

## Interleukin-18 genetic polymorphisms contribute differentially to the susceptibility to Crohn's disease

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### Abstract

**AIM:** To investigate the correlation between interleukin-18

(*IL-18*) gene polymorphisms and the risk of developing Crohn's disease (CD).

**METHODS:** The PubMed, CISCOM, CINAHL, Web of Science, EBSCO, Cochrane Library, MEDLINE, EMBASE and CBM databases were searched without any language restrictions using combinations of keywords relating to CD and *IL-18* for relevant articles published before November 1<sup>st</sup>, 2013. Screening of the published studies retrieved from searches was based on our stringent inclusion and exclusion criteria and resulted in seven eligible studies for meta-analysis. A meta-analysis was conducted using a random-effects model with STATA 12.0 software. Crude odds ratios (ORs) with 95% confidence intervals (95%CI) were calculated.

**RESULTS:** Seven case-control studies, with a total of 1930 CD cases and 1930 healthy subjects, met our inclusion criteria. The results of our meta-analysis indicated that the *IL-18* rs1946518 A>C and rs187238 G>C polymorphisms may correlate with an increased risk of CD under five genetic models (all  $P < 0.05$ ). Furthermore, we observed positive associations between the *IL-18* rs360718 A>C polymorphism and CD risk under three genetic models (C allele vs A allele: OR = 2.03, 95%CI: 1.20-3.43,  $P = 0.008$ ; CC vs AA+AC: OR = 2.39, 95%CI: 1.2-4.43,  $P = 0.006$ ; CC vs AC: OR = 2.31, 95%CI: 1.22-4.38,  $P = 0.010$ ). However, such associations were not found for the *IL-18* rs917997 C>T, codon 35 A>C and rs1946519 G>T polymorphisms (all  $P > 0.05$ ). A subgroup analysis was conducted to investigate the effect of ethnicity on an individual's susceptibility to CD. Our results revealed positive correlations between *IL-18* genetic polymorphisms and an increased risk of CD among Asians and Africans (all  $P < 0.05$ ), but not among Caucasians (all  $P > 0.05$ ).

**CONCLUSION:** This meta-analysis indicated that the *IL-18* rs1946518 A>C, rs187238 G>C and rs360718 A>C polymorphisms may contribute to susceptibility

to CD, especially among Asians and Africans. These polymorphisms are known to reduce *IL-18* mRNA and protein levels.

**Key words:** Interleukin-18; Single nucleotide polymorphism; Crohn's disease; Meta-analysis

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**Core tip:** This meta-analysis was performed to evaluate the relationships between genetic polymorphisms in the Interleukin-18 gene and the risk of developing Crohn's disease.

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## INTRODUCTION

Crohn's disease (CD), also known as Crohn syndrome and regional enteritis, is an inflammatory bowel disease that can affect any part of the gastrointestinal tract from the mouth to the anus<sup>[1]</sup>. Clinically, the symptoms of CD include abdominal pain, diarrhea, vomiting, and weight loss<sup>[2]</sup>. It is estimated that CD affects 400000 to 600000 people, with an incidence of 1/1000 per year in western countries<sup>[3]</sup>. CD is largely caused by interactions among environmental, immunological and genetic factors<sup>[4]</sup>. Environmental factors, such as age, sex, tobacco smoking and intake of animal protein, may lead to CD<sup>[1,5,6]</sup>. Current studies have shown that the development of CD may involve known genetic polymorphisms found in several inflammation-related genes<sup>[7,8]</sup>.

Interleukin (IL)-18, which belongs to the IL-1 cytokine superfamily, is a pro-inflammatory cytokine with pleiotropic activities extending from Th1/Th2 polarization to activation of innate immunity and inflammatory pathways<sup>[9,10]</sup>. IL-18 is mainly produced by macrophages, dendritic cells, keratinocytes, osteoblasts and intestinal epithelial cells<sup>[11]</sup>. IL-18 increases interferon (IFN)- $\gamma$  production by T helper 1 (Th1) cells together with IL-12<sup>[12,13]</sup>. In addition, IL-18 stimulates the expression of tumor necrosis factor (TNF)- $\alpha$  and IL-1 $\beta$ , increases the differentiation of T cells to the proinflammatory Th1 phenotype and impairs the synthesis of the anti-inflammatory cytokine IL-10<sup>[14,15]</sup>. Epidemiological studies have demonstrated that IL-18 may interfere with the regulation of the T helper 2 (Th2)-mediated immune response, which is involved in the pathogenesis of Th1 and Th2 chronic inflammatory diseases, including CD<sup>[16,17]</sup>.

The human *IL-18* gene comprises six exons and five introns, and has been mapped to chromosome 11q22.2-q22.3, with an overall length of approximately 19.5 kb<sup>[18]</sup>. Although the specific pathogenesis of CD is still not completely understood, single nucleotide polymorphisms (SNPs) in the *IL-18* gene alter IL-18 production and function, leading to an imbalance in the Th1/Th2 cytokine response, thereby affecting an individual's susceptibility to CD<sup>[19,20]</sup>. Several studies have shown that common polymorphisms in the *IL-18* gene may contribute to the development of CD<sup>[21,22]</sup>. However, findings from these studies have been contradictory with respect to individual SNPs<sup>[22]</sup>. Consequently, we performed the present meta-analysis of all available data to evaluate the relationships between *IL-18* genetic polymorphisms and CD risk.

## MATERIALS AND METHODS

### Search strategy

The PubMed, CISCOP, CINAHL, Web of Science, EBSCO, Cochrane Library, and CBM databases were searched without language restrictions for relevant articles published before November 1<sup>st</sup>, 2013. The following key words and MeSH terms were used: ("SNP" or "mutation" or "genetic polymorphism" or "variation" or "polymorphism" or "single nucleotide polymorphism" or "variant") and ("Crohn's disease" or "CD" or "Crohn syndrome" or "regional enteritis") and ("interleukin-18" or "IL-18" or "interleukin-18 receptors" or "IL-18 receptors"). We also performed a manual search of the reference lists of the relevant articles to find other potential articles.

### Selection criteria

The included studies met all four of the following criteria: (1) the study design must be a case-controlled study that focused on the relationships between *IL-18* genetic polymorphisms and the risk of developing CD; (2) all patients diagnosed with CD must be confirmed by endoscopy and histopathological examinations; (3) the genotype frequencies of healthy controls should follow the Hardy-Weinberg equilibrium (HWE); and (4) the study must provide sufficient information about the genotype frequencies. If the study did not meet the inclusion criteria, it was excluded. When the authors published several studies using the same subjects, the publication that was the most recent or contained the largest sample was included.

### Data extraction

Relevant data were systematically extracted from all included studies by two observers using a standardized form. The researchers collected the following data: publication language, publication year, the first author's surname, geographical location, study design, sample size, the source of the subjects, genotype frequencies, sample source, genotyping method and evidence of the HWE.

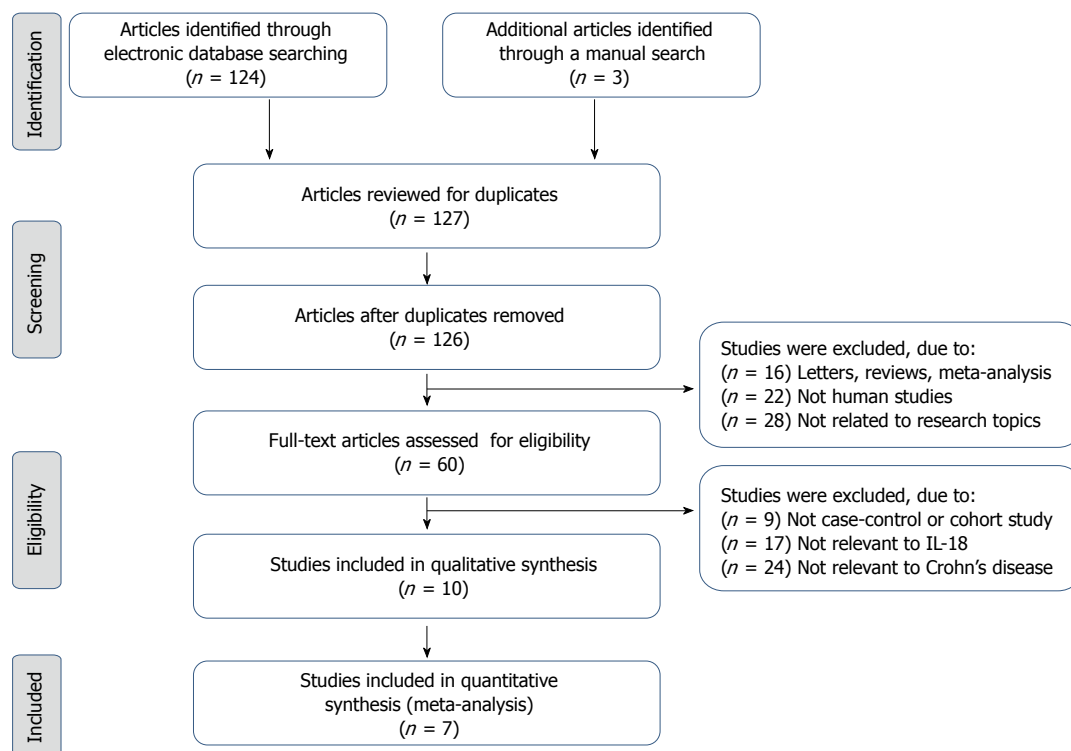


Figure 1 Flow chart of the literature search and study selection. Seven case-control studies were included in this meta-analysis.

### Quality assessment

Methodological quality was evaluated separately by two observers using the Newcastle-Ottawa Scale (NOS) criteria<sup>[23]</sup>. The NOS criteria include three aspects: (1) subject selection: 0-4; (2) comparability of subject: 0-2; and (3) clinical outcome: 0-3. NOS scores ranged from 0 to 9, with a score  $\geq 7$  indicating good quality.

### Statistical analysis

STATA version 12.0 (Stata Corp, College Station, TX, United States) software was used for the meta-analysis. We calculated crude odds ratios (ORs) with their 95% confidence intervals (95%CI) to evaluate the relationships with five genetic models. Genotype frequencies of healthy controls were tested for the HWE using the  $\chi^2$  test. The statistical significance of pooled ORs was assessed using the Z test. The Cochran's Q-statistic and  $I^2$  test were used to evaluate potential heterogeneity between studies<sup>[24]</sup>. If the Q-test showed a  $P < 0.05$  or the  $I^2$  test scored  $> 50\%$ , indicating significant heterogeneity, the random-effects model or the fixed-effects model was used. We also performed subgroup and meta-regression analyses to investigate potential sources of heterogeneity. We conducted a sensitivity analysis to assess the influence of single studies on overall ORs. Funnel plots and the Egger's linear regression test were used to investigate publication bias<sup>[25]</sup>.

## RESULTS

### Baseline characteristics of included studies

Initially, the keyword searches identified 127 articles.

We reviewed the titles and abstracts of all of the articles and excluded 66 articles. Next, the full text and data integrity were reviewed, and 54 additional articles were excluded. Finally, seven case-control studies with a total of 1930 CD cases and 1930 healthy subjects met our inclusion criteria for qualitative data analysis<sup>[21,26-31]</sup>. Publication years of the eligible studies ranged from 2005 to 2011. Figure 1 shows the selection process of the eligible articles. Overall, three studies were conducted in Asians, three in Caucasians, and only one in Africans. Six common polymorphisms in the *IL-18* gene were assessed: rs1946518 A>C, rs187238 G>C, rs360718 A>C, rs917997 C>T, codon 35 A>C and rs1946519 G>T. Genotyping methods included polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP), PCR-sequence-specific primers (PCR-SSP), direct DNA sequencing and TaqMan assay methods. None of the studies deviated from the HWE (all  $P > 0.05$ ). The NOS scores of all included studies were  $\geq 5$ . We summarized the study characteristics and methodological quality in Table 1.

### Quantitative data synthesis

The meta-analysis findings of the relationships between *IL-18* genetic polymorphisms and the risk of CD are shown in Table 2. The random effects model was used because of the heterogeneity between studies. Our meta-analysis showed that the *IL-18* rs1946518 A>C and rs187238 G>C polymorphisms were associated with increased risk of CD under five genetic models (all  $P < 0.05$ ). We also found positive associations between the *IL-18* rs360718 A>C polymorphism and CD risk under three genetic models

**Table 1 Main characteristics and methodological quality of all eligible studies of the relationship between interleukin-18 genetic polymorphisms and the risk of developing Crohn's disease**

Ref.	Year	Country	Ethnicity	Number		Gender (M/F)		Age (yr)		Genotyping method	SNP type	HWE test (P value)	NOS score
				CD	Control	CD	Control	CD	Control				
Ben Aleya <i>et al</i> <sup>[21]</sup>	2011	Tunisia	African	105	100	50/55	52/48	23-60	-	PCR-SSP	rs1946518 A>C	0.051	6
											rs187238 G>C	0.284	
Dema <i>et al</i> <sup>[27]</sup>	2009	Spain	Caucasian	722	794	274/448	-	-	-	TaqMan	rs917997 C>T	0.609	5
Haas <i>et al</i> <sup>[29]</sup>	2005	Germany	Caucasian	470	347	139/331	122/225	-	-	TaqMan	rs187238 G>C	0.637	6
Glas <i>et al</i> <sup>[28]</sup>	2005	Germany	Caucasian	210	265	83/127	141/124	39.1 ± 13.6	43.2 ± 12.5	PCR-RFLP	rs1946518 A>C	0.592	8
											rs187238 G>C	0.123	
											codon 35 A>C	0.774	
Tamura <i>et al</i> <sup>[31]</sup>	2008	Japan	Asian	134	110	102/32	55/55	15-65	15-75	Direct sequencing	codon 35 A>C	0.606	8
Takagawa <i>et al</i> <sup>[30]</sup>	2005	Japan	Asian	210	212	150/60	97/115	32.4 ± 9.8	38.2 ± 13.7	PCR-SSP	rs1946518 A>C	0.298	8
											rs187238 G>C	0.197	
Aizawa <i>et al</i> <sup>[26]</sup>	2005	Japan	Asian	79	102	61/18	50/52	36.8 ± 9.2	37.6 ± 6.9	Direct sequencing	rs1946519 G>T	0.947	8
											rs1946518 A>C	0.840	
											rs187238 G>C	0.586	
											rs360718 A>C	0.327	

M/F: Male/female; CD: Crohn's disease; SNP: Single nucleotide polymorphism; HWE: Hardy-Weinberg Equilibrium; NOS: Newcastle-Ottawa Scale; PCR-SSP: Polymerase chain reaction-sequence-specific primers; RFLP: Restriction fragment length polymorphism.

**Table 2 Meta-analysis of subgroups for the relationships between IL-18 genetic polymorphisms and Crohn's disease risk**

	W allele vs M allele (Allele model)			WW + WM vs MM (Dominant model)			WW vs WM + MM (Recessive model)			WW vs MM (Homozygous model)			WW vs WM (Heterozygous model)		
	OR	95%CI	P value	OR	95%CI	P value	OR	95%CI	P value	OR	95%CI	P value	OR	95%CI	P value
SNP type															
rs1946518 A>C	1.45	1.22-1.72	0.000	1.62	1.22-2.14	0.001	1.59	1.26-2.01	0.000	1.98	1.45-2.72	0.000	1.43	1.12-1.84	0.005
rs187238 G>C	1.69	1.39-2.06	0.000	2.04	1.48-2.81	0.000	1.81	1.42-2.31	0.000	2.53	1.82-3.52	0.000	1.66	1.29-2.13	0.000
rs360718 A>C	2.03	1.20-3.43	0.008	2.33	0.46-11.88	0.308	2.39	1.29-4.43	0.006	3.17	0.61-16.40	0.169	2.31	1.22-4.38	0.010
rs917997 C>T	0.91	0.77-1.06	0.229	0.80	0.55-1.18	0.267	0.91	0.74-1.11	0.349	0.78	0.52-1.16	0.220	0.93	0.76-1.15	0.525
codon 35 A>C	1.15	0.91-1.45	0.256	1.30	0.75-2.26	0.355	1.15	0.85-1.55	0.360	1.41	0.79-2.52	0.250	1.11	0.81-1.52	0.523
rs1946519 G>T	1.14	0.74-1.77	0.545	1.24	0.51-3.03	0.641	1.17	0.64-2.13	0.604	1.32	0.51-3.43	0.566	1.13	0.60-2.13	0.697
Ethnicity															
Asians	1.54	1.28-1.85	0.000	1.81	1.29-2.53	0.001	1.65	1.28-2.12	0.000	2.25	1.56-3.24	0.000	1.54	1.18-2.00	0.001
Africans	1.99	1.42-2.79	0.000	2.69	1.55-4.67	0.000	2.11	1.38-3.22	0.001	3.55	1.67-7.53	0.001	1.66	1.07-2.59	0.025
Caucasians	1.23	0.97-1.54	0.083	1.27	0.92-1.77	0.148	1.29	0.97-1.73	0.079	1.44	0.94-2.22	0.096	1.25	0.97-1.61	0.086
Genotyping method															
PCR-SSP	1.67	1.35-2.07	0.000	1.91	1.37-2.67	0.000	1.84	1.45-2.34	0.000	2.35	1.55-3.56	0.000	1.67	1.30-2.15	0.000
TaqMan	1.20	0.69-2.10	0.521	1.17	0.55-2.53	0.681	1.29	0.64-2.58	0.479	1.32	0.46-3.80	0.603	1.27	0.68-2.36	0.450
PCR-RFLP	1.25	1.07-1.46	0.005	1.36	1.00-1.85	0.053	1.31	1.06-1.63	0.013	1.55	1.11-2.16	0.011	1.25	0.99-1.56	0.059
Direct sequencing	1.56	1.16-2.11	0.003	2.46	1.37-4.43	0.003	1.61	1.08-2.42	0.021	3.21	1.72-5.99	0.000	1.46	0.98-2.18	0.061
Sample size															
Small sample-size (n ≤ 200)	1.61	1.29-2.01	0.000	2.29	1.60-3.27	0.000	1.66	1.25-2.20	0.001	2.85	1.93-4.20	0.000	1.46	1.12-1.90	0.005
Large sample-size (n > 200)	1.33	1.08-1.63	0.007	1.33	1.02-1.74	0.038	1.44	1.11-1.86	0.007	1.54	1.07-2.21	0.019	1.38	1.08-1.76	0.009

W: Wild-type allele; M: Mutant allele; WW: Wild-type homozygote; WM: Heterozygote; MM: Mutant homozygote; OR: Odds ratio; SNP: Single nucleotide polymorphism.

(C allele vs A allele: OR = 2.03, 95%CI: 1.20-3.43, P = 0.008; CC vs AA+AC: OR = 2.39, 95%CI: 1.29-4.43, P = 0.006; CC vs AC: OR = 2.31, 95%CI: 1.22-4.38, P = 0.010). However, the IL-18 rs917997 C>T, codon 35 A>C and rs1946519 G>T polymorphisms exhibited no associations with the risk of CD (all P > 0.05) (Figure 2). A subgroup analysis was performed to investigate the effect of ethnicity on an individual's susceptibility to CD. Our results revealed positive correlations between IL-18 genetic polymorphisms and an increased risk of CD among Asians and Africans (all P < 0.05), but not among Caucasians (all P > 0.05) (Figure 3). We also performed a subgroup analysis by genotyping method

and sample size: the results indicated significant associations between IL-18 genetic polymorphisms and an increased risk of CD in the majority of subgroups (Table 2).

The univariate meta-regression analyses confirmed that SNP type and ethnicity may be the main sources of heterogeneity, while multivariate meta-regression analyses revealed that SNP type and ethnicity were not the sources of heterogeneity (Table 3). The results of the sensitivity analysis indicated that the overall pooled ORs were not affected by a single study (Figure 4). No evidence of asymmetry was observed in the funnel plots (Figure 5). The Egger's

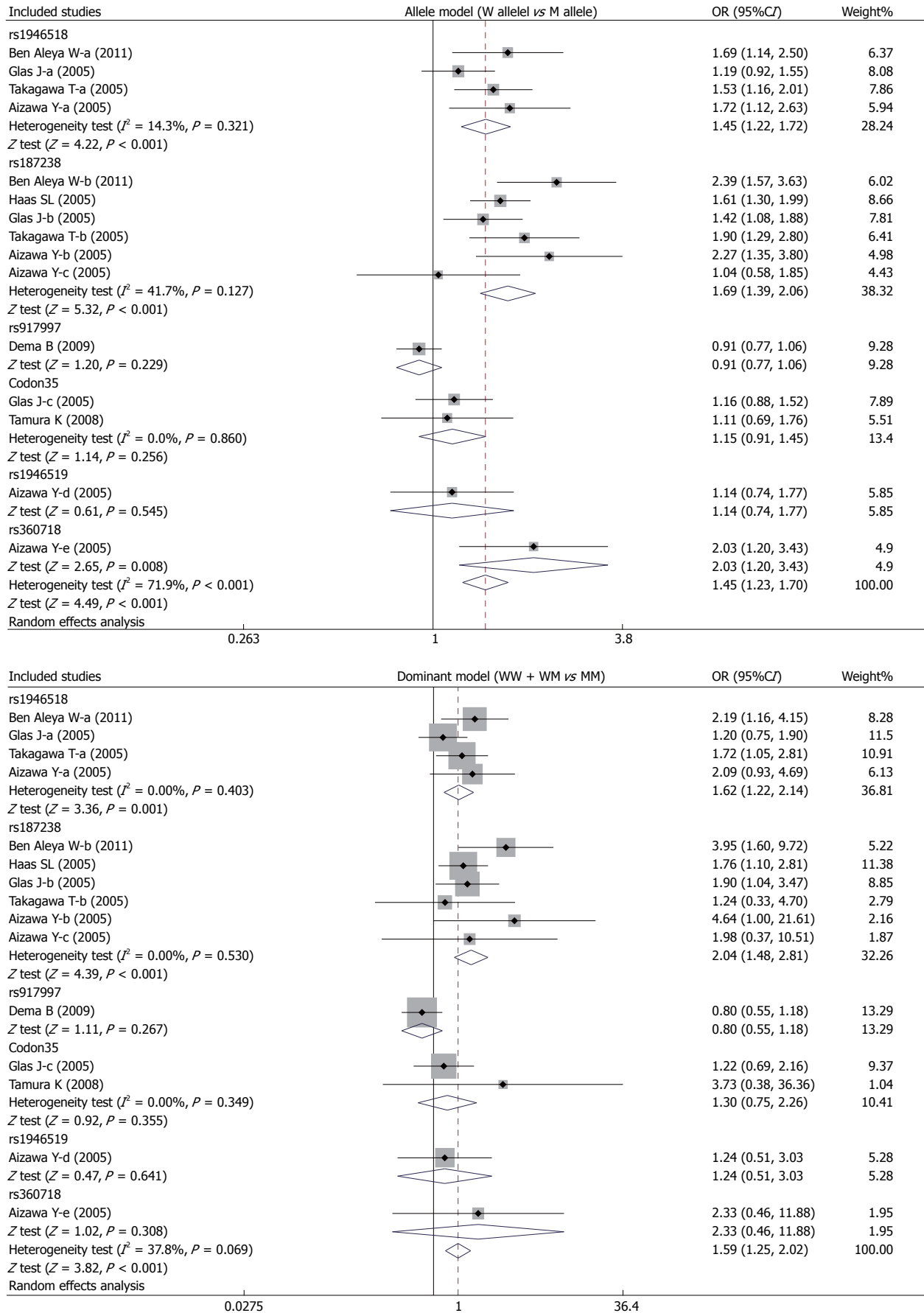
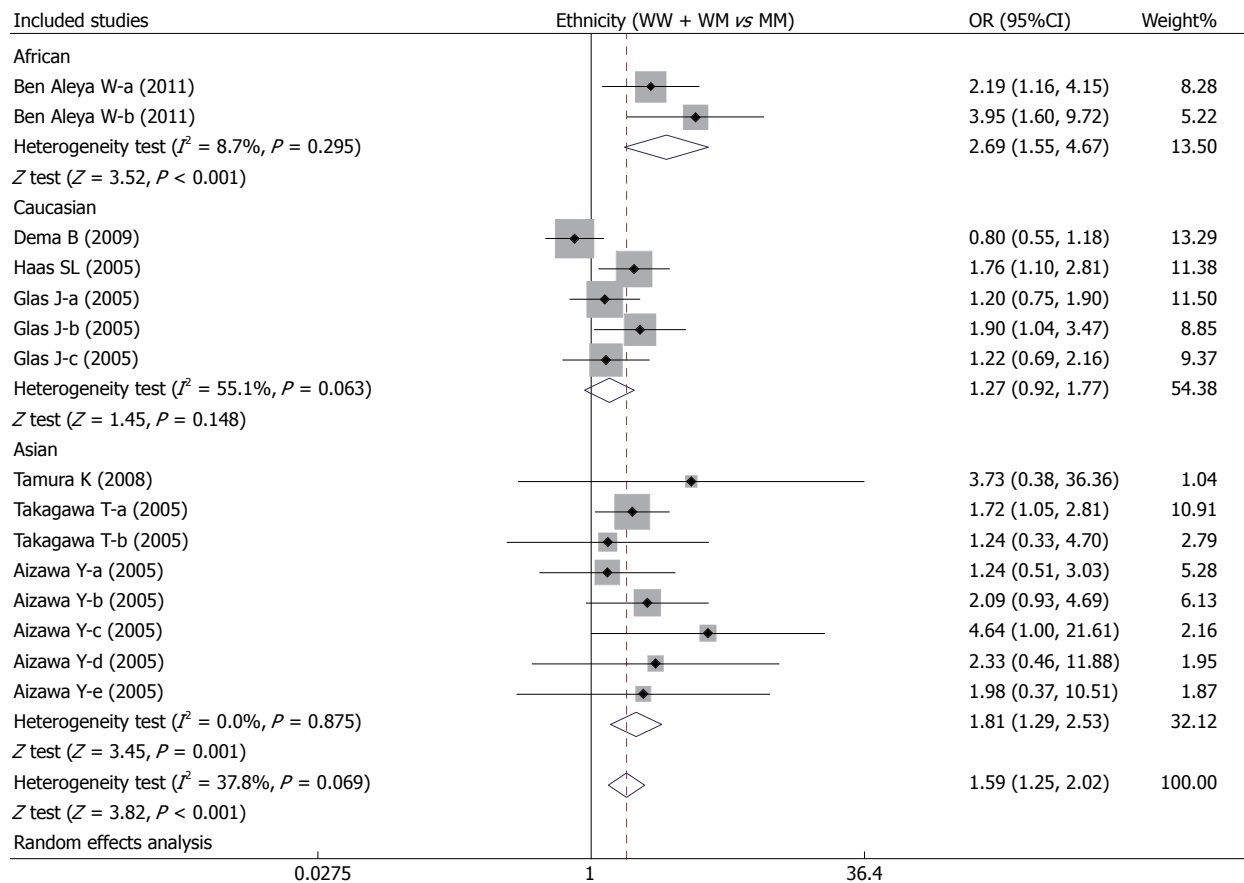
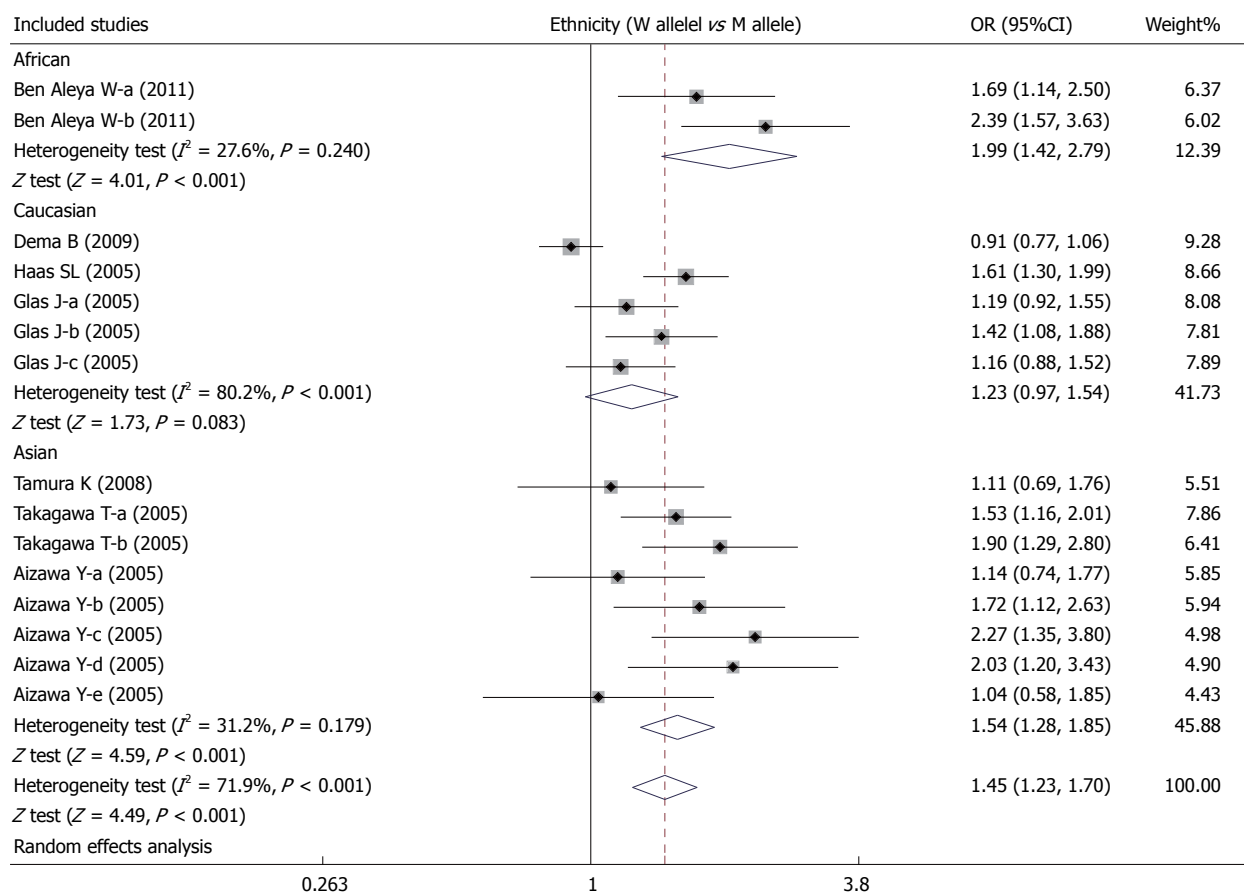
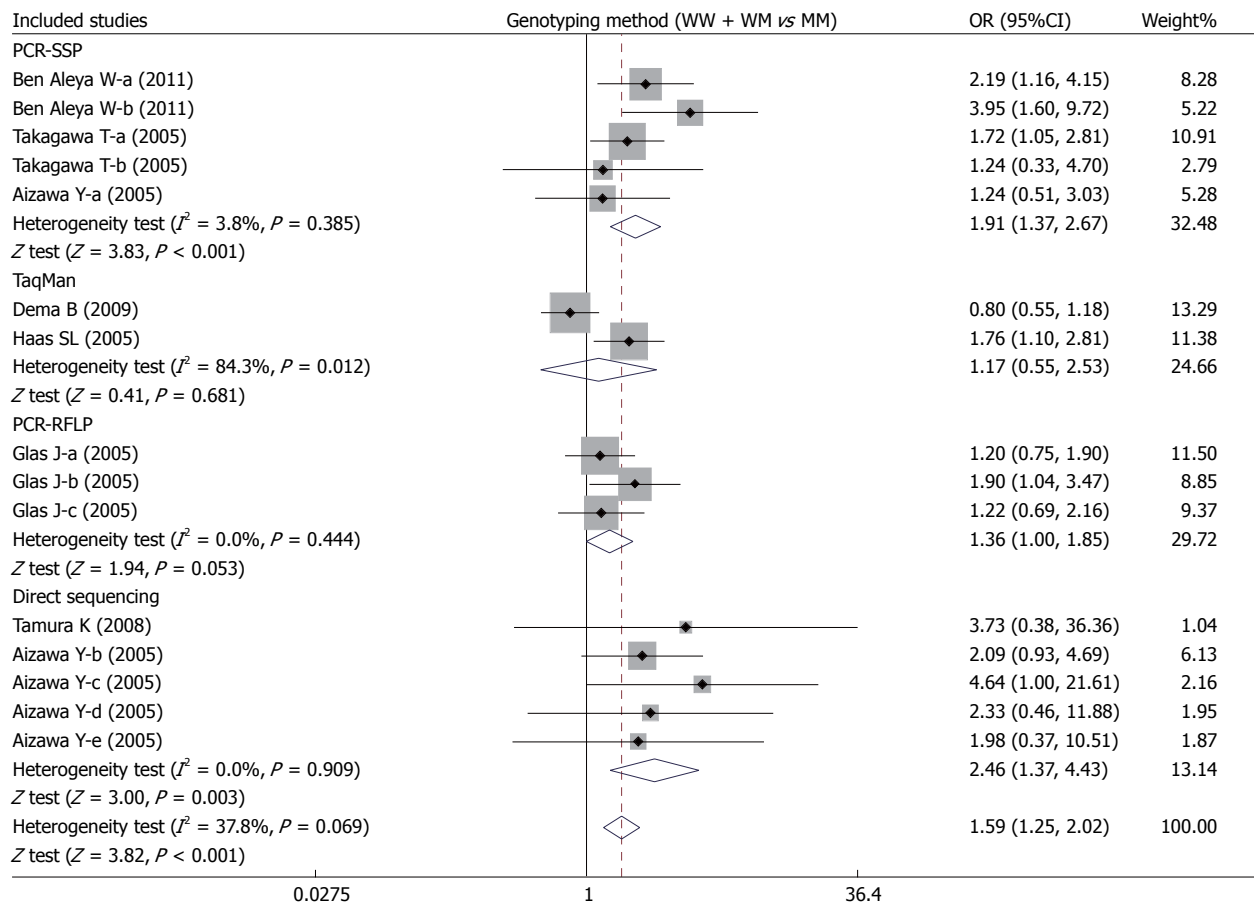
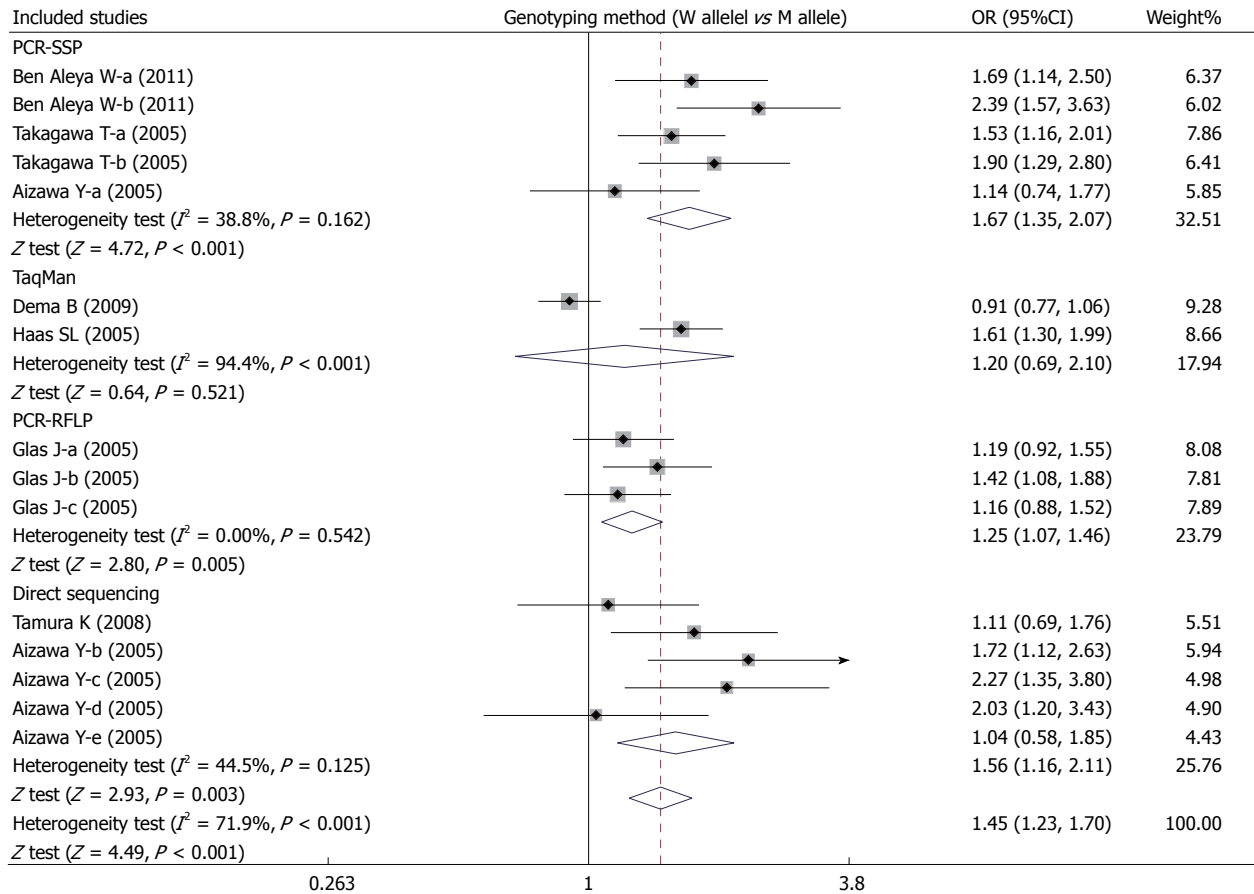


Figure 2 Forest plots of the relationships between interleukin-18 genetic polymorphisms and the risk of developing Crohn's disease, using the allele and dominant models.







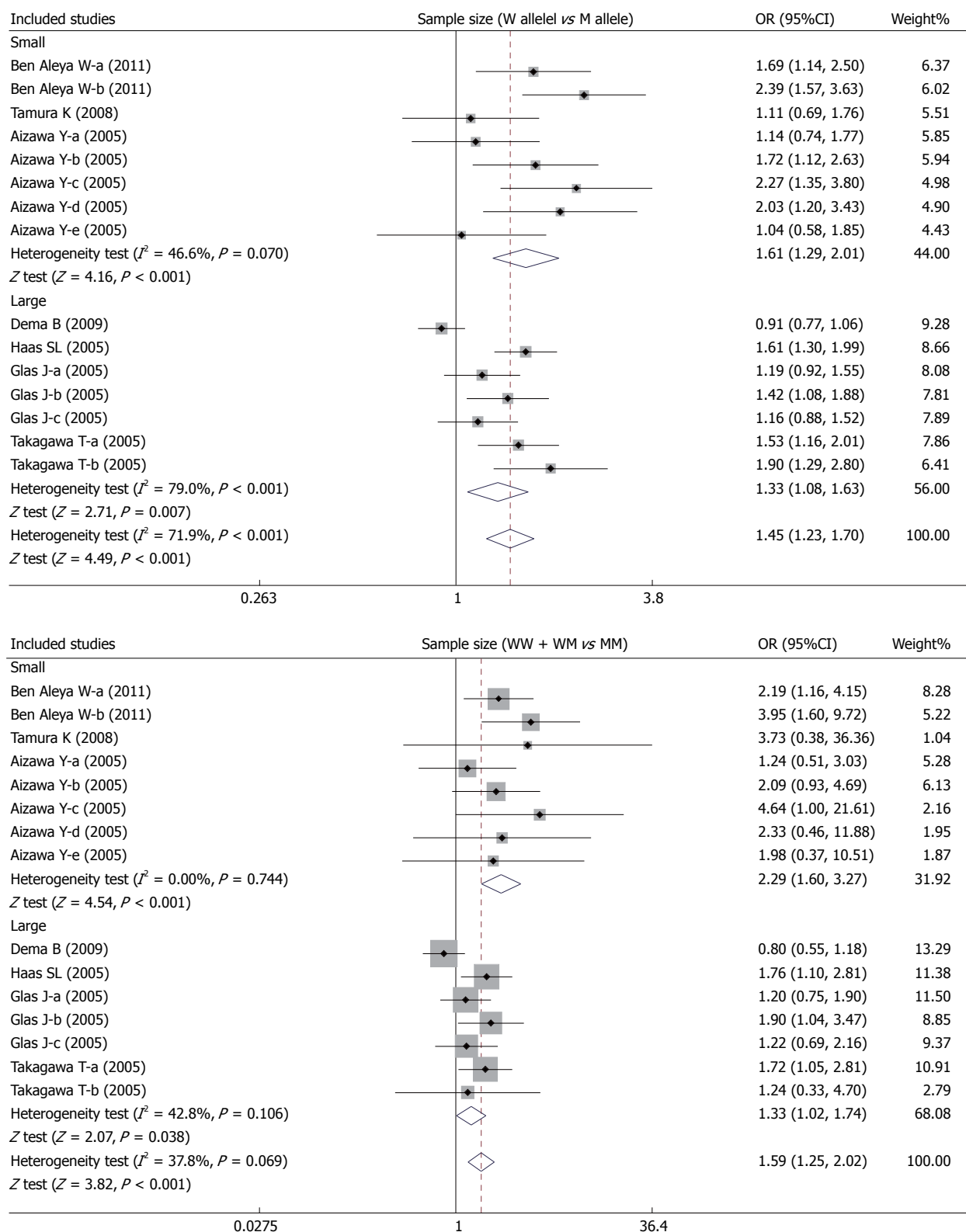


Figure 3 Subgroup analyses of the relationships between interleukin-18 genetic polymorphisms and the risk of developing Crohn's disease, using the allele and dominant models.

test also failed to reveal any evidence of publication bias (all  $P > 0.05$ ). Univariate analysis demonstrated that SNPs and ethnicity may be the main sources of heterogeneity (SNP:  $P = 0.025$ ; Ethnicity:  $P = 0.011$ ),

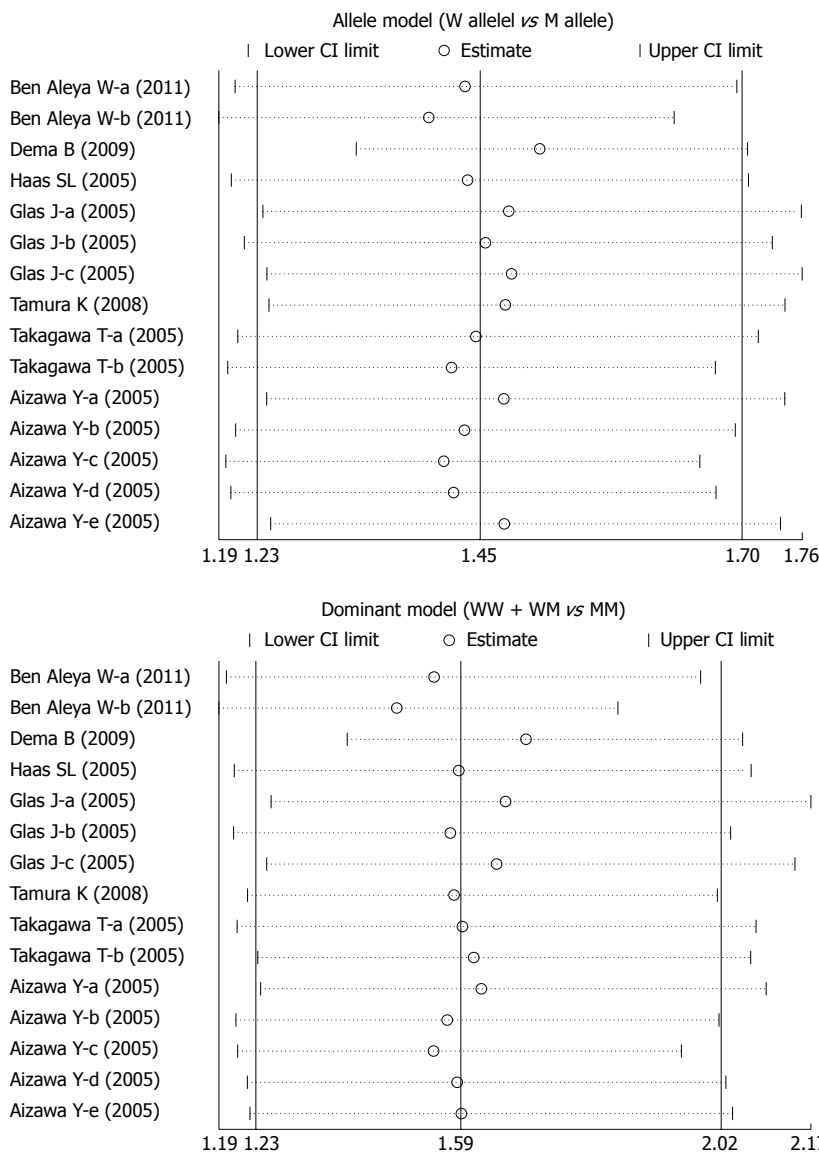
while multivariate regression analysis showed that publication year, SNPs, ethnicity, genotyping method and sample size were not the key factors for overall effect size (all  $P > 0.05$ ).



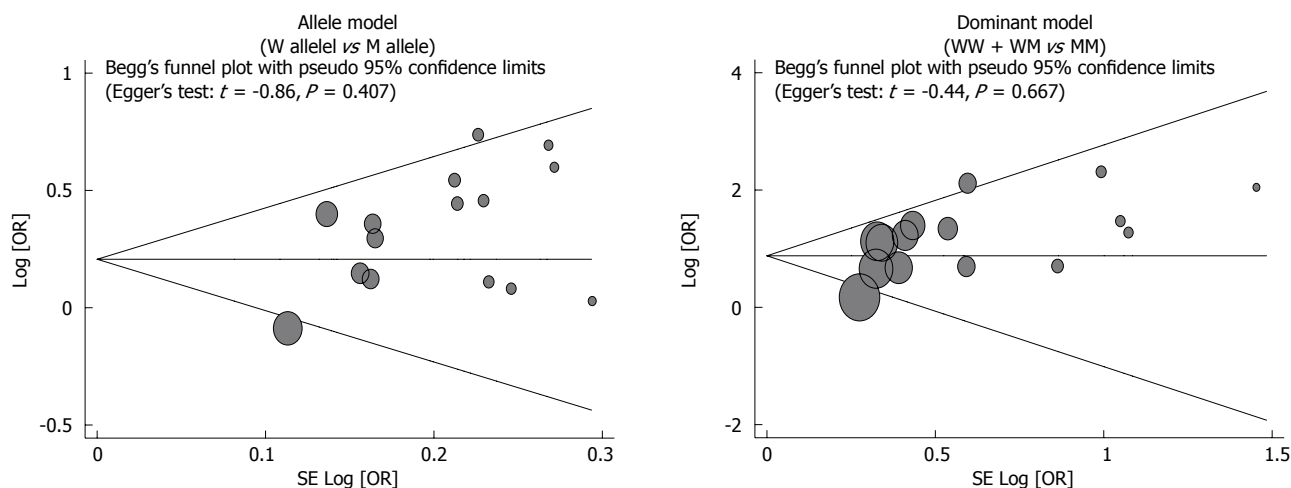
**Table 3** Univariate and multivariate meta-regression analyses of potential sources of heterogeneity

Heterogeneity factors	Coefficient	SE	Z	P value	95%CI	
					LL	UL
Publication year						
Univariate	0.004	0.036	0.12	0.908	-0.066	0.075
Multivariate	-0.052	0.038	-1.39	0.166	-0.126	0.022
SNP type						
Univariate	-0.188	0.084	-2.25	0.025	-0.353	-0.024
Multivariate	-0.077	0.091	-0.84	0.398	-0.256	0.102
Ethnicity						
Univariate	0.241	0.095	2.55	0.011	0.056	0.427
Multivariate	0.476	0.250	1.90	0.057	-0.014	0.967
Genotyping method						
Univariate	-0.082	0.066	-1.25	0.211	-0.211	0.047
Multivariate	0.075	0.082	0.92	0.360	-0.085	0.235
Sample size						
Univariate	0.194	0.148	1.31	0.190	-0.096	0.485
Multivariate	-0.216	0.244	-0.89	0.376	-0.696	0.263

SE: Standard error; SNP: Single nucleotide polymorphism; UL: Upper limit; LL: Lower limit.



**Figure 4** Sensitivity analysis of the summary odds ratio coefficients for the relationships between interleukin-18 genetic polymorphisms and the risk of developing Crohn's disease, using the allele and dominant models.



**Figure 5** Funnel plot of publication biases of the relationships between interleukin-18 genetic polymorphisms and the risk of Crohn's disease under the allele and dominant models. W: Wild-type allele; M: Mutant allele; WW: Wild-type homozygote; WM: Heterozygote; MM: Mutant homozygote; OR: Odds ratio.

## DISCUSSION

The results of the present meta-analysis demonstrated a significant association between three *IL-18* genetic polymorphisms and a high risk of CD, specifically for the rs1946518 A>C, rs187238 G>C and rs360718 A>C polymorphisms, implying that these polymorphisms have causative roles in the development and progression of CD. *IL-18*, together with *IL-1 $\beta$* , contributes to the host defense against infections by augmenting antimicrobial properties of phagocytes and initiating Th1 and Th17 adaptive immune responses<sup>[32]</sup>. Several epidemiological studies have reported previously that *IL-18* is involved in the regulation of both innate and acquired immune responses, and may be involved in the pathogenesis of autoimmune and inflammatory diseases<sup>[33-35]</sup>. It should be noted that *IL-18* is capable of stimulating the expression of TNF- $\alpha$  and *IL-1 $\beta$* , enhancing the differentiation of T cells to the proinflammatory Th phenotype<sup>[36]</sup>. CD is considered a Th1-cytokine (*IL-12*, IFN- $\gamma$ , and TNF- $\alpha$ ) or Th2-induced inflammatory disease<sup>[19,37]</sup>. Although the precise function of *IL-18* in the development of CD is not completely understood, it is reasonable to speculate that *IL-18* genetic polymorphisms alter *IL-18* expression levels, which may play a pivotal role in the disease process<sup>[13]</sup>. Specifically, genetic variants in *IL-18* that lead to reduced expression of *IL-18*, such as the *IL-18* rs1946518 A>C, rs187238 G>C and rs360718 A>C polymorphisms, exhibit loss of transcription factor binding because the polymorphisms alter the binding sites. The resulting low *IL-18* production also causes major disruptions in the immune pathways responsible for mediating T-cell regulation, thereby contributing to the pathogenesis of CD<sup>[22]</sup>.

To address the possibility of heterogeneity in our data, which may have a negative influence on the results of relevant studies, we carefully performed stratified analyses based on ethnicity, genotyping

method and sample size. The results of the subgroup analysis by ethnicity suggested that *IL-18* genetic polymorphisms were closely linked to an increased risk of CD among Asians and Africans, but not among Caucasians. These results revealed that ethnic differences may cause heterogeneity between studies of *IL-18* genetic polymorphisms and their role in the pathogenesis of CD. Nevertheless, we failed to find evidence of any associations between the *IL-18* rs917997 C>T, codon 35 A>C and rs1946519 G>T polymorphisms and the risk of CD, revealing that these polymorphisms might not be important determinants for the pathogenesis of CD.

The current meta-analysis also had limitations that should be acknowledged. First, our results lacked sufficient statistical power to assess the correlations between *IL-18* genetic polymorphisms and CD risk. Second, a meta-analysis is a retrospective study that may be susceptible to selection bias and thereby influence the reliability of our results. Third, our meta-analysis failed to obtain original data from the included studies, which may limit further evaluation of the potential role of *IL-18* genetic polymorphisms in the pathogenesis of CD. Although our study has several limitations, this is the first meta-analysis focusing on the relationship between *IL-18* genetic polymorphisms and the risk of CD. Furthermore, we performed a highly sensitive strategic literature search of electronic databases. A manual search of the reference lists from the relevant articles was also conducted to find other potential articles. The selection process for eligible articles was based on strict inclusion and exclusion criteria. Importantly, rigorous statistical analysis of SNP data provided a basis for pooling information from individual studies.

In conclusion, the current meta-analysis indicates that the *IL-18* rs1946518 A>C, rs187238 G>C and rs360718 A>C polymorphisms contribute to susceptibility to CD, especially among Asians and Africans. However, the *IL-18* rs917997 C>T, codon

35 A>C and rs1946519 G>T polymorphisms may not be important determinants of the pathogenesis of CD, and their effects on IL-18 mRNA and protein levels need to be investigated further. In this context, because of the limitations acknowledged above, more studies with larger sample sizes are needed to provide a more representative statistical analysis and combine the analysis with experimental evidence describing the polymorphisms.

## COMMENTS

### Background

Single nucleotide polymorphism (SNPs) in several inflammation-related genes, including interleukin-18 (IL-18), may be implicated in the development of Crohn's disease (CD).

### Research frontiers

Approximately half of the overall risk is related to genetics, and more than thirty genes have been associated with CD.

### Innovations and breakthroughs

This article comprehensively assessed the correlation between six common polymorphisms in the IL-18 gene and CD.

### Applications

SNPs in the IL-18 gene have the potential to act as biomarkers for the screening, diagnosis and treatment of CD.

### Peer-review

This is a good research study with practical results suggesting that SNPs in IL-18 may be regarded as a potential index for CD diagnosis and treatment.

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