

## Original Article

# Mediterranean fever (MEFV) gene polymorphisms and ankylosing spondylitis risk: a meta-analysis

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Received November 16, 2015; Accepted March 25, 2016; Epub November 15, 2016; Published November 30, 2016

**Abstract:** Background: Some studies investigated the association between Mediterranean fever (MEFV) polymorphisms and Ankylosing Spondylitis (AS) risk. However, results of these studies remained inconclusive. Thus, we performed this systematic review and meta-analysis to clarify the association between MEFV polymorphisms and AS risk. Method: PubMed, EMBASE, and Cochrane databases were searched to find relevant studies by two authors. The data were extracted by these two authors independently. The strength of association between the MEFV polymorphisms and AS risk was assessed by calculating OR with 95% CI. Results: Subjects with MEFV polymorphisms was associated with a significantly increased risk of AS (OR=2.46; 95% CI, 1.66-3.63). Subjects with MEFV M694V polymorphism had increased AS risk (OR=4.19; 95% CI, 2.19-8.02). In the race subgroup analysis, Caucasians with MEFV M694V polymorphism had increased AS risk (OR=4.02; 95% CI, 1.96-8.22). However, Subjects with E148Q, V726A, or M680I polymorphism did not show significant increased AS risk (OR=1.37; 95% CI, 0.74-2.55; OR=1.81; 95% CI, 0.65-5.01; OR=1.59; 95% CI, 0.64-3.95), respectively. In the race subgroup analysis, Caucasians with MEFV M680I polymorphism also had no increased AS risk (OR=1.53; 95% CI, 0.58-4.08). Conclusion: This meta-analysis suggested that MEFV M694V polymorphism may be associated with the risk of AS.

**Keywords:** Ankylosing spondylitis, MEFV, meta-analysis, association

## Introduction

Ankylosing Spondylitis (AS) is a chronic inflammatory arthritis that predominantly affects the spinal joints and often times the peripheral joints and entheses. AS is one of the most severe forms of spondyloarthritis and the prevalence rates reported are as high as 1.4%. AS has a male predominance with a male-to-female ratio of 3:1. The peak age of onset is typically in the second or third decade of life. AS is strongly associated with human leukocyte antigen (HLA)-B27, with the prevalence of the B27 allele approaching 90% worldwide, but the pathogenic mechanism underlying this association remains unclear.

The Mediterranean fever (MEFV) gene product is pyrin, a protein thought to play an important role in the regulation of interleukin 1 $\beta$  (IL1 $\beta$ ) and thereby of inflammation [1]. Up to now, 281 mutations have been identified in the MEFV gene and 81 of these were identified in exon 10 [2]. Among these mutations, M694V, M680I,

M694I and V726A were reported to be the most common, accounting for nearly 80.0% of all abnormal alleles in patients. Some studies investigated the association between MEFV polymorphisms and AS risk. However, the results remained inconclusive [3-7]. Thus, we performed a meta-analysis to clarify the association of MEFV polymorphisms and AS risk.

## Methods

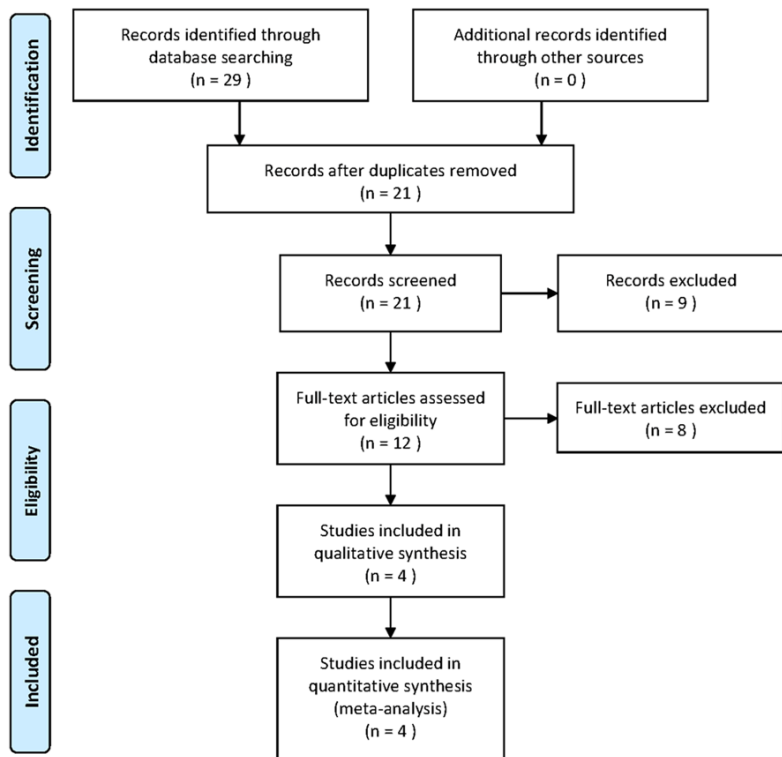
### Publication search

Online electronic databases (PubMed, EMBASE, and Cochrane database) was searched using the search terms: Mediterranean fever or MEFV and Ankylosing Spondylitis. Additional studies were identified by a hand search from reference of original studies or review articles on this topic. There was no language restriction.

### Inclusion and exclusion criteria

The following inclusion criteria were used: (1) the study should have evaluated the associa-

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**Figure 1.** Flow of study identification, inclusion, and exclusion.

tion between the MEFV polymorphisms and AS risk; (2) the study should have a case-control or cohort design; (3) sufficient data should have been provided in order to calculate odds ratios (OR) and 95% confidence interval (CI). Studies were excluded if any of the following conditions applied: (1) only abstracts or reviews were available, without sufficient data; (2) animal studies; (3) studies were repeated or publications overlapped.

### Data extraction

The following data were recorded from each article: first author, years of publication, country, ethnicity, gender, age, numbers of subjects, and polymorphisms. The data were extracted by two of the authors independently. Discrepancies between these two authors were resolved by discussion.

### Quality assessment

The included studies were assessed independently by the two reviewers using the Newcastle-Ottawa Scale (NOS). The NOS employs a star rating system to assess quality from 3 broad

perspectives of the study: (1) selection of the study groups, (2) comparability of the groups, and (3) identification of the exposure (for case-control studies) or outcome of interest (for cohort studies). Scores ranged from 0 to 9 stars.

### Statistical analysis

The strength of association between the MEFV polymorphisms and AS risk was assessed by calculating OR with 95% CI. A statistical test for heterogeneity was performed based on the Q statistic. The  $P > 0.10$  of the Q-test indicated a lack of heterogeneity among studies. The summary OR estimate of each study was calculated by the random-effects model. Stratified analysis was performed by race. Potential publication

bias was examined by funnel plot and Egger's test if more than 10 studies were included. All statistical tests were performed with the software Reviewer Manager version 5.1. A  $P$  value  $< 0.05$  was considered statistically significant.

## Results

### Study characteristics

According to the searching strategy, 29 papers were found. We reviewed the titles, abstracts and the full texts of all retrieved articles through defined criteria. **Figure 1** showed the flow diagram. A total of 4 studies with 558 cases and 473 controls on the association between MEFV polymorphisms and AS risk were included for this meta-analysis. There was 1 study of Asian population and 3 studies of Caucasian population. The characteristics of each study are presented in **Table 1**. The NOS scores were showed in **Table 2**.

### Results of meta-analysis

The results of the association between MEFV polymorphisms and AS risk are summarized in **Table 3**. Subjects with MEFV polymorphisms

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**Table 1.** Characteristics of included studies

Author	Year	Country	Ethnicity	No. of cases	No. of controls	Age	Female (%)	MEFV variants
Akkoc	2010	Turkey	Caucasian	62	50	42.8±12.5	66	M694V, E148Q, V726A, M680I, P760P, K695R
Cosan	2010	Turkey	Caucasian	193	103	38.2±11.5	68	M694V, E148Q, V726A, M680I
Yigit	2012	Turkey	Caucasian	103	120	38.7±9.2	52	M694V, E148Q, V726A, M680I, P369S
He	2014	China	Asian	200	200	34±10.55	19	M694V, M680I, I729V, S749C

**Table 2.** Quality scores of studies using Newcastle-Ottawa Scale (maximum score of 9)

Study	Selection	Comparability	Outcome	Overall quality
Akkoc	4	2	2	8
Cosan	3	2	2	7
Yigit	3	2	2	7
He	4	2	2	8

**Table 3.** Summary of the meta-analysis results

		OR (95% CI)	P	P <sub>heterogeneity</sub>
MEFV variants	Overall	2.46 (1.66-3.63)	<0.00001	0.95
M694V	Overall	4.19 (2.19-8.02)	<0.0001	0.75
	Caucasian	4.02 (1.96-8.22)	0.0001	0.56
E148Q	Overall	1.37 (0.74-2.55)	0.32	0.76
V726A	Overall	1.81 (0.65-5.01)	0.26	0.57
M680I	Overall	1.59 (0.64-3.95)	0.31	0.73
	Caucasian	1.53 (0.58-4.08)	0.39	0.53

was associated with a significantly increased risk of AS (OR=2.46; 95% CI, 1.66-3.63; **Figure 2**). Subjects with MEFV M694V polymorphism had increased AS risk (OR=4.19; 95% CI, 2.19-8.02; **Figure 3**). In the race subgroup analysis, Caucasians with MEFV M694V polymorphism had increased AS risk (OR=4.02; 95% CI, 1.96-8.22). However, Subjects with E148Q, V726A, or M680I polymorphism did not show significant increased AS risk (OR=1.37; 95% CI, 0.74-2.55; OR=1.81; 95% CI, 0.65-5.01; OR=1.59; 95% CI, 0.64-3.95; **Figures 4-6**), respectively. In the race subgroup analysis, Caucasians with MEFV M680I polymorphism also had no increased AS risk (OR=1.53; 95% CI, 0.58-4.08). Since only 4 studies were included in the meta-analysis, we did not perform funnel plot and Egger's test.

## Discussion

To our knowledge, this is the first meta-analysis about the association between the MEFV polymorphisms and AS risk. We found that individu-

als with MEFV polymorphisms showed an increased risk of AS in the overall population. Most importantly, the significant association was observed in individuals with MEFV M694V polymorphism. No significant result was found in subjects with E148Q, V726A, or M680I polymorphism. Only 4 studies were included in this meta-analysis. The possible reason might be the low sample size. Thus, more studies with large sample size should be conducted in the future.

Deniz et al. found that Carrier rate for the studied MEFV mutations was slightly lower in the systemic lupus erythematosus (SLE) group, which is in agreement with previous observations that FMF may confer

some protection from SLE [8]. Nonaka et al. found that low-frequency variants of MEFV gene may be one of the susceptibility factors of adult-onset Still's disease [9]. Fujikawa et al. suggest that MEFV gene polymorphisms and TNFRSF1A mutation are susceptibility and modifier genes in inflammatory myopathy with abundant macrophages (IMAM) [10]. Tasliyurt and colleagues suggested that MEFV mutations appear to have a role in the pathogenesis of Behcet's disease [11].

In this meta-analysis, no significant heterogeneity was observed. However, some limitations should be addressed. First, due to the limited availability of published results, the number of studies included in each meta-analysis was small. Second, the studies investigating genetic associations should be based on a large sample size, similar study designs and standardised case and control definitions. Third, we did not have enough data to conduct any gene-gene interaction analyses. Finally, our results

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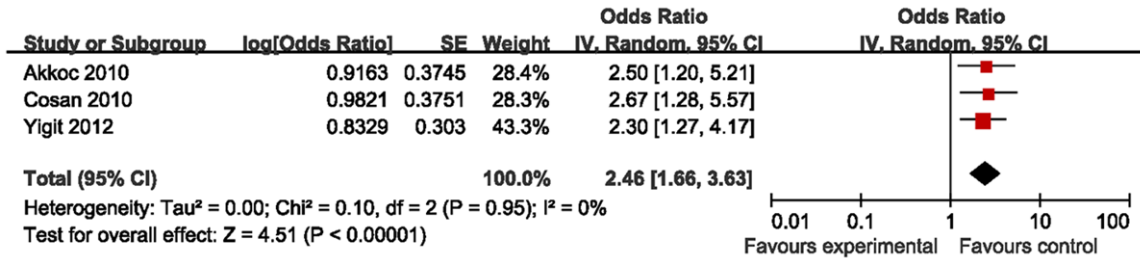


Figure 2. Meta-analysis for the association between MEFV polymorphisms and AS risk.

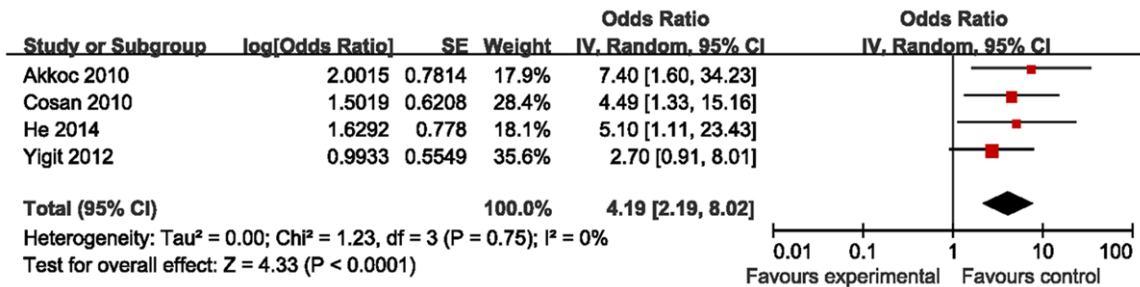


Figure 3. Meta-analysis for the association between MEFV M694V polymorphism and AS risk.

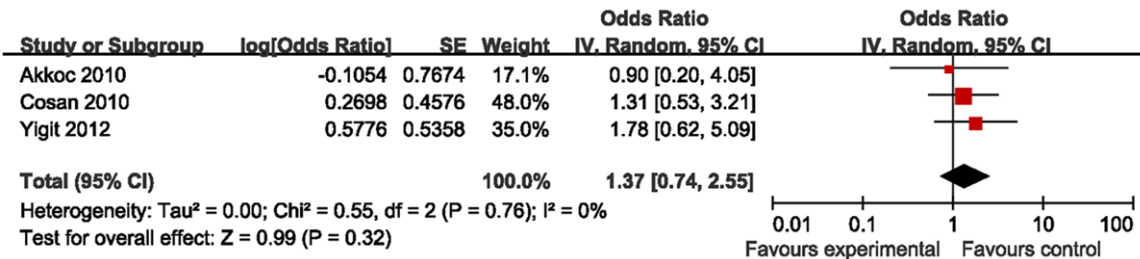


Figure 4. Meta-analysis for the association between MEFV M694V polymorphism and AS risk.

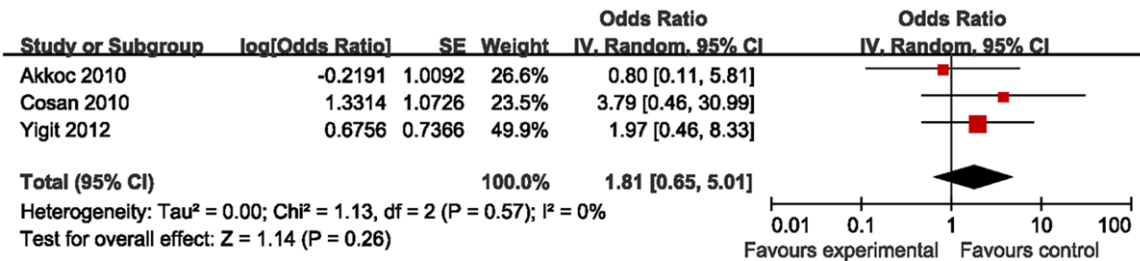


Figure 5. Meta-analysis for the association between MEFV M694V polymorphism and AS risk.

were based on single-factor evaluations without adjustment for other risk factors, including tobacco, alcohol, environmental factors, or lifestyle.

In conclusion, this meta-analysis suggested that MEFV M694V polymorphism may be associated with the risk of AS.

### Acknowledgements

This work was supported by Yunnan Applied Basic Research Project (Grant No. 2015FD073).

### Disclosure of conflict of interest

None.

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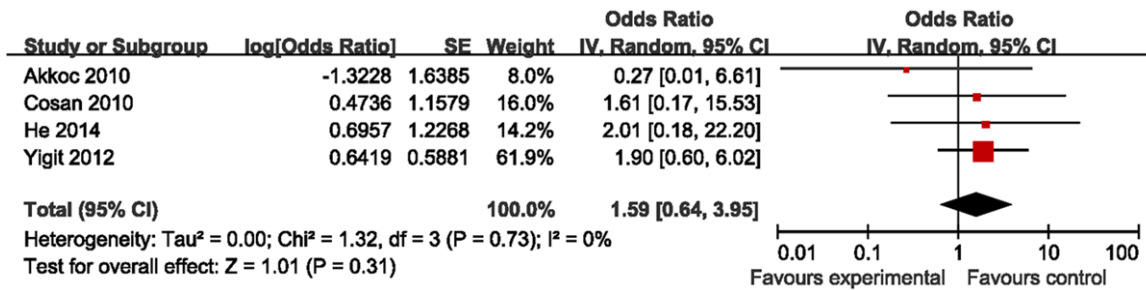


Figure 6. Meta-analysis for the association between MEFV M680I polymorphism and AS risk.

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