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Association of rs2910164 polymorphism in MiR-146a gene with psoriasis susceptibility

A meta-analysis

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Abstract

The rs2910164 single nucleotide polymorphism (SNP) in miR-146a has been implicated in the etiology of psoriasis in different relevant studies with contradictory conclusions and limited sample size. Therefore, the aim of this study was to undertake a systematic review and meta-analysis to estimate the association between rs2910164 SNP and psoriasis. We searched the databases of PubMed, EMBASE, Web of Science, WanFang, and Chinese National Knowledge Infrastructure (CNKI) to identify relevant literatures published before July 15, 2018. Four case–control studies including 2212 cases and 2274 healthy controls from 4 different countries met the predetermined criteria. The effect size was pooled by odds ratios (ORs) and 95% confidence intervals (95%CIs). Recessive model (CC vs CG+GG) was confirmed to be the optimal model. The results indicated that rs2910164 SNP was significantly associated with psoriasis (OR = 0.74, 95%CI 0.60–0.91, $P = .004$), and individuals with CC-genotype were predisposed to have decreased risk of psoriasis.

Abbreviations: CI = confidence interval, CNKI = Chinese National Knowledge Infrastructure, EGFR = epidermal growth factor receptor, GWAS = genome-wide association studies, HWE = Hardy–Weinberg equilibrium, IRAK1 = interleukin -1 receptor-associated kinase 1, miR-146a = microRNA 146a, human, MOOSE = Meta-analysis of Observational Studies in Epidemiology, OR = odds ratio, SNP = single nucleotide polymorphism, TRAF6 = tumor necrosis factor receptor–associated factor 6.

Keywords: meta-analysis, MiR-146a, polymorphism, psoriasis, Rs2910164

1. Introduction

Psoriasis is a commonly seen chronic inflammatory disorder manifesting on skin and joints. Five types of psoriasis that includes psoriasis vulgaris, eruptive psoriasis, inverse psoriasis, pustular psoriasis, and erythrodermic psoriasis have been reported.[1,2] As with other dermatoses, psoriasis poses both physical and psychological burden to affected individuals. The underlying pathogenesis of psoriasis is the complex interaction of genetic factors, environmental factors, as well as immunological factors. The past few years have witnessed great progress in the accumulating knowledge of pathogenesis and therapies in psoriasis.[3–5] In recent years, powerful genome-wide association studies (GWAS) and lots of more targeted candidate gene approaches have identified more than 40 regions of the genome which associated with psoriasis susceptibility.[6,7] Corresponding genes to these loci may play profound and ubiquitous role in the process of psoriasis. Thus, many challenges remain before we have a full understanding of how these genetic loci confer risk to psoriasis.[8]

Single nucleotide polymorphisms (SNPs) are the most variations in the human gene. SNPs in the miRNA genes can lead to aberrant miRNA regulation by altering their expression or maturation process.[8] A lot of researches have examined the association of SNPs in miR-146a with cancer and autoimmune disease susceptibility.[9,10] For rs2910164 of miR-146a, studies indicated that CC-genotype carriers appeared to have a higher risk of suffering lung cancer and gastric cancer.[11,12] In addition, another study demonstrated that rs2910164 was significantly associated with the susceptibility to inflammatory bowel disease.[13]

Psoriasis is an immune-mediated disorder strongly associated with genetic factor. Whether polymorphisms in miR-146a contribute to psoriasis is still an unanswered question. To date, studies on this issue have been carried out in different countries and ethnicities. Concerning the sample size was limited and the statistical effect was weak of an individual study, we conducted this meta-analysis to obtain a comprehensive association between rs2910164 polymorphism and psoriasis vulnerability.

2. Material and methods

2.1. Search strategy

Two independent investigators (HG and XJW) searched the databases of PubMed, EMBASE, Web of science, WanFang, and

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Compliance with Ethical Standards: All analyses of this article were based on previous published literatures; human participants were not involved in our study. Thus, no ethical approval and patient consent are required.

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China National Knowledge Infrastructure (CNKI) prior to July 15, 2018. The searching strategy of PubMed database was displayed as following:(((((((“Genes”[Mesh]) OR gene)) OR ((variation) OR “Genetic Variation”[Mesh])) OR ((“Mutation”[Mesh]) OR mutation)) OR ((polymorphism) OR “Polymorphism, Genetic”[Mesh]))) AND ((((“MIRN146 microRNA, human” [Supplementary Concept]) OR miR-146a)) AND ((“Psoriasis”[Mesh]) OR psoriasis)). Bibliographic lists of all relevant articles were manually retrieved to acquire potential studies. The literature screening process was presented in Figure 1.

2.2. Inclusion and exclusion criteria

Original studies included in the present meta-analysis were selected in accordance with the following criteria: case–control studies; studies on the evaluation of rs2910164 and psoriasis risk; sufficient data to calculate the odds ratios (ORs) and 95% confidence intervals (CIs). Exclusion criteria of the studies were: lack of available data; animal studies were involved; and repeated publications.

2.3. Data extraction

Two investigators (HG and XJW) independently carried out the process of data extraction. Information extracted from each eligible study including: year of publication, name of the first author, country, ethnicity, sample size of cases and controls, genotype data. Disagreements during this process were resolved by discussion. If these 2 authors could not meet an agreement, final decision would be made by the third investigator (XMP).

2.4. Statistical analysis

The present statistical analysis was performed in accordance with the reporting guidelines of Meta-analysis of Observational

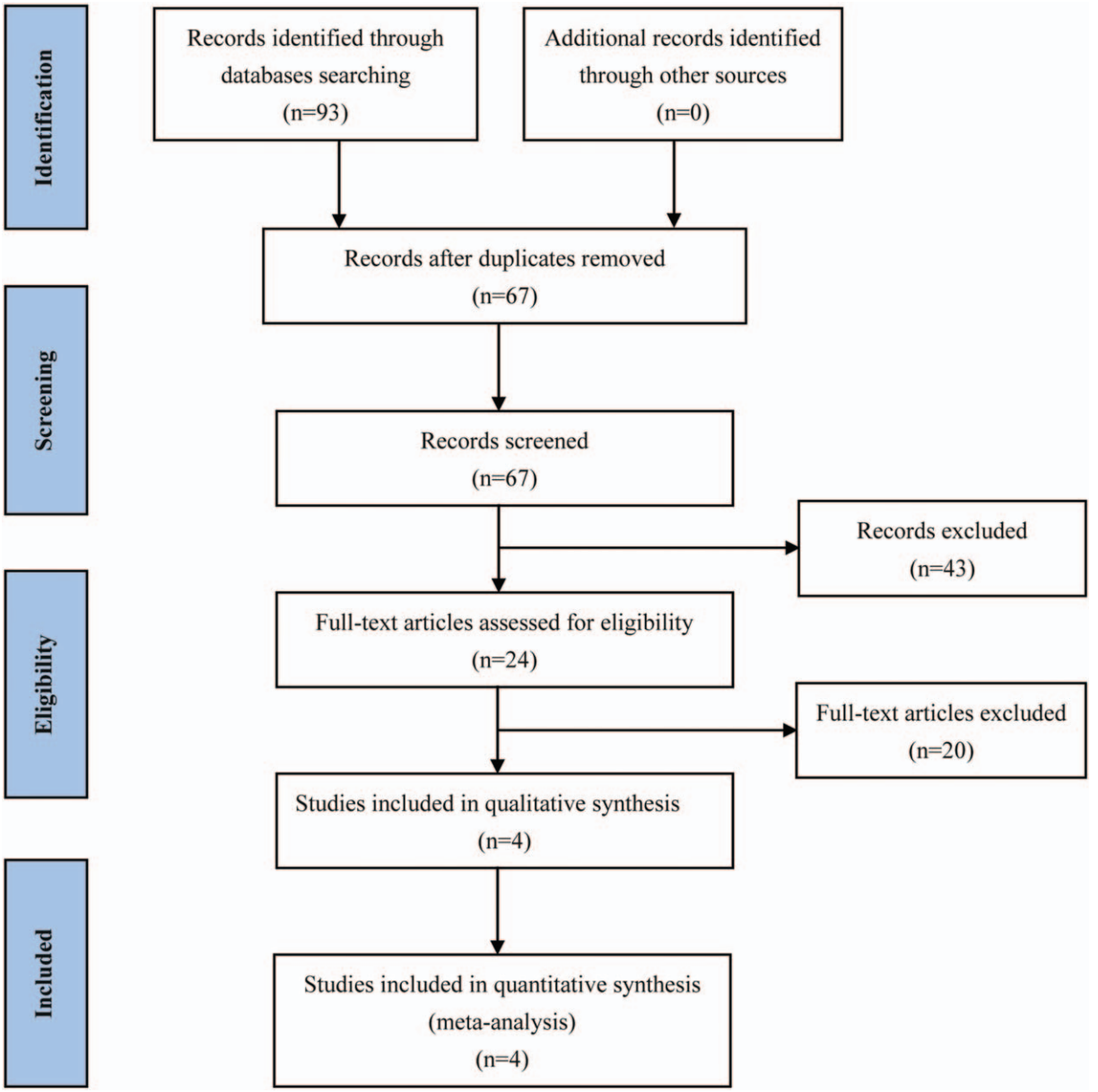

Figure 1. Flowchart of literature selection.

Table 1

Main characteristics of included studies.

Study	Year	Country	Ethnicity	Sample size	Case			Control			HWE
					CC	GC	GG	CC	GC	GG	
Chatzikyriakidou A[17]	2010	Greece	Caucasian	29/66	3	12	14	9	18	39	<0.05
Maharaj AB I[18]	2018	South Africa	Indian	84/62	7	46	31	3	22	37	0.91
Maharaj AB II[18]	2018	South Africa	Caucasian	32/38	3	17	12	1	22	15	<0.05
Srivastava A[19]	2017	Sweden	Caucasian	1546/1526	53	503	990	76	501	949	0.35
Zhang W[20]	2014	China	Asian	521/582	132	276	113	185	300	97	0.18

HW = Hardy–Weinberg equilibrium.

Studies in Epidemiology (MOOSE) .[14] For rs2910164 in miR-146a, we used G-allele as reference. A model-free approach recommended by Thakkinstian et al[15] was employed to analyse the data. Pooled odds ratios with 95% confidence intervals were calculated using RevMan5.3 software (Nordic Cochrane Centre, Cochrane Collaboration, Copenhagen, Sweden). Agreement or disagreement of genotype distribution of controls with Hardy–Weinberg Equilibrium (HWE) in each included study was assessed using Chi-square test. *Q*-statistical test and I^2 test were used to evaluate the heterogeneity between studies. The random-effect model was used for data combination in the presence of heterogeneity ($P<.1$, $I^2>50\%$), while the fixed-effect model was used when it is out of heterogeneity ($P>.1$, $I^2<50\%$). Model-free approach[15] was used to conduct the meta-analysis. There were no prior assumptions regarding the genetic model. OR1 (CC vs GG), OR2 (CG vs GG), OR3 (CC vs CG) were computed. Funnel plots were examined for the evidence of publication bias if the number of included studies were equal or more than ten.[16]

3. Results

3.1. Study characteristics

Four articles containing 5 studies were included in the present meta-analysis.[17–20] The included studies were conducted in Greece,[17] South Africa,[18] Sweden,[19] and China,[20] respectively. The detailed information of all studies was displayed in Table 1. Quality assessment was performed according to Newcastle–Ottawa scale for nonrandomized controlled trials, each of the included studies obtained a score of ≥5 stars, indicating a good methodological quality (Table 2).

3.2. Meta-analyses results

The estimated OR1 (CC/GG, OR = 0.69, 95%CI 0.54–0.88, $P=.003$), OR2 (CG/GG, OR = 1.11, 95%CI 0.79–1.56, $P=.53$), and OR3 (CC/CG, OR = 0.76, 95%CI 0.61–0.94, $P=.01$) showed that OR1 and OR3 were statistically significant, while OR2 was not significant. The outcomes suggested that recessive model might be the most suitable genetic model. When using a recessive mode, CG and GG genotype were analyzed and compared with CC genotype. The combined OR showed that subjects with CC genotype was significantly associated with a lower risk of psoriasis (CC vs CG+GG, OR = 0.74, 95%CI 0.60–0.91, $P=.004$, Fig. 2).

3.3. Sensitivity analysis

Sensitivity analysis was performed to test the influence of every study on the overall ORs by omitting one study at a time. The results of sensitivity analysis suggested the overall effects were not influenced by any individual study, which guaranteed the credibility and reliability of our results. Owing to the number of included studies was <10, publication bias evaluation by funnel was not performed.

4. Discussion

MiR-146a was initially observed significantly over expressed in psoriasis by Sonkoly et al.[21]. It functions as a negative regulator of inflammation and the innate immune response by inhibiting the expression of its target gene.[22] IRAK1 (interleukin-1 receptor-associated kinase 1) and TRAF6 (tumor necrosis factor receptor-associated factor 6) played a key role of pro-inflammatory signaling, Boldin et al[23] found that miR-146a works as a brake role of autoimmunity by targeting IRAK1 and TRAF6 in the process of innate immune response. A genome-wide analysis conducted by Hermann et al[24] containing over 4000 psoriasis cases and more than 8000 healthy controls have confirmed that there was a moderate correlation of genetic variants in the miR-146a with psoriasis risk. In Yang et al's[25] study, the expression of miR-146a was found upregulated in both compartments of psoriatic skin and peripheral blood mononuclear cells. The G to C polymorphism of rs2910164 makes a

Table 2

Quality assessment of included studies according to the Newcastle–Ottawa scale.

Item/Study	Maharaj AB I	Maharaj AB II	Srivastava A	Zhang W	Chatzikyriakidou A
Adequate definition of cases	★	★	★	★	★
Representativeness of cases	☆	☆	☆	☆	☆
Selection of control subjects	☆	☆	☆	☆	☆
Definition of control subjects	★	★	★	★	★
Control for important factor or additional factor	★☆	★☆	☆☆	★☆	★★
Exposure assessment	★	★	★	★	★
Same method of ascertainment for all subjects	★	★	★	★	★
Non-response rate	★	★	★	★	★

★,star given; ☆, star not given.

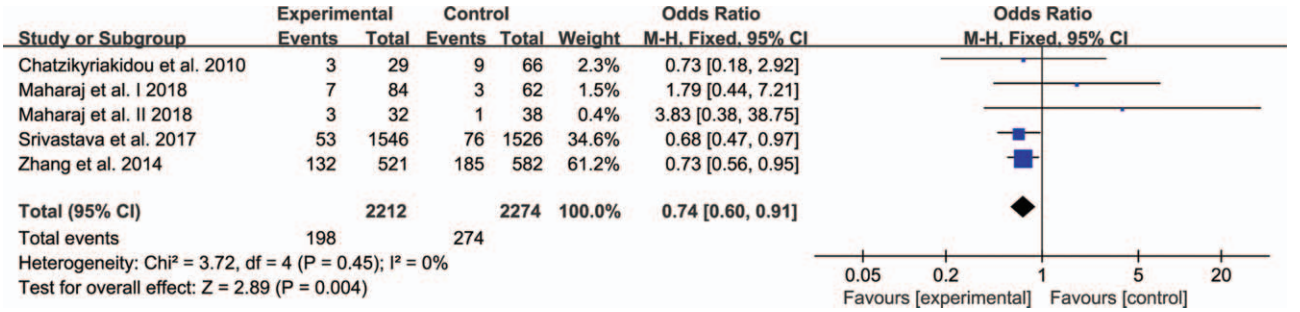

Figure 2. Forest plot of rs2910164 for psoriasis using a recessive model.

mismatch from G: U to C: U in the stem region of miR-146a precursor, which leads to an alteration of miR-146a expression level.[26] Accumulating evidence suggests that the SNPs in miR-146a might contribute to the functional role in the occurrence and development of psoriasis. Therefore, a lot of researches have been conducted to explore the relationship between rs2910164 and susceptibility to psoriasis.

In the present meta-analysis, we investigated 4 articles including 5 eligible case–control studies. Those studies came from different countries and different ethnicities. However, their conclusions were contradictory or incomplete, which make our meta-analysis meaningful and necessary. Zhang et al.'s[20] study from China in showed that the combined genotypes (CG+GG) of rs2910164 polymorphism were associated with an increased risk of psoriasis compared with CC genotype. In addition, G-allele in rs2910164 inhibited the expression level of mature miR-146a and thus had a weaken effect on inhibitory regulation of epidermal growth factor receptor (EGFR) expression level, and then the growth of human keratinocytes would be accelerated. All these evidences suggested that the G-allele of rs2910164 in miR-146a might play a pivotal role in the pathogenesis of psoriasis. However, Maharaj et al. 's[18] study showed the opposite results. They found that C-allele of rs2910164 in psoriasis patients was significantly higher than healthy controls. Indicating that the rs2910164 variant C-allele may possibly play a role in the aetiology of psoriasis in South African Indian Population. Srivastava et al.'s study[19] showed that no significant correlation of genotype distribution between miR-146a rs2910164-C and psoriasis risk was found. However, the genotype analyzing revealed that CC genotype was a protective factor when compared with GC or GG genotypes. And Chatzikyriakidou et al[17]'s results showed that no distributional difference of miR-146a rs2910164 genotypes was observed between psoriatic arthritis patients and controls.

Previously meta-analyses focusing on rs2910164 polymorphism mainly fall into 2 categories: tumor and autoimmune disease. There were only 2 studies on psoriasis included in Park et al.'s[10] meta-analysis, which showed C-allele of rs2910164 was linked to decreased risk of psoriasis. For study interest in the miR-146a is growing, another 2 researches on the association between rs2910164 and psoriasis have been done in recent years. Two more studies on rs2910164 and psoriasis risk were included in our present meta-analysis. Our results suggested that recessive model appeared to be an appropriate genetic model. CC-genotype carriers appeared to have a reduced risk of psoriasis vulnerability.

Despite we have collected the existing evidence on the correlation of rs2910164 polymorphism and psoriasis, several limitations in our study should not be ignored. First, the number of included studies is relatively small; only one Asian study was included. Second, we only searched the database in English and Chinese, which may cause selection bias. Third, 2 of our included studies did not meet HWE, which may lead to a restriction of our analyzing. Fourth, despite some studies have tried to explore the mechanism underlying this phenomenon, more researches are necessary to investigate the exact mechanism between rs2910164 and the risk of psoriasis.

5. Conclusion

The rs2910164 polymorphism in miR-146a might be associated with the susceptibility to psoriasis. Since the study number of this hypothesis is limited, similar studies are strongly encouraged in the future.

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Author contributions

Hai-bo Gong conceived of the idea and the did the final version of this paper. Hai-bo Gong and Xiu-juan Wu did the literature searching. Shi-lei Zhang was involved in the revising of the manuscript, including some important intellectual ideas and some grammatical mistakes in our original manuscript. Xiong-ming Pu and Xiao-jing Kang critically revised the final manuscript.
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Supervision: Xiao-jing Kang, Xiong-ming Pu.
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