

Association between interleukin 37 (rs3811047) polymorphism and multiple autoimmune diseases in a Chinese population

A PRISMA-compliant meta-analysis

Xiao-Yan Lin, MM, Xue-Jun Guo, MM*, Yu-Zhuo He, MM, Shu-Fang Hou, MM, Hong-Bin Zhu, MM, Ying Cheng, MM, Zhen Nan, MM

Abstract

Objective: Emerging evidence suggests that interleukin 37 (IL-37) plays an important role in the pathogenesis of several autoimmune diseases (ADs), but the correlations are still unclear. We conducted a meta-analysis to explore whether *IL-37* gene (*rs3811047*) polymorphism was associated with susceptibility to multiple ADs in a Chinese population.

Methods: Relevant studies were searched in the PubMed, Embase, Chinese National Knowledge Infrastructure, and Chinese Wangfang databases up to August 31, 2017. Odds ratio (OR) and its 95% confidence interval (95% CI) was used to estimate the strength of the association in different genetic models. The results of fixed or random models were adopted according to the heterogeneity. Publication bias and sensitive analysis were also performed to evaluate the reliability of results.

Results: A total of 3161 patients and 4078 controls from 6 studies were included in this meta-analysis. Pooling all data together, a significant association between *IL-37* gene (*rs3811047* A/G) polymorphism and susceptibility to ADs in the Chinese population was found in all 4 genetic models (allelic model A vs G: OR = 0.73 95% CI = 0.67~0.79; recessive model AA + AG vs GG: OR = 0.72, 95% CI = 0.65~0.79; dominant model AA vs AG + GG: OR = 0.59, 95% CI = 0.45~0.77; homozygous model AA vs GG: OR = 0.55, 95% CI = 0.42~0.72). No heterogeneity and publication bias was detected in all models. Sensitive analysis indicated that all of the positive results are reliable.

Conclusion: The *IL-37* (*rs3811047*) polymorphism contributes to the development of ADs in a Chinese population.

Abbreviations: ADs = autoimmune diseases, CIs = confidence intervals, IL-37 = interleukin-37, OR = odds ratio, SNP = single nucleotide polymorphism.

Keywords: autoimmune diseases, interleukin 37, meta-analysis, polymorphism

1. Introduction

Autoimmune diseases (ADs) are a heterogeneous group of complex disorders with a clinical manifestation of a broken immune tolerance, and intermittent inflammation, which leads to the immune system produces antibodies against the body's own tissues.^[1] Although the onset of ADs is not fully known so far, it

is confirmed that the diseases are caused by interactions between genetic and environmental factors.^[2] Furthermore, these diseases share some characteristics that suggest common etiologic mechanisms or pathways. This hypothesis is strengthened by some genetic association studies and meta-analysis in patients with ADs in different populations.^[3-5]

Interleukin (IL)-37, formerly named as IL-1 family member 7 (IL-1F7), is an anti-inflammatory cytokine that suppresses the innate inflammatory and immune responses.^[6,7] Evidence shows that IL-37 plays a protective role in inflammatory and ADs in animal models via inhibition of the generation of pro-inflammatory cytokines and the activation of macrophage and dendritic cells (DCs).^[8] Recently, several studies have shown that the expression of IL-37 was abnormal in ADs, such as rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), ankylosing spondylitis (AS), Graves disease (GD), inflammatory bowel disease (IBD), and psoriasis.^[9-11] Furthermore, the functional analysis indicated that IL-37 is negatively involved in the development and pathogenesis of these autoimmune disorders.^[12]

The *IL1* gene cluster is located on chromosome 2q12-13 and spans a 360-kb region, including the following *IL1*-related genes: *IL1A*, *IL1B*, *IL1F5*, *IL1F6*, *IL1F7* (*IL-37*), *IL1F8*, *IL1F9*, *IL1F10*, and *IL1RN*.^[13] Recently, many genetic studies have demonstrated that *IL37* gene SNP rs3811047 G>A is related to

Editor: Kou Yi.

Funding/support: There was no funding support in this study.

The authors declare that they have no conflict of interest.

Department of Hemopathology, Puyang City Oilfield General Hospital, Puyang City, Henan, P.R. China.

* Correspondence: Xue-Jun Guo, Department of Hemopathology, Puyang City Oilfield General Hospital, No. 124 Daqing Road, Puyang City 457001, Henan, P. R. China (e-mail: xjgpyh@sina.com).

Copyright © 2018 the Author(s). Published by Wolters Kluwer Health, Inc. This is an open access article distributed under the terms of the Creative Commons Attribution-Non Commercial License 4.0 (CCBY-NC), where it is permissible to download, share, remix, transform, and buildup the work provided it is properly cited. The work cannot be used commercially without permission from the journal.

Medicine (2018) 97:15(e0386)

Received: 9 November 2017 / Received in final form: 18 March 2018 /

Accepted: 20 March 2018

<http://dx.doi.org/10.1097/MD.0000000000010386>

the susceptibility to ADs, such as AS, disease activity of RA, and gastric cardiac adenocarcinoma; however, the results were controversial and inconsistent.^[14–18] This discrepancy is perhaps because of small sample sizes with lack of statistical power in most studies, and/or clinical heterogeneity. Therefore, a meta-analysis of published case–control studies was undertaken to precisely evaluate whether the IL37 gene SNP rs3811047 G>A polymorphism is associated with the risk of ADs. Meanwhile, heterogeneity, stability of results, and publication bias were carefully analyzed in this study.

2. Methods

2.1. Eligible studies search

We execute a comprehensive article search in the following databases: PubMed, EMBASE, Chinese National Knowledge Infrastructure, and Chinese Wanfang, with search time range from the register to August 31, 2017. The following combination of keywords was used: “polymorphisms or variants,” “IL-1F7 or IL-1 family member 7 or IL-37 or interleukin 37 or rs3811047,” and “autoimmune diseases.” References of potential articles were also manually screened to identify additional studies not indexed in these referred databases.

2.2. Inclusion and exclusion criteria

To acquire valid articles we needed, some inclusion and exclusion criteria were established. Inclusion criteria were as follows: focus on the association of rs3811047 with ADs risk; study design was a case–control study; and genotype distributions or allele counts were available to calculate an OR and its 95% CI. Studies involving larger samples or published more recently were selected in cases of repeated studies or overlapping data. If the reported data were incomplete, the corresponding author was contacted to obtain complete data. Exclusion criteria were as follows: reviews, comments, abstracts, and genotype only in cases; genotype distribution in controls that deviated from Hardy–Weinberg disequilibrium (HWE); and repeated publication.

2.3. Quality score assessment

The quality of all included studies was evaluated independently using the Newcastle–Ottawa scale, which constituted of 3 aspects such as selection, comparability, and exposure with a maximum score of 9.^[19] A total of scores of each study in ≤ 3 , 4 to 6, ≥ 7 was considered as low, medium, and high-quality study, respectively. If there was discrepancy in the process of evaluation, a third investigator would adjust in the ultimate.

2.4. Data extraction

After we identified all eligible studies and finished the quality evaluation of each study, 2 investigators independently and carefully extract the following information from all eligible studies: name of the first author; publication year; ethnicity of population; sample size of cases and controls, results of the HWE test; and genotype distribution in cases and controls. Any discrepancies in the information of extraction were resolved by discussing with our research team until a consensus was reached between the 2 investigators.

2.5. Statistical analysis

The pooled odds ratios (ORs) and its 95% confidence intervals (95% CIs) were calculated to assess the strength of association between the rs3811047 and ADs risk using all 4 genetic models: allelic model (A vs G), recessive model (AA+AG vs GG), dominant model (AA vs AG+GG), and homozygous model (AA vs GG).

Heterogeneity across all eligible studies was assessed using Q-test, and $P < .10$ indicated that heterogeneity existed evidently among all studies.^[20] According to the heterogeneity among different comparisons, the fixed effects model results on Mantel–Haenszel method ($P \geq .10$) or the random effects model results on DerSimonian–Laird method ($P < .10$) were adopted.^[21] Heterogeneity was also quantified by the I^2 test; the values of I^2 in 0% to 25%, 26% to 50%, and 50% to 100% were considered as lower, moderate, and high heterogeneity, respectively.

The potential publication bias was assessed by the Begg funnel plot and the Egger linear regression test.^[22,23] Sensitive analysis by omitting study one by one was performed to evaluate which study has a significant impact on the stability of results.

The 2-sided P value of less than .05 was considered statistically significant. All statistical analyses were performed using STATA version 12.0 software (STATA Corporation, College Station, TX).

2.6. Ethnic statement

The meta-analysis was based on previous published studies; thus, no ethical approval and patient consent are required.

3. Results

3.1. Characteristics of eligible studies

The specific process of studies selection according to PRISMA 2009 flow diagram is shown in Fig. 1. First, a total of 104 articles were obtained from databases. After we screened the titles and abstracts, 20 duplicates were removed from retrieval, and another 77 studies were removed due to irrelevant topics (not about ADs or IL-37 gene) and reviews, meta-analysis, and animal study. Then, the full-text of the rest of 7 studies were downloaded for reading carefully; we removed 1 study due to insufficient data for calculating OR and 95% CI^[24]; 1 article contains 2 types of ADs and each one was considered as a separate study.^[18] Finally, a total of 6 studies were included in this meta-analysis. All of the studies were of high quality (NOS score ≥ 7). The basic characteristics of these studies are summarized in Table 1.

3.2. Meta-analysis of IL-37 rs3811047 polymorphism in ADs

A summary of meta-analysis findings concerning associations between the IL-37 rs3811047 polymorphism and ADs is provided in Table 2. No cross-study heterogeneity was found in all genetic models, so that fixed-model results were adopted ultimately. A meta-analysis revealed a significant association between IL-37 gene (rs3811047 A/G) polymorphism and susceptibility to ADs in the Chinese population in all 4 genetic models (allelic model A vs G: OR=0.73, 95% CI=0.67~0.79; recessive model AA+AG vs GG: OR=0.72, 95% CI=0.65~0.79; dominant model AA vs AG+GG: OR=0.59, 95% CI=0.45~0.77; homozygous model AA vs GG: OR=0.55, 95% CI=0.42~0.72) (forest plot in Fig. 2).

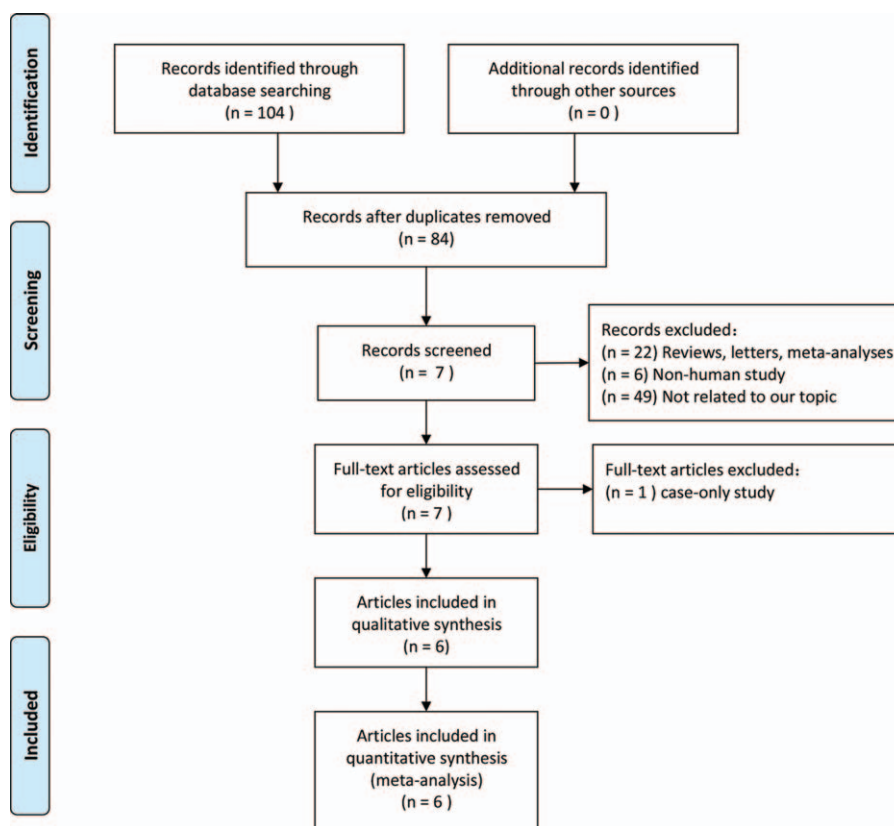


Figure 1. Flow diagram of studies included in the meta-analysis.

Table 1

Basic characteristics of the eligibility studies included in this meta-analysis.

First author (ref)	Publication year	Disease	Population	Sample size		Genotyping method	NOS Score	HWE	Genotype distribution (cases/controls)					
				Cases	Controls				AA	AG	GG	AA	AG	GG
Chen et al [14]	2011	AS	Chinese	158	181	LDR-PCR	7	Y	0	38	120	5	54	122
Pei et al [15]	2013	RA	Chinese	184	184	LDR-PCR	8	Y	4	51	127	5	55	124
Shi t al [16]	2013	RA	Chinese	276	276	LDR-PCR	8	Y	6	77	193	8	82	186
Yan et al [17]	2015	AITD	Chinese	1061	938	PCR	7	Y	42	313	688	38	288	581
Tan et al [18]	2016	BD	Chinese	1063	1872	LDR-PCR	8	Y	22	233	808	66	586	1220
Tan et al [18]	2016	VKH	Chinese	419	627	LDR-PCR	8	Y	16	221	390	5	185	229

AITD=autoimmune thyroid disease, AS=ankylosing spondylitis, BD=Behcet disease, HWE=Hardy-Weinberg disequilibrium, LDR-PCR=ligase detection reactions polymerase chain reaction, NOS=Newcastle-Ottawa scale, RA=rheumatoid arthritis, VKH=Vogt-Koyanagi-Harada disease, Y=indicate genotype distribution in control conform to HWE.

Table 2

Meta-analysis of the association of IL-37 gene (rs3811047) polymorphism with multiple autoimmune diseases.

Groups	Statistical model	Allele/genotype	Genetic model	I ² (%)	P*	OR (95% CI)	P†	Begg (P)	Egger (P)
ADs	Allelic	A vs G	Fixed	38.9	.147	0.73 (0.67~0.79)	.000	1.000	.353
	Recessive	AA + AG vs GG	Fixed	48.5	.100	0.72 (0.65~0.79)	.001	1.000	.435
	Dominant	AA vs AG + GG	Fixed	45.9	.100	0.59 (0.45~0.77)	.001	.707	.588
	Homozygous	AA vs GG	Random	40.0	.139	0.55 (0.42~0.72)	.001	1.000	.595

CI = confidence interval, OR = odds ratio.

* P value for between-study heterogeneity.

† P value for test of the association.

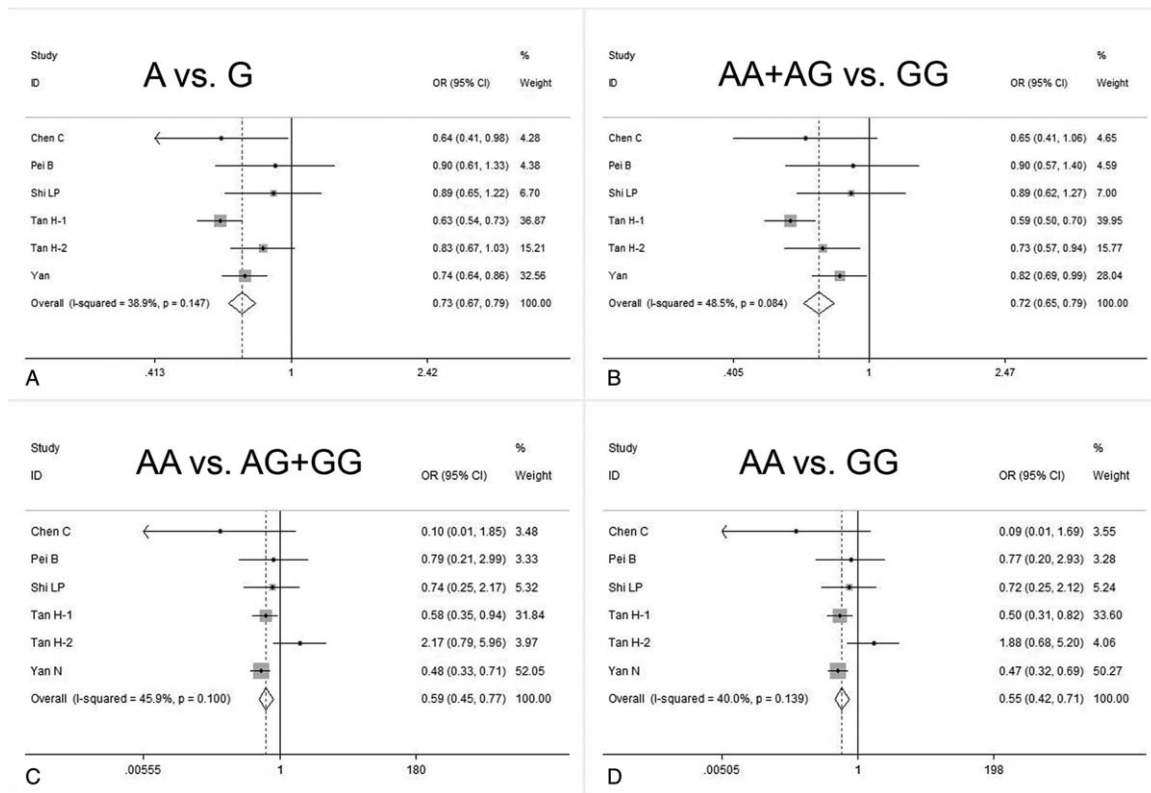


Figure 2. Forest plot for the meta-analysis of the *IL-37* (*rs3811047*) polymorphism and ADs in a Chinese population.

3.3. Publication bias and sensitive analysis

Begg and Egger tests were performed in all comparisons to detect publication bias. Begg funnel plots showed no evident asymmetry and Egger linear regression analysis did not reveal any evidence of publication bias in the meta-analysis (Table 2 and Fig. 3).

Sensitive analysis by omitting 1 study at a time was performed to determine whether any single study had an impact on the overall meta-analysis estimate. Our results showed that omission of any individual study did not make a significant difference in the pooled effects, suggesting that our results of this meta-analysis were robust and reliable under all models (Fig. 4).

4. Discussion

ADs are a group of complex diseases that has a strong link with a combination of genetic and environmental factors. The failure of the host immune system to recognize self-antigens often leads to the formation of auto-antibody, immune complex deposition, and immune-mediated tissue destruction. In the past years, several genome-wide association studies (GWAS) and pathway analyses share genes associated with multiple ADs and may suggest common mechanisms that lead to the development of ADs.^[25,26]

IL-37 is a recently identified member of the *IL-1* cytokine family and has received an increasing attention on the role of ADs.^[6,7] Genetic polymorphisms may affect the transcription of inflammatory cytokines and then further affect susceptibility to ADs. In recent years, many studies on the association of *IL-37* polymorphism with ADs have been reported with inconsistent results. Chen et al^[14] showed a significant difference in the distribution of *IL-1F7* (*rs3811047*) genotypes and allele

frequencies between AS patients and healthy controls. In addition, the positive rate of *HLA-B27* in AS patients, which represented as AG genotype, was statistically lower than that in AS patients, which represented as GG genotype; erythrocyte sedimentation rate and C-reactive protein levels were conspicuously lower than that in GG genotype. Pei et al^[15] and Shi et al^[16] showed that the allele frequency and genotype distribution of *rs3811047* in *IL-1 F7* gene in RA (276 and 284 patients, respectively) and control groups was not statistically significant difference in the Chinese population. However, they found that RA patients with A allele were better than those with G allele in joint swelling index, rest pain, health assessment questionnaire (HAQ) score, and blood sedimentation. Yan et al^[17] performed a case-control study with a relatively large sample size comprising 1061 autoimmune thyroid disease (AITD) patients and 939 controls showed that the *rs3811047* A allele was significantly associated with a decreased risk of AITD. Tan et al^[18] conducted a genetic association study including 419 VKH cases, 1063 BD cases, and 1872 healthy controls, and showed that the frequency of the A allele and AG genotype of *rs3811047* was significantly lower in BD, but not in VKH, as compared with controls.

The above inconsistent results may due to the small number of samples and the corresponding low statistical power to detect a slight association. Meta-analysis is a quantitative, formal, epidemiological study design used to systematically assess previous research studies to derive conclusions about that body of research.^[27] In the present study, we pooled individual study together, which comprised a total of 3161 patients with ADs and 4078 healthy controls in the Chinese population. The results of this meta-analysis provide evidence of associations between *IL-37* gene (*rs3811047A/G*) polymorphism and susceptibility to

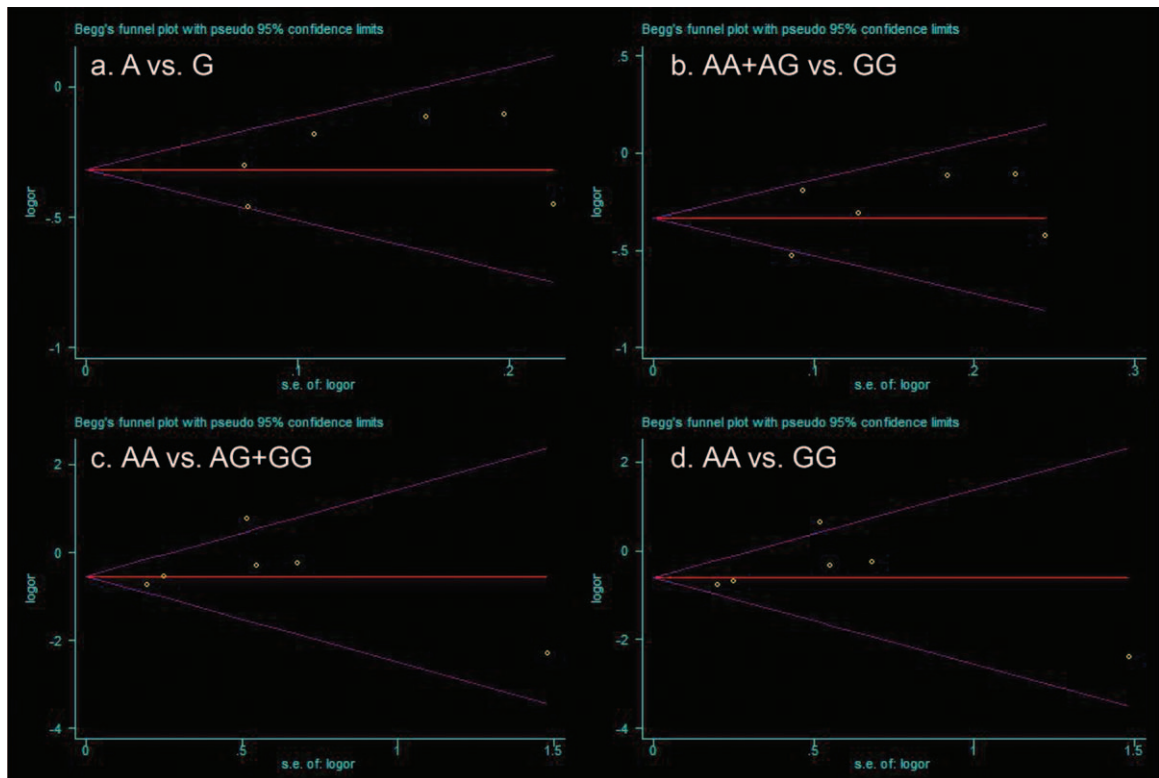


Figure 3. Begg funnel asymmetry plot of the *IL-37* (*rs3811047*) polymorphism and ADs in a Chinese population.

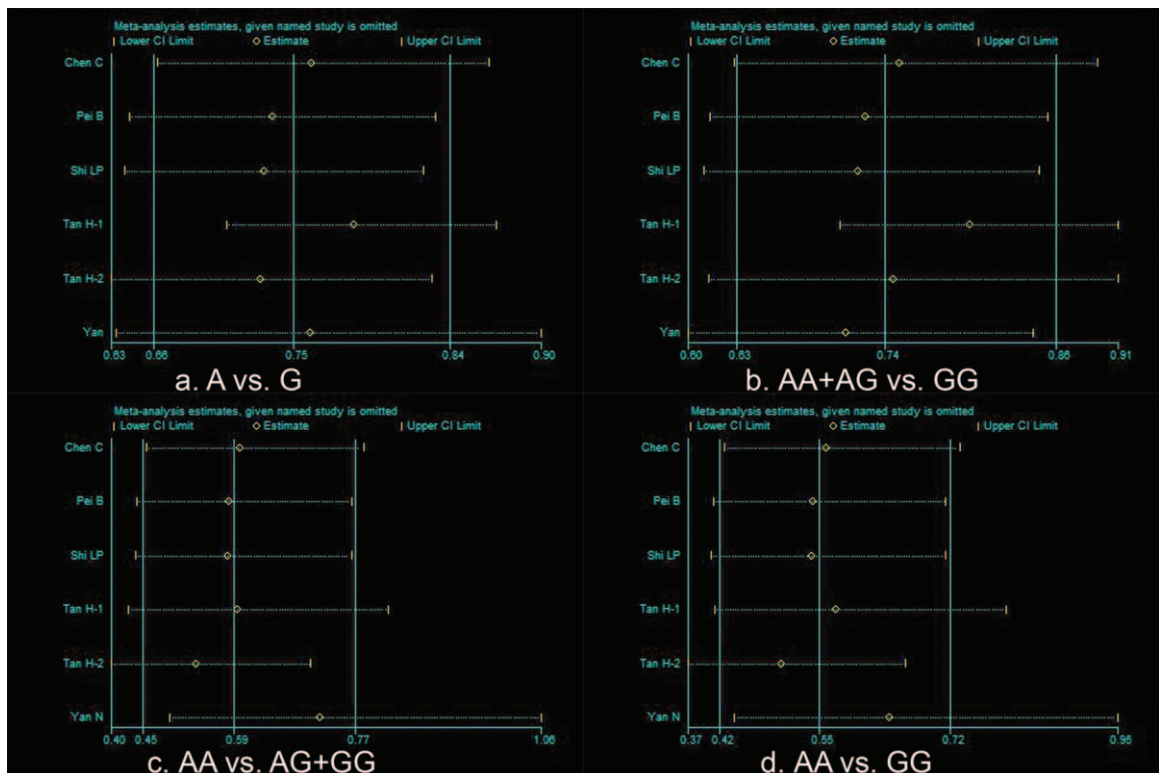


Figure 4. Sensitivity analysis of the *IL-37* (*rs3811047*) polymorphism and ADs in a Chinese population.

ADs. No significant heterogeneity was detected in all genetic models, which indicated that studies of our synthesis were homogeneous. In addition, no publication bias was detected in all genetic models, and sensitive analysis showed no substantial change after 1 study was omitted at a time, indicating that the results of our meta-analysis were reliable.

To our knowledge, this is the first comprehensive meta-analysis to investigate the association between *IL-37* gene (*rs3811047A/G*) polymorphism and susceptibility to ADs in the Chinese population. The strength of this study is that a large number of subjects was included with an increased statistical power. Nevertheless, there are several limitations in the present meta-analysis that should be taken into consideration. First, although the overall sample size is relatively large, the number of studies in different types of ADs is scanty, and lots of another AD were not included in the analysis, and this might cause insufficient representative for all ADs. Second, the studies for ethnicity were mainly from the Chinese population. Thus, the findings apply to only these populations, and further studies in other populations were required. Furthermore, the present meta-analysis was based on uncorrected estimates. A more precise analysis could be performed if the potential confounding factors including sex, age, environmental factors, and other lifestyle factors were available. Further, the effects of gene–environment interactions on the initiation and development of ADs need to be analyzed further in individual patients.

In summary, this meta-analysis demonstrates that *IL-37* (*rs3811047*) polymorphism contributes to the development of ADs in a Chinese population. Further studies with more sample size in other populations and other ADs are still needed to confirm this finding.

Author contributions

Conceptualization: Hong-Bin Zhu.

Conceptualization: Xue-Jun Guo, Hong-Bin Zhu, Ying Cheng, Zhen Nan.

Data curation: Xiao-Yan Lin, Yu-Zhuo He, Shu-Fang Hou, Hong-Bin Zhu, Ying Cheng, Zhen Nan.

Formal analysis: Yu-Zhuo He, Shu-Fang Hou, Ying Cheng.

Methodology: Shu-Fang Hou, Zhen Nan.

Supervision: Xue-Jun Guo.

Writing original draft: Xiao-Yan Lin.

Writing review and editing: Xue-Jun Guo.

References

- [1] Gupta S, Louis AG. Tolerance and autoimmunity in primary immunodeficiency disease: a comprehensive review. *Clin Rev Allergy Immunol* 2013;45:162–9.
- [2] Cantorna MT, Mahon BD. Mounting evidence for vitamin D as an environmental factor affecting autoimmune disease prevalence. *Exp Biol Med* 2004;229:1136–42.
- [3] Li YR, Li J, Zhao SD, et al. Meta-analysis of shared genetic architecture across ten pediatric autoimmune diseases. *Nat Med* 2015;21:1018–27.
- [4] Li J, Lin SY, Lv YB, et al. Association study of MMP-9-1562C/T gene polymorphism with susceptibility to multiple autoimmune diseases: a meta-analysis. *Arch Med Res* 2017;48:105–12.
- [5] Lee YH, Bae SC. Association between interferon-(+874 T/A polymorphism and susceptibility to autoimmune diseases: a meta-analysis. *Lupus* 2016;25:710–8.
- [6] Xu WD, Zhao Y, Liu Y. Insights into IL-37, the role in autoimmune diseases. *Autoimmun Rev* 2015;14:1170–5.
- [7] Ye L, Huang Z. IL-37 restrains autoimmune diseases. *Oncotarget* 2015;6:21775–6.
- [8] McNamee EN, Masterson JC, Jedlicka P, et al. Interleukin 37 expression protects mice from colitis. *Proc Natl Acad Sci U S A* 2011;108:16711–6.
- [9] Yang L, Zhang J, Tao J, et al. Elevated serum levels of interleukin-37 are associated with inflammatory cytokines and disease activity in rheumatoid arthritis. *APMIS* 2015;123:1025–31.
- [10] Wu GC, Li HM, Wang JB, et al. Elevated plasma interleukin-37 levels in systemic lupus erythematosus patients. *Lupus* 2016;25:1377–80.
- [11] Fawzy RM, Ganeb SS, Said EA, et al. Serum level of interleukin-37 and expression of its mRNA in ankylosing spondylitis patients: possible role in osteoporosis. *Egypt J Immunol* 2016;23:19–29.
- [12] Akdis M, Burgler S, Cramer R, et al. Interleukins, from 1 to 37, and interferon-gamma: receptors, functions, and roles in diseases. *J Allergy Clin Immunol* 2011;127:701–21.
- [13] Nicklin MJ, Barton JL, Nguyen M, et al. A sequence-based map of the nine genes of the human interleukin-1 cluster. *Genomics* 2002;79:718–25.
- [14] Chen C, Xu SQ, Pan FM, et al. Study of the interleukin-1F7 gene single nucleotide polymorphism in patients with ankylosing spondylitis. *Chin J Rheumatol* 2011;15:74–8.
- [15] Pei B, Xu S, Liu T, et al. Associations of the IL-1F7 gene polymorphisms with rheumatoid arthritis in Chinese Han population. *Int J Immunogenet* 2013;40:199–203.
- [16] Shi LP, He Y, Liu ZD. Correlation between single nucleotide polymorphism of rs3811047 in IL-1 F7 gene and rheumatoid arthritis susceptibility among Han population in central plains of China. *Asian Pac J Trop Med* 2013;6:73–5.
- [17] Yan N, Meng S, Song RH, et al. Polymorphism of IL37 gene as a protective factor for autoimmune thyroid disease. *J Mol Endocrinol* 2015;55:209–18.
- [18] Tan H, Deng B, Yu H, et al. Genetic analysis of innate immunity in Behcet's disease identifies an association with IL-37 and IL-18RAP. *Sci Rep* 2016;6:35802.
- [19] Li P, Yang XK, Wang X, et al. A meta-analysis of the relationship between MYO9B gene polymorphisms and susceptibility to Crohn's disease and ulcerative colitis. *Hum Immunol* 2016;77:990–6.
- [20] Li P, Tao SS, Zhao MQ, et al. Association study of matrix metalloproteinases gene polymorphisms with susceptibility to rheumatoid arthritis: a meta-analysis. *Immunol Invest* 2015;44:603–15.
- [21] Ades AE, Lu G, Higgins JP. The interpretation of random-effects meta-analysis in decision models. *Med Decis Making* 2005;25:646–54.
- [22] Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. *Biometrics* 1994;50:1088–101.
- [23] Egger M, Davey Smith G, Schneider M, et al. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997;315:629–34.
- [24] Ge R, Pan F, Liao F, et al. Analysis on the interaction between IL-1F7 gene and environmental factors on patients with ankylosing spondylitis: a case-only study. *Mol Biol Rep* 2011;38:2281–4.
- [25] Kreiner E, Waage J, Standl M, et al. Shared genetic variants suggest common pathways in allergy and autoimmune diseases. *J Allergy Clin Immunol* 2017;140:771–81.
- [26] Dinarello CA, Nold-Petry C, Nold M, et al. Suppression of innate inflammation and immunity by interleukin-37. *Eur J Immunol* 2016;46:1067–81.
- [27] Haidich AB. Meta-analysis in medical research. *Hippokratia* 2010;14 (Suppl 1):29–37.