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Review article

Interleukin 7 receptor polymorphisms and the risk of multiple sclerosis: A meta-analysis

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ABSTRACT

Background: Multiple sclerosis (MS) is considered as the most common chronic inflammatory neurologic disorder diagnosed in young adults. Both environmental and genetic factors may influence risk of MS development. Interleukin 7 receptor (IL7R) is one of the most studied gene polymorphism on MS that may play a possible role in MS development. The most studied polymorphism of IL7R gene is "rs6897932" polymorphism on IL7Rα gene (IL7RA).

Methods: PubMed, Scopus, and Google scholar databases were searched for all of related studies on the association of IL7RA polymorphism with single nucleotide polymorphism (SNP) ID of "rs6897932" and the risk of MS through August 07, 2015. After exclusion of irrelevant articles, 11 eligible studies were selected, which were analyzed to determine an association between the MS and IL7R T244I polymorphism (rs6897932). For identification of this association, odds ratios (ORs) and 95% confidence interval (95% CI) were calculated. Four models of allelic (T vs. C), co-dominant genotype (TT vs. CC), dominant (TT+CT vs. CC), and recessive genotypes (TT vs. CT+CC) were considered to check the possible role of rs6897932 polymorphism in MS. A sensitivity analysis was conducted to find the reliability of this study. Furthermore, funnel plots were used to evaluate publication bias.

Results: A total of 11 case-control studies were identified through this meta-analysis, which containing 6752 cases and 7349 controls. In overall, the frequency of the C allele was found to be higher in patients with MS compared to healthy controls (75.66% vs. 72.19%). T allele was significantly associated with the decreased risk of MS in a random effect model (T vs. C: OR=0.84, 95% CI=0.77–0.92, *P*-value <0.001). In the co-dominant, dominant, and recessive genotypes models, a significant association between the IL7R T244I polymorphism and MS risk was demonstrated (TT vs. CC: OR=0.70, 95% CI=0.61–0.80, *P*-value <0.001; TT+CT vs. CC: OR=0.82, 95% CI=0.73–0.92, *P*-value <0.001; TT vs. CT+CC: OR=0.76, 95% CI=0.66–0.87, *P*-value <0.001). Sensitivity analysis revealed that this study is reliable. There was no evidence of publication bias.

Conclusion: It was demonstrated that the IL7R T244I polymorphism was associated with susceptibility to MS. However, more well-designed studies with large sample size are needed to validate this association between this single nucleotide polymorphism and MS.

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1. Introduction

Multiple sclerosis (MS) is a chronic inflammatory demyelinating disease of the central nervous system which results in demyelination and axonal damage (Pender and Greer, 2007). It can be categorized as an autoimmune disease that affects the central nervous system and is characterized by multiple lesions of the central nervous system (Hafler, 2004; Rosati, 2001). It is estimated that this disease affects almost 2.5 million people around the world (Rosati, 2001). There are four different types of MS, including relapsing-remitting (RR), secondary-progressive (SP), primary-progressive (PP), and progressive-relapsing (PR). Among these subtypes, RR is the most common subtype of MS, which usually is followed by SP in more than half of the patients (Compston and Coles, 2008). The rarest type is PR, with approximately five percent among MS patients. With time, recovery from each episode is incomplete and persistent symptoms accumulate (Compston and Coles, 2008).

The frequently of MS is more in women compared to the men. In fact, the ratio of women with MS to men with this disease is 2–1 (Hawkins and McDonnell, 1999). MS is not considered an inherited disorder. However, there is some evidence that genetic variations may affect the risk of MS development. Indeed, it is believed that MS development is attributed mainly to genetic susceptibility combined with environmental factors (Belbasis et al. , 2015; Dyment et al. , 2004; Ebers, 2008).

Several studies have demonstrated that cytokines have key roles in oligodendrocyte death and axonal degeneration (Bjartmar et al., 2003; Matsushita et al., 2013; Stepien et al., 2013). Recently, the therapeutic potential of targeting of interleukins in treatment of autoimmune diseases, such as MS were discussed, which highlights the critical roles of interleukins in development of these diseases (Tavakolpour, 2016). There are several lines of evidence that the receptor of interleukin 7 (IL-7) is associated with the risk of MS. IL-7 receptor (IL-7R) gene is located on short arm of chromosome 5 at position 13 (5p13). It consists of common γ-chain (IL7Rγ) and α-chain (IL7Rα), which are also known as CD132 and CD127, respectively.

Several studies have discussed on the role of T244I variant of the IL7RA gene, rs6897932 in the MS disease. The majority of them provided evidence for the association of MS and this variant. Nevertheless, some of them did not report any association. According to previous studies, C allele is significantly more frequent compared to the T allele. It was indicated that C allele in rs6897932 position can result in a higher risk of MS. Indeed, CC and CT genotypes can increase the risk of MS by 1.5 and 1.3 fold, if TT genotype be considered with a normal risk. Based on several studies on polymorphism of rs6897932 with the inconsistent results, it is difficult to speculate about the association of this SNP with the MS risk. In order to gain a unique conclusion, a meta-analysis was performed, which used the eligible studies that met all of designed criteria. Although this association was confirmed in previous studies, it is essential to re-check that with the more up-to-date studies.

2. Material and methods

PubMed, Scopus and Google scholar databases were searched to find associated articles with the MS and rs6897932 polymorphism. The last search update was for August 07, 2015 using the keywords “T244I” or “rs6897932” and “polymorphism” or “genotype” or “SNP” and “interleukin 7 receptor” or “IL7R” and “Multiple sclerosis” or “MS”.

2.1. Selection criteria

No restrictions were placed on race, ethnicity or geographic area. However, the included studies must meet all of following criteria.

1. The studies must be designed as a case-control study.
2. The outcome should be MS, regardless of the subtype.
3. At least two groups, including case (patients with MS) group and control (healthy control) group have to be in study.
4. The frequency of allele and all of three genotypes, including CC, CT, and TT for both groups of case and control must be given, or it could be calculated.
5. The full articles have to be published in English language.

During the full-text analyzing, studies in which the number of wild-type genotypes could not be ascertained were excluded. Review articles, systematic reviews, and meta-analyses were excluded, but their references were checked for possible eligible studies, which followed above criteria.

2.2. Data extraction

Essential data were extracted from each article. All the extracted data, including year of publishing, country, genotyping method, number of cases and controls, and frequency of genotypes and alleles were categorized. The final extended data were rechecked carefully and were compared with the original articles to ensure the accuracy of data. Patients with different MS subtypes, including RR, SP, PP, and PR were included within the case group.

2.3. Statistically analysis

Statistically analyses were carried out using the Review manager software, version 5.3 and Comprehensive Meta-Analysis (CMA) software, version 2. All analyses were conducted using the Review manager except sensitivity analysis, which was analyzed using CMA. Odd ratios (ORs) and 95% confidence intervals (CIs) were used to measure the association between single nucleotide polymorphism (SNP) with rs ID number of rs6897932 and the risk of MS development. *P*-value was considered as statistical significance when it is calculated less than 0.05 (P-value < 0.05). In order to examine heterogeneity among studies, the Cochran Q test and I2 statistics were used. When a significant heterogeneity