the experiments and wrote the first draft. M.D. performed sensitivity analysis and cumulative meta-analysis. Y.L. and B.X. participated in reviewing potential articles and created tables and figures. X.L. and Z.H. designed this research study and revised this manuscript. Additionally, all authors have approved the final draft.

Additional Information

Competing Interests: The authors declare that they have no competing interests.

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