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Association between miR-146a rs2910164 polymorphism and autoimmune diseases susceptibility: A meta-analysis

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ABSTRACT

Published data on the rs2910164 in microRNA-146a (miR-146a) are shown to be associated with increased or decreased autoimmune diseases risk. To derive a more precise estimation of the relationship, we performed a meta-analysis to systematically summarize the possible. A meta-analysis including 11 studies with 3042 controls and 2197 cases was performed for genotypes CC (recessive effect), CC + CG (dominant effect) and C allele in fixed or random-effects models based on between-study heterogeneity. Overall, no significant association between miR-146a G/C rs2910164 polymorphism and autoimmune diseases risk was found in all genetic models when all studies were pooled into the meta-analysis. SLE (OR = 0.99, 95% CI: 0.90–1.10), RA (OR = 0.98, 95% CI: 0.85–1.14) did not yield statistical significance as for C allele pooled studies. In the subgroup analysis by ethnicity, still no significant association was detected in all genetic models. Our meta-analysis suggests that there is no association between miR-146a G/C rs2910164 polymorphism and the development of autoimmune diseases.

1. Introduction

MicroRNAs (miRNAs), non-coding single-stranded RNA molecules that inhibit the expression of protein-coding genes by either translational repression or messenger RNA degradation (Bartel, 2004; Filipowicz et al., 2005; Pauley et al., 2009), may affect immune cells development and differentiation in both innate and adaptive immune response (Baltimore et al., 2008; Leng et al., 2011; Tomankova et al., 2012), Among them, the microRNA-146a (miR-146a), the widely reported gene, is involved in modulating the negative regulation of Toll like receptor (TLR) signaling and airway remodeling-associated proteins (MMP-13 and collagen II), and the expression of pivotal inflammatory cytokines (Chatzikyriakidou et al., 2010a,b; Jimenez-Morales et al., 2012; Li et al., 2010; Xu et al., 2012). Downregulated or upregulated in serum and urinary is found in patients with autoimmune diseases and correlate with the severity of autoimmune pathologies (Balasubramanyam et al., 2011; Jazdzewski et al., 2008; Niimoto et al., 2010; Vinci et al., 2012; Wang et al., 2010a). That miR-146a may have a pathologic/pathogenic role is suggested by the fact that miR-146a has an effect in autoimmune diseases.

Autoimmune diseases are a diverse group of complex diseases characterized by the production of antibodies that react with host tissues or immune effector cells that are auto-reactive to endogenous peptides. Increasing evidences indicated that autoimmune diseases are multifactorial caused by complex interactions between multiple genetic and environmental factors (Xu et al., 2012). Some of these underlying predisposing factors may be shared among many autoimmune diseases. Association and linkage studies in different populations have revealed that genetic susceptibility of autoimmune diseases often has underlying commonalities. This led to the hypothesis that autoimmune diseases may be controlled by a common set of susceptibility genes (Anaya et al., 2006).

Single nucleotide polymorphisms (SNPs) or mutations in miRNAs gene region may alter miRNA expression and/or maturation. Several studies have examined the relationship between miR-146a rs2910164 polymorphism and autoimmune diseases, including rheumatoid arthritis (RA) (Chatzikyriakidou et al., 2010a; Jimenez-Morales et al., 2012; Qian et al., 2012; Yang et al., 2011), systemic lupus erythematosus (SLE) (Jimenez-Morales et al., 2012; Lofgren et al., 2012; Zhang et al., 2011), psoriatic arthritis (PsA) (Chatzikyriakidou et al., 2010b), systemic scleroderma (SSc) (Sakoguchi et al., 2012), multiple sclerosis (MS) (Fenoglio et al., 2011), and ulcerative colitis (UC) (Okubo et al., 2011), etc. The identification of possible association between miR-146a rs2010164 polymorphism and autoimmune diseases might provide effective evidence of prevention for these autoimmune diseases. However, previous results are either inconsistent or lack strength owing to small sample sizes. Regarding detection of a possible effect of the gene polymorphism on autoimmune diseases, our purpose in this work was to assess the association between miR-146a G/C SNP and autoimmune diseases susceptibility by performing a meta-analysis.

Abbreviations: SLE, systemic lupus erythematosus; RA, rheumatoid arthritis; MS, multiple sclerosis; PsA, psoriatic arthritis; UC, ulcerative colitis; SSc, systemic scleroderma; HWE, Hardy–Weinberg equilibrium; SNPs, single nucleotide polymorphisms.

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2. Materials and methods

2.1. Publication search

We conducted a systematic search in PubMed, HighWire and Chinese National Knowledge Infrastructure (CNKI) databases covering all papers published prior to October 2012 that had examined the association of miR-146a G/C SNP with autoimmune disease. 'MicroRNAs', 'miR-146', 'rs2910164', 'polymorphism', 'autoimmune diseases' and 'autoimmunity' were entered as both medical subject heading (MeSH) terms and text words. Manual search of references from original research or review articles was performed to identify additional studies. No language and time restrictions were applied. All patients with autoimmune diseases for their respective disease met the international classification criteria.

2.2. Inclusion criteria

Studies were included in the analysis if they met all the following criteria: (a) evaluation of the rs2910164 and autoimmune diseases risks, (b) including original data (independence among studies), (c) using a case–control design, and (d) enough data for estimating odds ratio (OR).

2.3. Exclusion criteria

Studies were excluded if: (a) containing overlapping data; (b) the number of wild and null genotypes could not be ascertained; (c) genotype distribution of the control population is not in Hardy–Weinberg equilibrium (HWE); and (d) studies in which family members had been studied because their analysis is based on linkage considerations.

2.4. Data extraction

Data extraction was carried out independently by two reviewers according to the inclusion and exclusion criteria listed above. Disagreements about eligibility were resolved during a consensus with a third reviewer. The following data were extracted from eligible studies including the name of first author, year of publication, ethnicity, control, total number of cases and controls, and numbers of cases and controls with miR-146a G/C genotypes respectively. Different ethnicity descents were categorized as Caucasian and Asian.

2.5. Statistical methods

Allele frequencies at the miR-146a G/C rs2910164 polymorphism from each respective study were determined by the allele counting method. Fisher's exact test was used to assess deviation from Hardy–Weinberg equilibrium (HWE) in the control group. The allelic effect of C versus G, homozygote comparison of CC versus GG, recessive model (CC versus GG + CG) and dominant model (CC + CG versus GG) models were examined for an optimal genetic model. Subgroup analyses were conducted by ethnicity and disease type. The odd radio (OR) and its 95% confidence interval (CI) were used to assess the strength of association between mir-146a G/C polymorphism and autoimmune diseases. The significance of the pooled OR was determined by the Z-test.

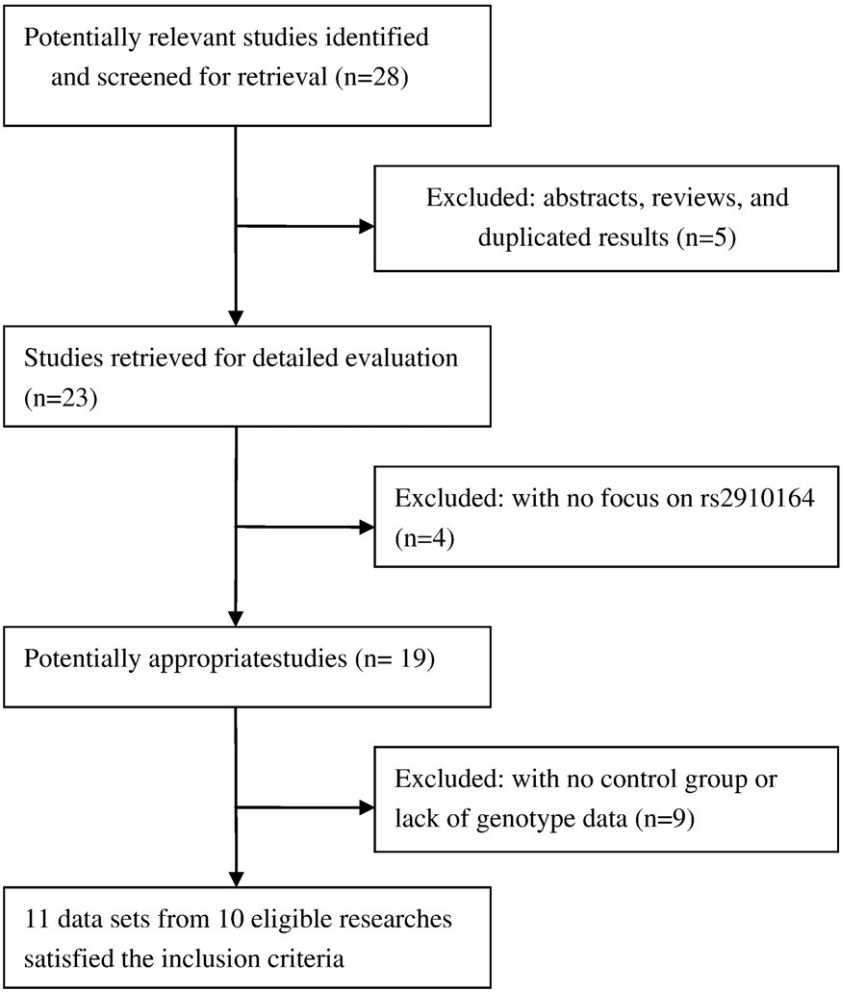

Fig. 1. Flow chart of selection of studies and specific reasons for exclusion from the meta-analysis.