SARCOIDOSIS VASCULITIS AND DIFFUSE LUNG DISEASES 2018; 35; 115-122

NOD2/CARD15 gene polymorphisms and sarcoidosis susceptibility: review and meta-analysis

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Abstract. *Background:* The association between *NOD2/CARD15* (nucleotide binding oligomerisation domain containing 2) gene polymorphisms and susceptibility to sarcoidosis have been extensively investigated in recent years. However, the results from previous studies remain controversial. To assess the association of *NOD2/CARD15* polymorphisms and sarcoidosis susceptibility, we performed a meta-analysis. *Methods:* PubMed, Embase, CNKI and Wanfang databases were examined for all relevant studies up until 8th October 2016. In all, 968 cases and 1549 controls in eight case-control studies were included which mainly consisted of Caucasian participants. The relevant data were extracted and the odds ratio (OR) with 95% confidence intervals (95% CI) calculated to assess the strength of any associations. Statistical analyses were calculated using STATA12.0 software and Revman5.3 software. The associations between *NOD2/CARD15* SNP rs2066844, rs2066845, rs2066847, rs1861759 polymorphisms and the risk of sarcoidosis were evaluated in allelic, dominant, recessive and additive models. *Results:* The pooled data showed that the *NOD2/CARD15* rs2066845 polymorphism was associated with sarcoidosis susceptibility in allelic model (C vs. G, OR=1.86, 95% CI: 1.14-3.04, P=0.01), dominant model (GC + CC vs. GG, OR=1.84, 95% CI: 1.11-3.05, P=0.02) and additive model (GC vs. GG, OR=1.79, 95% CI: 1.08-2.97, P=0.02). However, the results suggested that the rs2066844, rs2066847 and rs1861759 polymorphisms might not be associated with a risk of sarcoidosis. *Conclusions:* This meta-analysis indicated that the 'C' allele of SNP rs2066845 may be a risk factor for sarcoidosis, especially in Caucasians, whilst rs2066844, rs2066847 and rs1861759 may not be associated with a risk of developing sarcoidosis. *(Sarcoidosis Vasc Diffuse Lung Dis 2018; 35: 115-122)*

Key words: CARD15. genetic susceptibility, meta-analysis, polymorphism, sarcoidosis

Introduction

Sarcoidosis is a multisystem disease that mainly affects the lung and lymph nodes via an unknown cause, characterised by a noncaseating epithelioid cell granuloma lesion (1). Although the aetiology of sarcoidosis still remains unclear, it is likely that both a genetic predisposition and environmental agents are involved in the pathogenesis of the disease. Among several potential genetic risk factors, the association of polymorphism of NOD2/CARD15 gene with a risk of sarcoidosis has been extensively evaluated with inconsistent results in recent decades.

The human nucleotide binding oligomerisation domain containing 2 (*NOD2*) gene, also named *CARD15* or *NOD2/CARD15*, is located on chromosome 16q12, recognised as a major susceptibility gene for Crohn's disease (CD) (2). This gene encodes a protein comprised of two caspase recruitment do-

Received: 7 March 2017
Accepted after revision: 25 May 2017
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mains (CARD) and six leucine-rich repeats (LRRs) (2). This protein is primarily expressed in peripheral leukocytes and plays a part in the inherent immune response through the recognition of the muramyl dipeptide (MDP) which is a component part of the bacterial cell wall (3).

Lots of studies have shown that Blau syndrome, thought to be an early-onset variant of sarcoidosis, is a rare genetic disorder caused by distinct mutations in the *CARD15* gene. Meanwhile, recent advances have suggested the similarities in the pathogenesis characterised by an excessive immune response to unknown stimuli between sarcoidosis and CD (1, 4). Based on these findings, a significant body of work has been carried out regarding the associations of CD and Blau syndrome-related mutations with sarcoidosis, and novel potential sarcoidosis-associated mutations have also been discovered. Among *NOD2/CARD15* genes involved in sarcoidosis, three CD-associated *CARD15* mutations, R702W (rs2066844), G908R (rs2066845) and L1007fs (rs2066847) are most frequently studied. They cluster near the LRR, causing the immune response to MDP to be lowered (3).

However, the results from earlier studies have been inconsistent. Furthermore, many studies were of a small size and may be not sufficient to establish comprehensive conclusions. We performed this meta-analysis to further assess the associations between *NOD2/CARD15* rs2066844, rs2066845, rs2066847, rs1861759 gene polymorphisms and the risk of sarcoidosis.

Methods

Study selection

This meta-analysis was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) criteria (5). Two investigators (Xuping Chen, Zhenxing Zhou) independently searched Embase, PubMed, China National Knowledge Internet (CNKI) database and Wanfang database up until 8th October 2016. Agreements were attained through discussion or judged by a third author (Xiaodong Yang). All eligible papers were screened and their references were checked for any relevant studies. The search words used were as follows: 'sarcoidosis' or 'sarcoidoses' and 'NOD2/CARD15' or, 'NOD2' or 'CARD15' and 'Allele' or 'variation' or 'Mutation' or 'polymorphism'. The language was not restricted. The inclusion criteria were as follows: (1) case-control designs on unrelated individuals; (2) evaluating the *NOD2/CARD15* polymorphisms and sarcoidosis risk; (3) the controls in accordance with the Hardy-Weinberg equilibrium (HWE); (4) odds ratios (OR) with 95% confidence intervals (95% CI) or enough data for their calculation were available; (5) In case of repeated or overlapping reports, only the one with most subjects was included. Exclusion criteria were as follows: (1) abstracts, reviews and studies with repeated data or without other essential information; (2) where allelic frequencies associated data could not be obtained; (3) sibling pairs or family-based research design.

Quality assessment

Two authors assessed the quality of included studies independently based on the Newcastle-Ottawa scale (NOS) (6), which evaluates the quality of observational studies according to the following three aspects: selection, comparability and exposure. The numbers of stars given for each aspect were cumulated to assess the study quality and studies which obtained 0-3 stars and 7-9 stars were rated as low and high quality, respectively.

Date Extraction

Data were extracted by two readers (Xuping Chen and Zhenxing Zhou) for each eligible study that included the necessary inclusion terms. Whenever there was a disagreement, a third author (Yi Zhang) evaluated these articles. For each individual report, information about the first author, year of publication, ethnicity, country, size of case and control, HWE, single-nucleotide polymorphisms (SNPs) and their genotype frequency data was collected.

Statistical Method

In this study, statistical analysis was calculated by STATA12.0 software and Revman5.3 software. For a measurement of the strength of associations between *NOD2/CARD15* rs2066844, rs2066845, rs2066847, rs1861759 gene polymorphisms and sar-

coidosis susceptibility in allelic, dominant, recessive and additive model selectively, the OR and 95% CI were employed. A Z-test was performed to determine the significance of the pooled OR. Heterogeneity among studies was evaluated by a Q test and I^2 test (I^2=100%×(Qdf)/Q). There was considered to be no significant heterogeneity among studies if p >0.10 and I^2 < 50% and then the fixed-effect model was chosen to test the OR; otherwise, the random effect model was used. Subgroup analysis was further assessed by ethnicity if possible. Publication bias was evaluated with several methods including funnel flots, Egger's test and Begg's test. As for the sensitivity analysis, a leave-one-out method was used to check the constancy of the results and to search for the source of heterogeneity if required. Statistically significant difference was considered if the P-value <0.05.

Results

Study characteristics

In all, 36 English studies and two Chinese studies conformed to the search strategy after an initial search of PubMed, Embase, CNKI and the Wanfang database. Eight relevant studies about the association of *NOD2/CARD15* gene polymorphisms with risk of sarcoidosis were ultimately incorporated into the meta-analysis. The flow diagram of selecting studies was presented in Figure 1.

Six studies were identified to evaluate the SNP rs2066844 of *NOD2/CARD15* and sarcoidosis (4, 7-11); five studies included data regarding SNP rs2066845 and rs2066847 (4, 7, 8, 11, 12) whilst three articles contained data about SNP rs1861759 (8, 9, 13). Among the eight articles, 2 were from

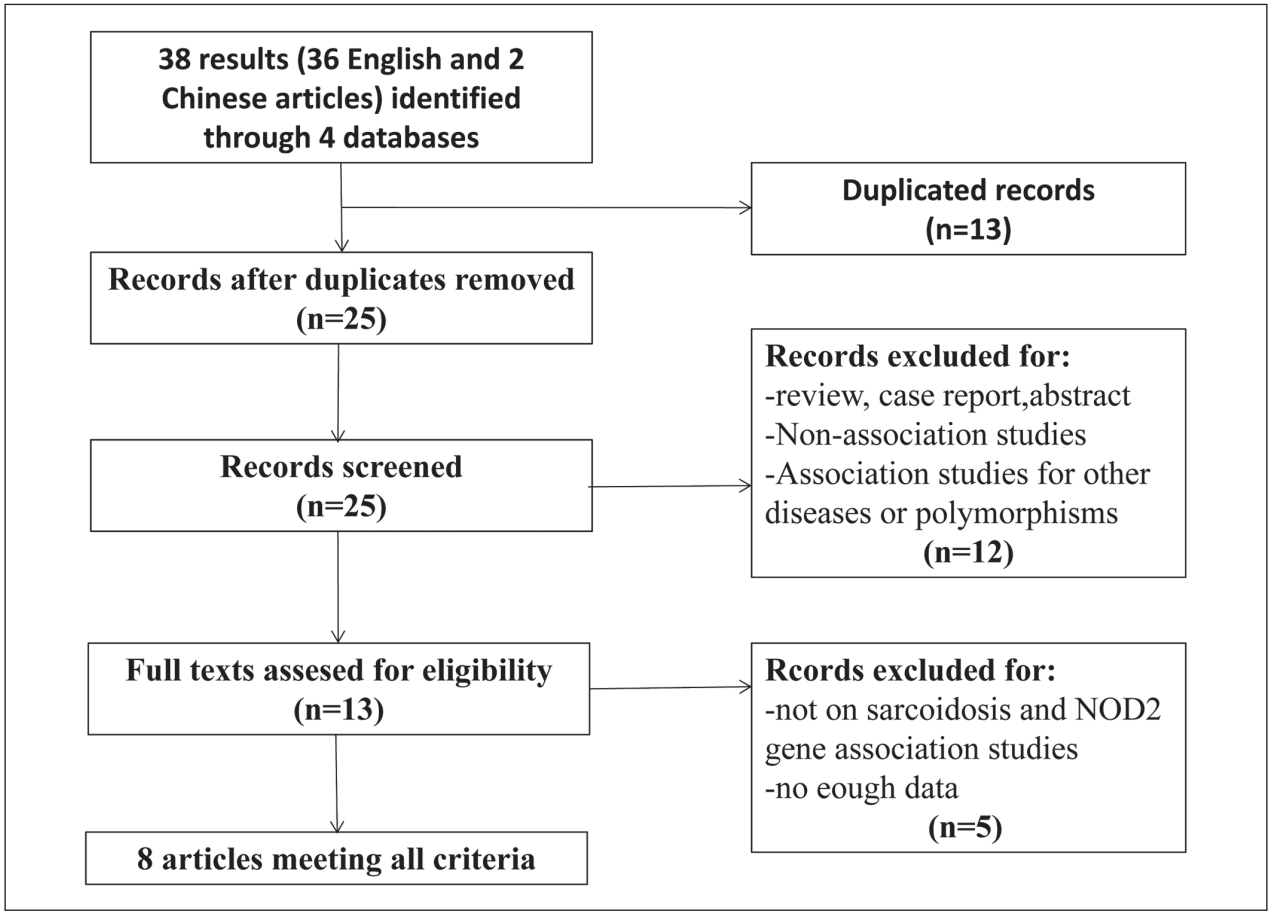

Fig. 1. The flow diagram of included and excluded studies

Germany, two from Denmark, whilst the others were from other countries (Greek, England, Italy, Japan etc.); the majority of the participants were Caucasians. Notably, since two studies (9, 12) used the same source of patients and controls, they contained information involving different SNPs and therefore they were taken as different studies. In case of double counting for the same SNPs in these two studies (9, 12), only data with the most subjects for each different SNP was chosen and calculated. The general features of all included studies are summarised in Table 1.

Assessment of study quality

To evaluate the quality of the included studies, the NOS scoring system was utilised. Three studies scored nine stars, another three scored eight stars, two studies two scored seven stars whilst two also scored six stars (Table 1). No study was rated to be low quality.

Quantitative analysis

NOD2/CARD15 rs2066844 and susceptibility to sarcoidosis

Six studies assessed the association between the SNP rs2066844 C/T polymorphism and sarcoidosis. However, no significant association was identified in the total analysis in either an allelic, dominant or recessive model (OR=1.08, 95% CI=0.81-1.42, P=0.61 for T vs. C; OR=0.97, 95% CI=0.73-1.30, P=0.85 for CT + TT vs. CC; OR=2.89, 95% CI=0.78-10.71, P=0.11 for TT vs. CT + CC). No significant heterogeneity across the studies was discovered (Table 2). All these studies involved Caucasians, so we did not perform the subgroup analysis.

NOD2/CARD15 rs2066845 and susceptibility to sarcoidosis

Five studies with available genotype data evaluated the association between SNP rs2066845 G/C polymorphism and the risk of sarcoidosis. We found

Table 1. The baseline characteristics of eight studies included in this meta-analysis

	Nucleotide change	Amino change acid	First author	Year	Country	Ethnicity	NOS Score	HWE	Total sample size Cases	Total sample size Controls	Allele distributions Cases		Allele distributions Controls	
rs2066844	2104C>T	R702W									C	T	C	T
			Gazouli	2006	Greek	Caucasian	9	Y	100	150	191	9	295	5
			H.SATO	2010	England	Caucasian	8	Y	185	347	351	19	658	36
			Milman N	2007	Danes	Caucasian	9	Y	52	103	100	4	198	8
			Pabst S	2011	Germany	Caucasian	8	Y	300	381	571	29	715	47
			Schurmann M	2003	Germany	Caucasian	7	Y	127	265	235	19	505	25
			Zorzetto M	2005	Italy	Caucasian	6	Y	68	208	130	6	398	18
rs2066845	2722G>C	G908R									G	C	G	C
			Gazouli M	2006	Greek	Caucasian	9	Y	100	150	182	18	289	11
			H. Sato	2010	England	Caucasian	8	Y	185	347	368	2	684	10
			Milman	2007	Danes	Caucasian	9	Y	53	103	104	2	204	2
			Schurmann M	2003	Germany	Caucasian	7	Y	127	265	246	8	526	4
			Zorzetto M	2005	Italy	Caucasian	6	Y	68	208	133	3	409	7
rs2066847	3020insC	1007fs									WT	insC	WT	insC
			Gazouli,M	2006	Greek	Caucasian	9	Y	100	150	178	22	278	22
			H. Sato	2010	England	Caucasian	8	Y	185	347	367	3	683	11
			Milman	2007	Danes	Caucasian	9	Y	53	103	104	2	202	4
			Schurmann M	2003	Germany	Caucasian	7	Y	127	265	246	8	511	19
			Zorzetto M	2005	Italy	Caucasian	6	Y	68	208	135	1	406	10
rs1861759	1761T>G	R587R									T	G	T	G
			H. Sato	2010	England	Caucasian	8	Y	185	347	222	148	439	255
			Akahoshi M	2008	Japanese	Japanese	8	Y	135	95	234	36	171	19
			Milman N	2007	Danes	Caucasian	9	Y	52	103	62	42	123	83

WT: wild-Type insC: insertion C HWE: Hardy-Weinberg Equilibrium

Table 2. Outcome, heterogeneity and publication bias of this meta-analysis

	Nucleotide change	Ethnicity	genetic model	OR with 95%CI	Z	P	Heterogeneity			Publication Bias	
							Chi²	P	I²(%)	Begg's test	Egger's test
rs2066844	2104C>T	Caucasian								0.26	0.29
			T vs C	1.08(0.81,1.42)	0.51	0.61	6.55	0.26	0.24		
			CT + TT vs CC	0.97(0.73,1.30)	0.2	0.85	6.54	0.26	0.24		
			TT vs CC + CT	2.89(0.78,10.71)	1.59	0.11	2.16	0.54	0		
rs2066845	2722G>C	Caucasian								0.46	0.41
			C vs G	1.86(1.14,3.04)	2.47	0.01	7.08	0.13	0.43		
		overall	GC + CC vs GG	1.84(1.11,3.05)	2.37	0.02	7.11	0.13	0.44		
			GC vs GG	1.79(1.08,2.97)	2.25	0.02	6.93	0.14	0.42		
		Removing	C vs G	2.54(1.46,4.40)	3.3	0.001	1.67	0.64	0	0.73	0.71
		'H.sato 2010'	GC + CC vs GG	2.55(1.45,4.49)	3.24	0.001	1.69	0.64	0		
			GC vs GG	2.47(1.40,4.36)	3.11	0.002	1.68	0.64	0		
rs2066847	3020insC	Caucasian								0.22	0.09
			insC vs WT	1.00(0.66,1.53)	0.01	0.99	4.45	0.35	0.1		
			WI + II vs WW	1.00(0.65,1.55)	0.01	0.99	4.71	0.32	0.15		
rs1861759	1761T>G									1	0.87
		Caucasian	G vs T	1.11(0.89,1.40)	0.92	0.36	0.23	0.63	0		
		Japanese	G vs T	1.38(0.77,2.50)	1.08	0.28					
		overall	G vs T	1.15(0.93,1.42)	1.26	0.21	0.69	0.71	0		

WT/W:wild-Type insC/I:insertion C

that the C allele of rs2066845 was associated with an increased risk of sarcoidosis in the allelic model (C vs. G, OR=1.86, 95%CI: 1.14-3.04, P=0.01), under the fixed-effect model, considering a moderate heterogeneity across the studies (I^2=43%, P=0.13). Similar results under a dominant model (GC + CC vs. GG, OR=1.84, 95%CI: 1.11-3.05, P=0.02) and additive model (GC vs. GG, OR=1.79, 95%CI: 1.08-2.97, P=0.02) were also found, which means individuals carrying the "C" allele (GC or CC carriers) were more susceptible to sarcoidosis compared with the GG carriers (Table 2) (Figure 2). No subgroup analysis was performed because these studies only involved Caucasians.

NOD2/CARD15 rs2066847 and susceptibility to sarcoidosis

Five studies evaluated the association between SNP rs2066847 WT/insC polymorphism and sarcoidosis. No statistically significant association was identified in the total analysis either in the allelic or dominant model (OR=1.00, 95%CI=0.66-1.53, P =0.99 for insC vs. WT; OR=1.00, 95%CI=0.65-1.55, P =0.99 for WI + II vs. WW). There was only a mild heterogeneity among the studies. (Table 2). No subgroup analysis was carried out for SNP rs2066847 as all studies included Caucasians.

NOD2/CARD15 rs1861759 and susceptibility to sarcoidosis

In total, three studies evaluated the association between SNP rs1861759 T/G polymorphism and the risk of sarcoidosis. We found no statistically significant association in the total analysis (OR=1.15, 95%CI=0.93-1.42, P=0.21 for G vs. T). Only an association in allelic model could be calculated with the limited data. No heterogeneity was revealed across the studies (Table 2).

Sensitivity analysis

For rs2066845, the sensitivity analysis was carried out by the change of effect model and leave-one-out method to check the stability of the results. The random effect model was carried out to test the OR. However, the opposite result (OR=1.79, 95%CI=0.84-3.84, P=0.13 for C vs. G) was obtained, which was contrary to the previous result. This sensitivity analysis showed the instability of the result of the association between rs2066845 and risk of sar-

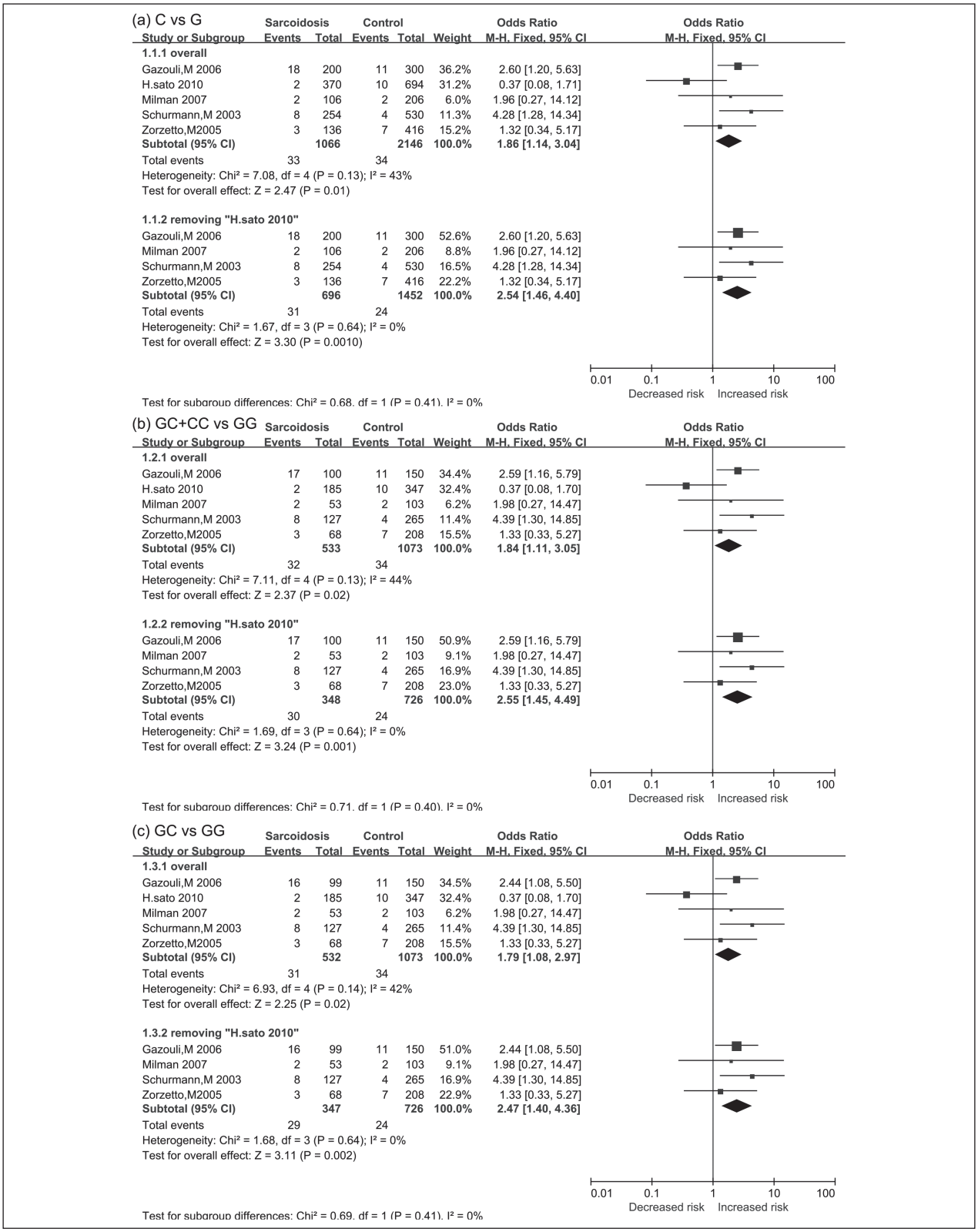

Fig. 2. Forest plots of OR with 95% CI for the association between rs2066845 and risk of sarcoidosis with results both in overall and removing 'H.sato 2010' analysis in allelic model(a), dominant model (b), and additive model (c) independently

coidosis. It was assumed that this inconsistency was caused by the existence of heterogeneity (I^2=43%, P=0.13). Thus, sensitivity analysis was further applied to search the source of heterogeneity by the leave-one-out method. Moreover, there was no significant influence on the heterogeneity between studies by sequentially removing each individual study except one published by H.sato et al 2010. After this, no heterogeneity was observed across the remaining studies (p=0.64, I^2=0%) and more statistically significant differences were found in allelic, dominant and additive model respectively after removing this single study (OR: 2.54, 95% CI: 1.46-4.4, P=0.001 for C vs. G; OR: 2.55, 95% CI: 1.45-4.49, P=0.001 for GC + CC vs. GG; OR: 2.47, 95% CI: 1.40-4.36, P=0.002 for GC vs. GG). The result after removing the study of Sato et al 2010 was consistent with the previous result in the total analysis (Table 2) (Figure 2).

Statistically similar results for rs2066844, rs2066847, rs1861759 were obtained after sequentially removing each individual study, suggesting the stability of this meta-analysis for the three mutations.

Publication bias

No significant publication bias was detected either by Egger's test or Begg's test in allelic model (Table 2), as were the funnel plots for the associations between *NOD2/CARD15* and sarcoidosis (figure not shown).

Discussion

The aetiology of sarcoidosis has been extensively studied but has so far remained unclear for more than 100 years. An increasing body of evidence suggested that various factors may contribute to the pathogenesis of sarcoidosis, such as microbe-rich environment, occupational exposure, seasonal factor and immune status (14). As well as this, the gene polymorphisms have also been reported to be strongly associated with the risk of sarcoidosis. Prior studies revealed that the gene polymorphisms of *ANXA11*, *BTNL2*, *CCR2-64I* and *TNF*-α might also be important risk factors (15-18). In addition, recent research have deeply explored the association of sarcoidosis risk with *NOD2/CARD15* gene, especially the mutations associated with Blau syndrome and CD (2, 9). However, the outcomes from these studies have not been consistent. Thus, this meta-analysis was first carried out to extensively analyse the associations between *NOD2/CARD15* gene polymorphisms and the risk of sarcoidosis.

A total of 2,517 people (968 cases and 1549 controls) in eight case-control studies were included in the present meta-analysis. The associations between *NOD2/CARD15* rs2066845, rs2066844, rs2066847, rs1861759 SNPs and the risk of sarcoidosis were rated. Since all participants included were Caucasian, the results of this study only be applicable to this ethnicity.

No statistical associations were found between the rs2066844, rs2066847, rs1861759 polymorphisms and a susceptibility of sarcoidosis for our overall analysis using different genetic models. There was only slight modification after sequentially excluding an individual study. Furthermore, no publication bias was documented. These features indicated a stable and reliable results about the associations between the three mutations and sarcoidosis susceptibility. Therefore, the consequences above indicated that the rs2066844, rs2066847 and rs1861759 polymorphisms in the *NOD2/CARD15* gene might not be a risk factor for sarcoidosis, especially in Caucasians.

For rs2066845, the results suggested that the individuals of Caucasians who carry the variant allele might be at an increased risk of developing sarcoidosis. There was moderate heterogeneity across the studies. The results of the sensitivity analysis revealed that the study of Sato et al 2010 was found to be highly responsible for the emergence of heterogeneity among studies. Other data statistics were calculated after removing the single study, with results showing similar statistically significant results but without any heterogeneity among the remaining studies. Further sensitivity analysis also revealed a reliable and stable character. We then carried out a thorough analysis of this study whose result indicated no association of rs2066845 with a risk of sarcoidosis. This study met both our inclusion and exclusion criteria. The difference might be from regional difference, linkage disequilibrium, the variation in the technique used or other underlying factors. All in all, cautions are required when interpreting this result.

The were some limitations of this meta-analysis. Firstly, only eight articles were included due to

limited studies on the associations between *NOD2/CARD15* polymorphisms and sarcoidosis risk, which most significantly limited the power of this study. Secondly, since the data included were primarily from Europeans, the outcomes might only be applicable to these ethnic groups. Thirdly, only one study from Asia was included, so caution must be taken when we make reference to this result. Finally, due to a lack of data on the clinical course, prognosis or other clinical variables of the original studies, further subgroup analysis was not able to be performed.

In conclusion, the meta-analysis revealed that *NOD2/CARD15* rs2066845 polymorphism might be a risk factor contributing to sarcoidosis susceptibility, especially for Caucasians. Meanwhile, no significant association between the *NOD2/CARD15* rs2066844, rs2066847, rs1861759 gene polymorphisms and risk of sarcoidosis were found. Despite this, larger case-control studies with appropriate design in diverse ethnicities are warranted to validate our results.

Acknowledgement

We thanks Dongze Li, MBBS, in Department of Emergency Medicine, West China Hospital, Sichuan University, Chengdu, Sichuan, China and Nan Chen, a Ph.D. student in West China Hospital, Sichuan University, Chengdu, P.R.China, in the writing of the report and the decision to submit the manuscript for publication.

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