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The association between tumor necrosis factor alpha promoter polymorphisms and ankylosing spondylitis: A meta-analysis

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ABSTRACT

Background: Studies investigating the association between tumor necrosis factor (TNF)-alpha promoter polymorphisms and ankylosing spondylitis have reported conflicting results. We here performed a meta-analysis based on the evidence currently available from the literature to make a more precise estimation of this relationship.
Methods: We performed a systematic search of the National Library of Medline and Embase databases before January 2013. This meta-analysis included 14 case–control studies, which included 1607 ankylosing spondylitis cases and 1910 controls.
Results: The combined results based on all studies showed that ankylosing spondylitis cases had a significantly lower frequency of -308GA [OR (codominant model) = 0.81, 95% CI = 0.66, 0.99, $P = 0.04$], -857CT [OR (codominant model) = 0.55, 95% CI = 0.32, 0.94, $P = 0.03$], -863AA [OR (codominant model) = 0.11, 95% CI = 0.01, 0.94, $P = 0.04$], -863CA [OR (codominant model) = 0.32, 95% CI = 0.18, 0.58, $P < 0.001$], and -1031TC [OR (codominant model) = 0.44, 95% CI = 0.25, 0.77, $P = 0.004$] genotype. However, ankylosing spondylitis cases had a significantly higher frequency of -238AA [OR (recessive model) = 7.43, 95% CI = 3.66, 15.05, $P < 0.001$] and -850TT [OR (recessive model) = 2.49, 95% CI = 1.16, 5.34, $P = 0.02$; OR (codominant model) = 2.83, 95% CI = 1.28, 6.25, $P = 0.01$] genotype. In the subgroup analysis by race, we found that ankylosing spondylitis cases had a significantly higher frequency of -238AA [OR (recessive model) = 7.43, 95% CI = 3.66, 15.05, $P < 0.001$] genotype in Caucasians and lower frequency of -857CT [OR (codominant model) = 0.53, 95% CI = 0.30, 0.94, $P = 0.03$] in Asians.
Conclusions: Our meta-analysis suggests that TNF-alpha promoter polymorphisms at positions -238, -308, -850, -857, -863 and -1031 could have a small influence on ankylosing spondylitis susceptibility. But there is a lack of association of the TNF-alpha-376G/A and -646G/A polymorphisms with ankylosing spondylitis.

1. Introduction

Ankylosing spondylitis is a chronic inflammatory rheumatic disease that can affect the axial skeleton, causing characteristic inflammatory back pain due to sacroiliitis and spondylitis, which can also lead to structural and functional impairments and a decrease in quality of life [1]. However, the precise pathogenesis and etiology of AS have not been elucidated. This disease appears to be multifactorial, with both genetic and environmental contributing factors [2]. Strong genetic factors have been implicated in the etiology of this disease [3]. The HLA-B27 is the first genetic factor that has been identified in ankylosing spondylitis and it confers the greatest susceptibility to ankylosing spondylitis [4–6]. However, increasing evidence indicated that other genetic factors were also involved in ankylosing spondylitis susceptibility except HLA-B27.

Tumor necrosis factor (TNF)-alpha is a potent proinflammatory cytokine and immune modulator secreted by macrophages and T lymphocytes with wide-ranging biological effects including protection from infection, surveillance against tumors and stimulation of inflammatory responses [7–9]. TNF blockers have proven to be highly effective in improving ankylosing spondylitis manifestations, suggesting that TNF is at least as important to the inflammatory process of ankylosing spondylitis [10,11]. TNF-alpha plays a crucial role in the pathogenesis of ankylosing spondylitis [12]. Sin-

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gle nucleotide polymorphisms (SNP) within TNF-alpha have the potential to cause structural changes within regulatory sites that could affect the function or regulation of TNF-alpha production [13].

Over the past few decades, a number of studies with conflicting results were performed to clarify the association between TNF-alpha promoter polymorphisms and ankylosing spondylitis [14–26]. Although two previous meta-analyses were performed to explore whether TNF-alpha-308 and -238 polymorphisms confer susceptibility to ankylosing spondylitis, no association was found between TNF-alpha-308 and -238 polymorphisms and ankylosing spondylitis susceptibility in both meta-analyses [27,28]. However, the role of TNF-alpha polymorphism in determining susceptibility to ankylosing spondylitis is still a topic of debate. We here performed a meta-analysis based on the evidence currently available from the literature to make a more precise estimation of this relationship.

2. Materials and methods

2.1. Literature search strategy

A systematic search was done in the following electronic databases: PubMed (1950 to January 2013) and EMBASE (1950 to January 2013). The following key words were used: 'tumor necrosis factor' or 'TNF', 'ankylosing spondylitis' or 'AS', 'polymorphism' or 'allele' or 'genetic variant'. No language restriction was used. The reference lists of the selected papers were screened by hand for potentially relevant new articles. If necessary, we attempted to contact the corresponding authors of retrieved articles to require additional information. Furthermore, if more than one paper was published with identical author using the same case series, we selected the research with more sample size.

2.2. Inclusion and exclusion criteria

Studies meeting the following criteria were included in the meta-analysis: (1) independent epidemiological studies (for humans only); (2) a clear description of TNF-alpha polymorphism in ankylosing spondylitis cases and controls; and (3) Basic characters of the participants including population source, age, gender, etc. were provided. The exclusion criteria were: (1) not an original paper (e.g. review or letter, etc.); (2) duplicate publications; and (3) no control.

2.3. Data extraction

Using a standardized form, data from published studies were extracted independently by two reviewers to populate the necessary information. The following data were extracted: the last name of the first author, publication year, country, study design, genotyping method, sample size and the results of studies.

2.4. Statistical analysis

Statistical analyses were conducted by use of STATA 11.0 (StataCorp LP, College Station, TX, USA). The Mantel–Haenszel method for fixed effects and the DerSimonian–Laird method for random effects were used to estimate pooled odds ratio (OR) and corresponding 95% confidence interval (CI). We used fixed-effects methods when statistical heterogeneity was not found. Otherwise, we calculated pooled estimates and confidence intervals assuming a random-effects model. Publication bias was assessed by visual inspection of funnel plots. Funnel plots are often used to detect publication bias. However, due to the limitations of funnel plotting, which requires a range of studies with varying sizes and subjective judgments, we evaluated publication bias using the Begg's rank correlation method and the Egger's weighted regression method. Also, subgroup analyses were performed on the basis of race. In this study, $P < 0.05$ was considered statistically significant, and all statistical tests were two sided.

3. Results

A total of 206 publications meet the searching words. Through the step of screening the title, abstracts, 183 articles were excluded, leaving 23 articles for full publication review. Of these, ten were excluded [27–34]. Finally, this meta-analysis included 14 case–control studies from 13 articles [14–26], which included 1607 ankylosing spondylitis cases and 1910 controls. Studies were conducted in England, Scotland, Germany, Spain, Greece, Mexico, Portugal, Colombia, Iran, Korea and China (Table 1). Genotype counts of TNF-alpha gene polymorphisms of studies included in the meta-analysis were shown in Table 2.

The combined results based on all studies showed that ankylosing spondylitis cases had a significantly lower frequency of -308GA [OR (codominant model) = 0.81, 95% CI = 0.66, 0.99, $P = 0.04$], -857CT [OR (codominant model) = 0.55, 95% CI = 0.32, 0.94, $P = 0.03$], -863AA [OR (codominant model) = 0.11, 95% CI = 0.01, 0.94, $P = 0.04$], -863CA [OR (codominant model) = 0.32, 95% CI = 0.18, 0.58, $P < 0.001$], and -1031TC [OR (codominant mod-

Table 1
Characteristics of studies included in the meta-analysis.

Study (author, year)	Design	Population	Country	Genotyping method	Cases	Controls	Polymorphisms
Romero-Sanchez et al. (2012)	HCC	Caucasians	Colombia	PCR-RFLP	17	83	-308G/A
Chung et al. (2011)	Cohort	Asians	Korea	PCR-RFLP	119	135	-1031T/C, -863C/A, -857C/T, -646G/A, -308G/A, -238G/A
Sousa et al. (2009)	HCC	Caucasians	Portugal	PCR-RFLP	141	117	-308G/A, -238G/A
Nicknam et al. (2009)	HCC	Caucasians	Iran	PCR-SSP	97	137	-308G/A, -238G/A
Chatzikyriakidou et al. (2009)	HCC	Caucasians	Greece	PCR-RFLP	49	68	-857C/T, -308G/A, -238G/A
Lu et al. (2008)	HCC	Asians	China	PCR-ARMS	67	60	-308G/A, -238G/A
Zhu et al. (2007)	HCC	Asians	China	PCR-RFLP	79	132	-850C/T
Shiau et al. (2007)	HCC	Asians	China	PCR-RFLP	143	112	-308G/A, -238G/A
Vargas-Alarcon et al. (2006)	HCC	Caucasians	Mexico	PCR-RFLP	113	169	-308G/A, -238G/A
Gonzalez et al. (2001)	HCC	Caucasians	Spain	PCR-RFLP	105	170	-308G/A, -238G/A
Milicic et al. (2000a)	HCC	Caucasians	Germany	PCR-ARMS	147	210	-308G/A, -238G/A, -376G/A
Milicic et al. (2000b)	HCC	Caucasians	England	PCR-ARMS	306	204	-308G/A, -238G/A, -376G/A
McGarry et al. (1999)	HCC	Caucasians	Scotland	PCR-RFLP	167	181	-308G/A
Fraile et al. (1998)	HCC	Caucasians	Spain	PCR-RFLP	57	132	-308G/A, -238G/A

Abbreviations: HCC, hospital-based case–control; PCR, polymerase chain reaction; RFLP, restriction fragment length polymorphism; SSP, sequence specific primers; ARMS, amplification refractory mutation system.