Joint Bone Spine 82 (2015) 166–171

Available online at ScienceDirect www.sciencedirect.com

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Original article

Is the microRNA-146a (rs2910164) polymorphism associated with rheumatoid arthritis? Association of microRNA-146a (rs2910164) polymorphism and rheumatoid arthritis could depend on gender

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ARTICLE INFO

Article history:
Accepted 9 December 2014
Available online 24 January 2015

Keywords:
MicroRNA-146a
Rs2910164
Meta-analysis
Rheumatoid arthritis
Single nucleotide polymorphism

ABSTRACT

Background: To investigate a possible effect of a gene mutation on rheumatoid arthritis (RA), we performed genotyping, in a hospital-based, case-control study in a Chinese cohort, relating the single nucleotide polymorphism (SNP) of microRNA (miRNA)-146a (rs2910164) to RA and undertook a meta-analysis using the available literature.
Methods: Six hundred and fifteen RA patients and 839 controls were enrolled in our study. A polymorphism of the miRNA-146a (rs2910164) gene was detected using a custom-by-design 48-Plex SNPscan TM Kit. In addition, we performed a systematic literature research and identified an additional 7 studies with 1066 cases and 1513 controls.
Results: We did not find a significant association of miRNA-146a polymorphism with an RA risk in our data. And the results of the meta-analyses suggested no significant association between miRNA-146a polymorphism and RA in any genetic model. However, when the subgroup analyses were performed, genotype GG was observed to be significantly associated with RA in females. And the DAS28 score may also be significantly influenced by CC genotype.
Conclusions: Our study suggested that miRNA-146a polymorphism might not be associated with RA susceptibility. However, the miRNA-146 GG genotype might increase the risk of RA in females, and CC genotype may influence disease activity when evaluated with DAS28 score.
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1. Introduction

Rheumatoid arthritis (RA), is a chronic inflammatory autoimmune disease in which hyperplasia, hypertrophy and angiogenesis of synovial tissue contribute to inflammatory joint destruction [1]. The mechanisms involved in the initiation and progression of RA are not completely understood because RA has a complex component induced by several genes that interact with environmental and stochastic factors [2,3]. Multiple inflammatory cytokines and related cells play different roles in the development and pathogenesis of RA. The major cellular contributors are T- and B-lymphocytes, monocytes/macrophages, neutrophils and proliferating synovial fibroblast-like cells. Modification of the synovial microenvironment by proinflammatory cytokines and chemokines attract T-lymphocytes, B-lymphocytes, and mononuclear antigen presenting cells (APCs), and promote secretion of proteases that promote joint destruction [4]. The major genetic factor for RA is the human leukocyte antigen–DRB1 (HLA-DRB1) gene; the HLA genes do not account for all for the genetic liability to the disease [5]. Many other non-HLA genes have been implicated in disease susceptibility in recent years, whereas many genes remain to be discovered [6]. One class of genetic variants that has been the focus of attention recently is the class of DNA polymorphisms that affect miRNA binding [7].

Abbreviations: CI, confidence interval; miRNA, microRNA; LD, linkage disequilibrium; OR, odds ratio; SNP, single nucleotide polymorphism; RF, rheumatoid factor; ACPA, anti-cyclic citrullinated peptide antibodies; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; DAS28, RA disease activity score.

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http://dx.doi.org/10.1016/j.jbspin.2014.12.009
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MiRNAs form a class of noncoding RNAs that regulates gene expression by binding the 3′-untranslated region (3′-UTR) of their target messenger RNA (mRNA), leading to translational repression or mRNA degradation [8,9]. Recent evidence indicates that miRNAs act as key regulators of various processes including early development, organ development, cell proliferation, differentiation, cell fate determination, apoptosis, stress resistance and signal transduction [10,11]. Recently, it has become clear that miRNAs play a role in the pathogenesis of RA. MiRNA-146a is strongly associated with C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) values [12] and plays an important role in the suppressor functions of T-regulatory cells [13]. Additionally, MiRNA-146a targets IL-1R-associated kinase 1 (IRAK1) and TNFR-associated factor 6 (TRAF6), which modulate the IL-1 induced gene MMP-13 [12,14]. Single nucleotide polymorphisms (SNPs) or mutations could affect the functions of miRNAs and in turn influence individual susceptibility to diseases. Several studies [15–21] have examined the relationship between miRNA-146a polymorphism rs2910164 and RA. The identification of a possible association between miRNA-146a polymorphism rs2010164 and RA might provide an effective route for the prevention of RA.

Previous results lacked statistical strength owing to their small sample sizes. Regarding the detection of a possible effect of gene mutation on RA, in this study, we performed genotyping in a hospital-based, case-control study in a Chinese cohort, which related the SNP represented by miRNA-146a polymorphism rs2910164 to RA and undertook a meta-analysis using the available literature.

2. Methods

The study was approved by the institutional review board of Nanjing Medical University (Nanjing, China). Inpatients ($n = 1454$) were consecutively recruited from Changzhou Second Hospital-Affiliated Hospital of Nanjing Medical University (Jiangsu, China), the Changzhou First Hospital and the Changzhou Traditional Chinese Medical Hospital, between September 2010 and October 2013; 615 patients who fulfilled the American College of Rheumatology classification criteria for RA [22] served as cases, and 839 patients served as controls. The controls were patients without RA, most of whom were admitted to the hospitals for the treatment of trauma; they were matched for age and sex and recruited from the same institutions during the identical time period. To obtain information regarding the demographic data and related risk factors, each patient was interviewed personally using a pre-tested questionnaire, after they provided written informed consent. Subsequently, 2 mL of peripheral blood was collected from each subject [23].

The genomic DNA was isolated from whole blood using a QIAamp DNA Blood Mini Kit (Qiagen, Hilden, Germany). The SNP genotyping work was performed using a custom-by-design 48-Plex SNP scan TM Kit (Genesky Biotechnologies, Inc., Shanghai, China), as previously described [24].

Aiming to clear the association of miRNA-146a polymorphism rs2910164 with rheumatoid arthritis, we performed a literature review for a meta-analysis. We searched the databases of Medline, PubMed, Embase, and the Cochrane Library to identify published epidemiological studies through April 2014 that were related to polymorphism rs2910164 in miRNA-146a and RA. The medical subject headings and free-text words of “polymorphism”, “SNP”, “rs2910164”, “microRNA-146a”, “miRNA-146a”, “rheumatoid arthritis”, and “RA” were combined for free research. No language or other restrictions were placed on the search. Full-texts were obtained if the abstracts did not allow us to include or exclude the studies. The reference lists of all the related papers were examined to identify any initially omitted studies.

The selection criteria was follows:

- studies that evaluated the association between miRNA-146a polymorphism and RA;
- studies that focused on human beings;
- studies that included detailed genotype data; and;
- studies in abstract form or meeting reports, for which the full paper could not be acquired, were included in our study.

Studies were excluded based on the following exclusion criteria:

- duplication of previous publications;
- review, editorial or other types of studies which were not focused on detailed genotype research;
- family-based studies of pedigrees;
- studies with no detailed genotype data;
- studies conducted on patients who were pregnant, who had cancer or other diseases that might have influenced the results.

Any publications with questionable inclusion/exclusion criteria were discussed and disagreements were resolved by consensus. Two reviewers independently evaluated the methodological quality of the included studies by applying an 11-item quality checklist, derived from the STREGA [25] (strengthening the reporting of genetic association studies) and STROBE [26] (strengthening the reporting of observational studies in epidemiology) checklists, as described in another study which was published previously [27]. Information was extracted from each selected study.

A Chi^2 test was used to evaluate the differences in the demographics, variables and genotypes of the miRNA-146a polymorphism variants; the Hardy–Weinberg equilibrium was tested by a goodness-of-fit Chi^2 test to compare the observed genotype frequencies with the expected frequencies among the controls [23]. The statistical analyses in our groups were performed with SAS software, version 9.1.3 (SAS Institute, Cary, NC). The meta-analysis data were checked independently and analysed, using Review Manager 5.0, by different reviewers. To determine the strength of a genetic association, the pooled odds ratio (OR) was calculated for each gene variant, and a 95% confidence intervals (CI) established. The dominant and recessive models were analysed. For each meta-analysis, tests for heterogeneity were performed with significance set at $P \leq 0.1$, and the degree of heterogeneity was measured using the I^2 value. A fixed effects analysis was used for comparing the trials without showing heterogeneity, whereas a random effects analysis was used for comparing trials showing heterogeneity. We performed sensitivity analyses by excluding each study individually to determine the effect on the test of heterogeneity and the overall pooled estimates. For assessment of publication bias, Begger’s test and Egger’s test were conducted for each genotype with five or more publications by Stata 12. P values of less than 0.05 were considered to indicate significance.

3. Results

Our study group consisted of 615 RA patients (472 females and 143 males) with an average age of 54.51 ± 15.19 years, and 839 control subjects (633 females and 206 males) with a mean age of $55.44.5 \pm 10.80$ years. No significant difference was found between the groups with respect to age ($P = 0.17$), and gender ($P = 0.57$) (Table 1). The frequency distribution of the miRNA-146a (rs2910164) genotypes in the RA patients and control subjects are demonstrated in Table 1 and were in Hardy–Weinberg equilibrium in each group. The genotyping was successful in: 598 cases and 821 controls. The genotypes and allele frequencies of miRNA-146a were not found to be significantly different between the RA patients and

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