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Review article

Association of IL4 and IL4R polymorphisms with multiple sclerosis susceptibility in Caucasian population: A meta-analysis

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ABSTRACT

Background: Previous studies have suggested a role for interleukin-4 (IL4) and its receptor (IL4R) gene in susceptibility to multiple sclerosis (MS), but the results remain controversial and under-powered.
Objectives: To investigate the contradictory results, we performed a meta-analysis to assess the possible association between polymorphisms of the IL4 rs2243250 (C/T), variable number of tandem repeat (VNTR) polymorphism in intron-3 (I3(709)VNTR), IL4R rs1801275 (T/C) and MS in Caucasian populations.
Methods: A comprehensive search was conducted to identify all case-control or cohort design studies. The fixed or random effect pooled measure was selected based on the homogeneity test among studies that was evaluated with I^2. Publication bias was estimated using the Begg's and Egger's test.
Results: A total of ten studies were included in the meta-analysis. The crude odds ratios (ORs) with 95% confidence intervals (95% CI) were calculated to evaluate the association. Overall, after excluding articles deviating from Hardy–Weinberg equilibrium in controls and sensitive analysis, the meta-analysis showed a significant association between polymorphism of IL4 rs2243250 and MS susceptibility in allele model (OR = 1.209, 95% CI = 1.022–1.429, $P = 0.026$) and dominant model (OR = 1.225, 95% CI = 1.013–1.480, $P = 0.036$). However, no significant association was found between polymorphisms of IL4 I3(709)*VNTR, IL4R rs1801275 and MS susceptibility, respectively.
Conclusions: The meta-analysis indicates that the T allele, CT and TT genotype of polymorphism of IL4 rs2243250 (C/T) may reduce the risk of MS in Caucasian populations, while polymorphisms of IL4 I3(709)*VNTR and IL4R rs1801275 may not associated with risk of MS in Caucasian populations.

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1. Introduction

Multiple sclerosis (MS) is a chronic inflammatory disorder of the central nervous system characterized by demyelination, diffuse neurodegeneration, varying degrees of axonal pathology and a relapsing or progressive course [1–2]. The etiology and the triggered mechanisms of MS are still not clear, in spite of many epidemiological, immunological and neurological studies. However, it is generally believed that lots of genetic, immunological and environmental factors are involved [3]. Owing to nature of the immune response modulation, a number of studies have focused on the content of cytokines in MS [4–6]. It has been long accepted that the daedal balance between cytokines of type 1 helper cells (Th1) and type 2 helper cells (Th2) in the immune system play important roles in the pathogenesis of MS [7–8]. Meanwhile, after a multitude of genome-wide linkage and association screens into the genetics of MS, many genes have emerged for the potential involvement with it [9–11].

Much of the research has examined in interleukin 4 (IL4) and its receptor (IL4R) which are associated with the balance and disease progression of MS [12–14]. IL4 is an 18 kDa glycoprotein that regulates Th1/Th2 cytokine balance with decisive effect [15–16]. It is encoded by IL4 gene at 5q23-31, which is 10 kb in size and consisting of 4 exons and 3 introns with a cluster of other cytokine genes (IL3, IL5, IL9, IL13, and IL15, etc.) [17]. Pleiotropic activities of IL4 are mediated by its specific receptor IL4R at the surface of the target cell to play a role in the immune system [18]. The IL-4R gene, at 16p11-p12, encodes a subunit of the IL4R heterodimer, a molecule critical to T helper cell differentiation and commitment [19]. Polymorphism of IL4R amino-acid residues, particularly the Ile50Val, Ser478Pro and Gln551Arg, are proposed to be functionally impact the signaling [20–22]. Some polymorphisms in the IL4 and IL4R gene were identified including rs2243250 (C/T), variable number of tandem repeat (VNTR) polymorphism in intron-3 (I3(709)VNTR and VNTR B1) and rs1801275 (T/C) (Q551R and Q576R). It had been confirmed that rs2243250 was associated with rheumatic arthritis, autoimmune thyroid diseases and liver disease, etc. [23–25]. It also reported that rs1801275 was involved in atopic eczema risk [26].

Recently several research groups have specifically explored the involvement of the rs2243250, I3(709)*VNTR and rs1801275 in the susceptibility and severity of MS [25,27–29]. However, the results in the publications remain controversial, and most of the individual studies have small sample sizes as well as lack power to detect mild gene effects. Hence, we performed a meta-analysis of population-based case-control studies to more accurately estimate the susceptibility of MS in Caucasian population and to evaluate the heterogeneity between different studies.

2. Methods and materials

2.1. Search strategy

We performed a search for all published papers in databases of PubMed, MEDLINE, EMBASE, Web of Science, CNKI (China National Knowledge Infrastructure) and WanFang Data up to December 10, 2015. The search strategy used the following keywords: ("Multiple sclerosis" or "MS") and ("interleukin 4" or "IL4" or "rs2243250" or "-590C-to-T" or "I3(709)*VNTR") and/or ("interleukin 4 receptor" or "IL4R" or "rs1801275" or "Q551*R" or "Q576*R") and/or ("polymorphism" or "SNP" or "variant"). We also reviewed the bibliographies of the included articles as well as those of relevant studies to identify additional studies not captured by our database searches.

2.2. Inclusion and exclusion criteria

The inclusion criteria were as follows: (1) full-text articles; (2) case-control study that focused on the relationships of IL4 rs2243250, I3(709)*VNTR and IL4R rs1801275 variants with MS; (3) provide sufficient data about IL4 rs2243250 or I3(709)*VNTR as well as IL4R rs1801275 genotypes and genotype distributions to estimate the odds ratio (OR) with 95% confidence intervals (95% CI); (4) the cases and controls recruited from the same geographic areas. Exclusion criteria: (1) irrelevant papers; (2) not case-control studies; (3) based on incomplete data; (4) letters, reviews, meta-analyses. Study selection was achieved by two investigators independently, according to the inclusion and exclusion criteria by screening the title, abstract and full-text. Any dispute was solved by discussion.

2.3. Data extraction

Data were independently extracted by two investigators who reached an agreement on all of the items. The following information was extracted from each study: first author, publication year, country, ethnic origin of the studied population, sample size, distributions of genotype and allele, mean age.

2.4. Statistical analysis

The MS susceptibility associated with IL4 rs2243250, I3(709)*VNTR and IL4R Q551*R was estimated for each study by crude odds ratios (ORs) with 95% confidence intervals (95% CI). We estimated the association under five different types of ORs, including allele model (rs2243250: C vs. T, I3(709)*VNTR: B1 vs. B2, rs1801275: T vs. C), homozygote model (rs2243250: CC vs. TT, I3(709)*VNTR: B2B2 vs. B1B1, rs1801275: TT vs. CC), heterozygote model (rs2243250: CC vs. CT, I3(709)*VNTR: B2B2 vs. B1B2, rs1801275: TT vs. CT), dominant model (rs2243250: CC vs. TT + CT, I3(709)*VNTR: B2B2 vs. B1B1 + B1B2, rs1801275: TT vs. CC + CT) and recessive model (rs2243250: CT + CC vs. TT, I3(709)*VNTR: B2B2 + B1B2 vs. B1B1, rs1801275: CT + TT vs. CC). We used the Chi-squared statistic to assess the Hardy–Weinberg equilibrium (HWE) of the genotype frequencies of control groups and the significance was set as $P < 0.05$. I^2-statistics and Q-test was used to assess the degree of heterogeneity between studies. If significant heterogeneity existed in studies ($I^2 > 50\%$), the random-effect model was used. Otherwise, the fixed-effect model was adopted as the pooling method [30]. Begg's funnel plots and Egger's linear regression test were performed to investigate potential publication bias [31], the *P*-value of Begg's test and Egger's test < 0.05 was considered a significant publication bias [32]. All statistical analyses were performed by using STATA version 12.0 (Stata Corporation, College Station, Texas 77845 USA).

3. Results

3.1. Characteristics of studies

We found 10 published articles with 12 outcomes eligible for this meta-analysis on the relation of polymorphisms in IL4 rs2243250, I3(709)*VNTR and IL4R rs1801275 variants with MS. The literature selection process was shown in Fig. 1. Forty-six articles were excluded. Finally, in the current study, ten eligible case-control studies that meet the inclusion criteria were included in our meta-analysis [8,19,27,29,33–38]. General characteristics, the IL4 and IL4R allele and genotype distributions in the included articles are showed in Table 1.

3.2. Association between IL4 rs2243250 polymorphism and MS susceptibility

The association between IL4 rs2243250 polymorphism and the risk of MS was analyzed in 5 independent studies. Results of pooled analysis are summarized in detail in Table 2. We performed a meta-analysis of overall Caucasian population. Fixed-effect model was used in allele model ($I^2 = 40.6\%$), homozygote model ($I^2 = 37.4\%$), heterozygote