

Original Article

Anthrax toxin receptor 2 gene (ANTXR2) rs4333130 is associated with ankylosing spondylitis

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Abstract: Results of recent published studies on the association between the ANTXR2 rs4333130 polymorphism and the risk of ankylosing spondylitis (AS) have often been conflicting. To make a more precise estimation of the potential relationship, a meta-analysis was performed. We conducted a comprehensive search in the electronic database of PubMed and Embase to retrieve relevant articles. Nine studies including 14,523 cases and 34,421 controls were finally selected in this meta-analysis. ANTXR2 rs4333130 was significantly associated with a decreased risk of AS (OR=0.87; 95% CI, 0.84-0.90; $P<0.00001$). In the subgroup analysis by race, ANTXR2 rs4333130 was significantly associated with a decreased risk of AS in both Asian (OR=0.80; 95% CI, 0.65-0.99; $P=0.04$) and Caucasian (OR=0.87; 95% CI, 0.84-0.90; $P<0.00001$). In the subgroup analysis by HLA-B27 status, HLA-B27 positive individuals with ANTXR2 rs4333130 showed decreased AS risk (OR=0.89; 95% CI, 0.83-0.96; $P=0.002$). However, HLA-B27 negative individuals with this polymorphism did not show decreased AS risk (OR=0.96; 95% CI, 0.88-1.06; $P=0.44$). In conclusion, this meta-analysis suggested a significant association between ANTXR2 rs4333130 polymorphism and AS risk.

Keywords: Ankylosing spondylitis, ANTXR2, meta-analysis, genetic

Introduction

Ankylosing spondylitis (AS) is a chronic inflammatory disorder that mainly affects the sacroiliac joints and lumbar spine. New bone formation is one of the hallmark characteristics of the disease, which is thereby associated with syndesmophytes and ankylosis [1]. Between 1% and 3% of the population may be affected by AS [2]. All of this leads to a substantial socio-economic burden in terms of both labour costs, due to the higher incidence of these diseases in the 20- to 60-year-old age range, and health care expenditure and social dependence, particularly in elderly patients [3].

Human leucocyte antigen (HLA)-B27 was the first molecule found to be associated with AS, but HLA-B27 positivity accounts for only some of the overall risk for AS [4]. Recent studies identified that the polymorphisms in ANTXR2 rs4333130 was found to be strongly associated with AS. However, other studies did not confirm this result [5-11]. Thus, we did a meta-

analysis to assess the association between this polymorphism and the risk of AS.

Methods

Publication search

We conducted a comprehensive search in the electronic database of PubMed and Embase to retrieve relevant articles. We retrieved the relevant articles using the following terms: “ankylosing spondylitis”, “ANTXR2”, and “polymorphism or variant or mutation” as well as their combinations. We searched the references of retrieved articles with no language restriction.

Inclusion and exclusion criteria

Studies were included if they met the following criteria: 1) evaluation of ANTXR2 rs4333130 and AS risk; 2) retrospective case-control studies or prospective cohort studies; 3) sufficient data to examine an odds ratio (OR) with 95% confidence interval (CI); 4) conforming to Hardy-Weinberg equilibrium (HWE) in the control gr-

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Table 1. Characteristics of included studies

Author	Year	Country	Ethnicity	Cases	Controls	HWE	HLA-B27 status
Bang	2010	Korea	Asian	1164	752	Yes	NA
Reveille 1	2010	Mixed	Caucasian	2053	5140	Yes	NA
Reveille 2	2010	Mixed	Caucasian	898	1518	Yes	NA
Evans 1	2011	Mixed	Caucasian	1787	4800	Yes	Reported
Evans 2	2011	Mixed	Caucasian	3023	8779	Yes	Reported
Evans 3	2011	Mixed	Caucasian	2111	4483	Yes	Reported
Chen	2012	China	Asian	200	200	Yes	NA
Guo	2012	China	Asian	309	384	Yes	NA
Karaderi	2014	UK	Caucasian	2978	8365	Yes	Reported

HWE, Hardy-Weinberg equilibrium.

Table 2. Summary of results from meta-analysis and subgroup analysis

	No. of studies	OR (95% CI)	P Value	$P_{\text{heterogeneity}}$
Overall	9	0.87 (0.84-0.90)	<0.00001	0.53
Asian	3	0.80 (0.65-0.99)	0.04	0.79
Caucasian	6	0.87 (0.84-0.90)	<0.00001	0.30
HLA-B27 positive	4	0.89 (0.83-0.96)	0.002	0.91
HLA-B27 negative	4	0.96 (0.88-1.06)	0.44	0.49

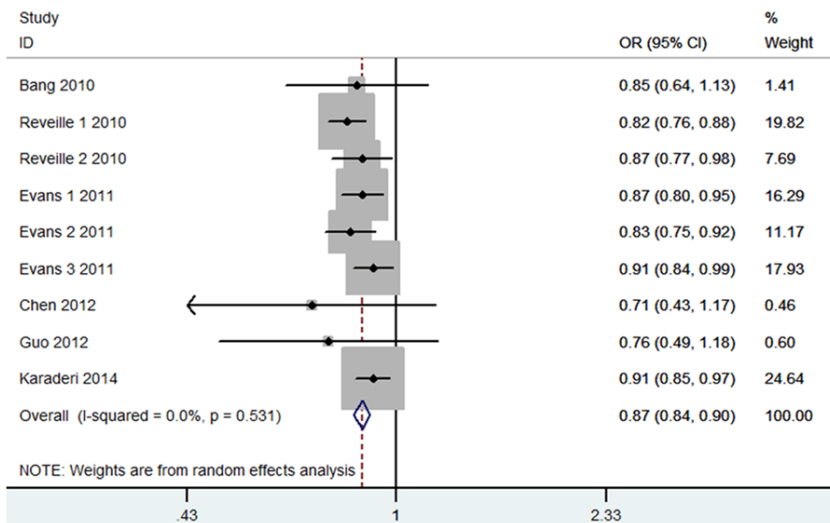


Figure 1. Meta-analysis for the association between ANXR2 rs4333130 and AS risk.

oup. Studies were excluded when: 1) not case-control studies; 2) case reports, letters, reviews, editorial articles, and animal studies; 3) duplicate or insufficient data; 4) family-based design; 5) controls were not in HWE.

Data extraction

Data from published studies were extracted carefully. For each study, we collected the fol-

lowing information: first author, year of publication, country, ethnicity, numbers of cases and controls, evidence of HWE and HLA-B27 status.

Statistical analysis

The overall effect was measured by ORs with its 95% CI. The significance of the pooled ORs was determined by the Z test with a P value less than 0.05 considering statistically significant. The perallele model was examined to assess this association. Between-studies heterogeneity was assessed by the I² test and the Qstatistic test. The random-effect model was used. The publication bias was estimated by visual funnel plot inspection. To assess whether our results were substantially influenced by the presence of any individual study, we proceed a sensitivity analysis by removing each study and recalculating the significance of the result. Statistical analyses were conducted in STATA version 11.0 (Stata Corporation, College station, TX, USA). All the tests were two-sided.

Results

Study characteristics

According to the inclusion and exclusion criteria, a total of 6 publications were included in this meta-analysis [5-11]. We noticed that 2 studies reported two and three independent studies and each group was considered separately in pooling analyses. Therefore, 9 studies

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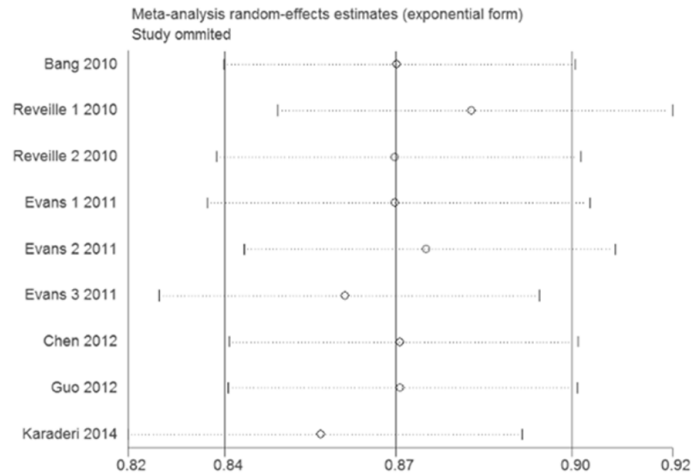


Figure 2. Sensitive analysis for the association between ANTXR2 rs4333130 and AS risk.

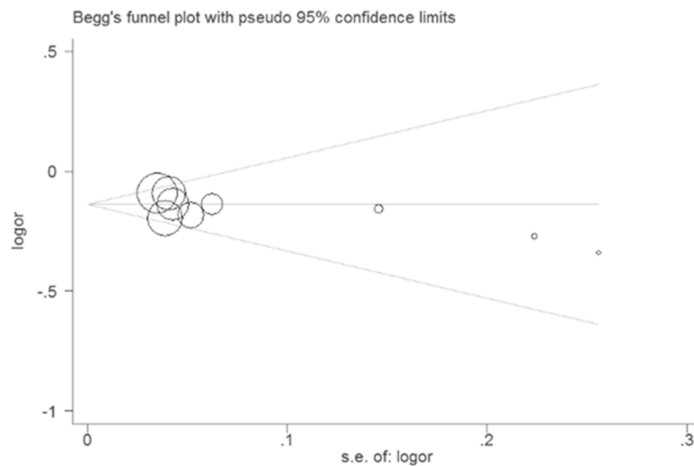


Figure 3. Funnel plot for the association between ANTXR2 rs4333130 and AS risk.

including 14,523 cases and 34,421 controls were finally selected in this meta-analysis. Characteristics in this meta-analysis are summarized in **Table 1**.

Results of meta-analysis

Table 2 presents the results of meta-analysis and the heterogeneity test. ANTXR2 rs4333130 was significantly associated with a decreased risk of AS (OR=0.87; 95% CI, 0.84-0.90; $P<0.00001$; **Figure 1**). In the subgroup analysis by race, ANTXR2 rs4333130 was significantly associated with a decreased risk of AS in both Asian (OR=0.80; 95% CI, 0.65-0.99; $P=0.04$) and Caucasian (OR=0.87; 95% CI, 0.84-0.90; $P<0.00001$). In the subgroup analysis by HLA-B27 status, HLA-B27 positive individuals with

ANTXR2 rs4333130 showed decreased AS risk (OR=0.89; 95% CI, 0.83-0.96; $P=0.002$). However, HLA-B27 negative individuals with this polymorphism did not show decreased AS risk (OR=0.96; 95% CI, 0.88-1.06; $P=0.44$).

Sensitivity analyses were conducted to assess the influence of each individual study on the pooled OR by removing one study at a time. In the overall meta-analysis, no single study changed the pooled results, which indicates that the results were statistically stable and reliable (**Figure 2**).

The shapes of the funnel plot appeared symmetrical (**Figure 3**). The p -value of the Egger's test is 0.654, suggesting no evidence of publication bias.

Discussion

AS is characterized by inflammation and destruction of sacroiliac joint and stiffness of spine. It is widely confirmed that genetic factors play a substantive role in the pathogenesis of AS. Increasing evidence demonstrates that a substantial proportion of AS susceptibility is associated with nonmajor histocompatibility complex genes. Harvey et al. suggested that ERAP1 is a good candidate for causing susceptibility to AS

[12]. Pimentel-Santos et al. indicated that IL23R and ERAP1 genes are also associated with susceptibility to AS in the Portuguese population [13].

The present meta-analysis including 9 case-control studies assessed the association between ANTXR2 rs4333130 polymorphism and AS risk. We found that individuals with the ANTXR2 rs4333130 polymorphism showed a decreased risk of AS. This result suggested that ANTXR2 rs4333130 polymorphism may be a protective factor of AS. Furthermore, we found that ANTXR2 rs4333130 polymorphism might also be a protective factor for both Asians and Caucasians. HLA-B27 positive individuals with ANTXR2 rs4333130 showed decreased AS risk. However, HLA-B27 negative individuals

with this polymorphism did not showed decreased AS risk.

ANTXR2, also known as the capillary morphogenesis protein gene-2 (CMG2), located on chromosome 4q21. ANTXR2 encodes a transmembrane protein in which the von Willebrand A (vWA) domain binds to both lamin and collagen IV, suggesting that this protein plays a role in basement-membrane matrix assembly and endothelial cell morphogenesis [14]. Reeves and coworkers showed that MT1-MMP activity is dependent on ANTXR2 expression levels in cells [15].

We should also be aware of some limitations in this meta-analysis. First, the overall outcomes were based on individual unadjusted ORs. The unadjusted ORs may lead to confounding bias due to lack of individual information of each study, such as joint effects of SNP-SNP or gene-environment factors. Second, there was no study of an African population and only one study of an Asian population. Thus, publication bias might exist. Third, recall and selection bias may exist since the meta-analysis is a type of retrospective study.

In conclusion, this meta-analysis suggested a significant association between ANTXR2 rs4333130 polymorphism and AS risk.

Disclosure of conflict of interest

None.

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