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Systematic meta-analysis of the association between monocyte chemoattractant protein-1 -2518A/G polymorphism and risk of tuberculosis

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ABSTRACT. Numerous studies have been conducted to investigate the association between 2518A/G polymorphisms in the monocyte chemoattractant protein-1 (*MCP-1*) gene and the risk of tuberculosis (TB). However, the results have been inconsistent and inconclusive. In this study, we performed a meta-analysis to evaluate the association between the *MCP-1* -2518A/G polymorphism and TB. The National Center for Biotechnology Information Global Cross Database and Google Scholar database were searched for relative studies. A total of 22 case-control studies that included 7332 cases and 8004 controls for the -2518A/G single-nucleotide polymorphism were identified. The results revealed an association between the *MCP-1* -2518A/G polymorphism and human TB susceptibility under a recessive model (GG *vs* GA+AA), dominant model

(GG+GA *vs* AA), and homozygote comparison (GG *vs* AA) model for the entire database. For the dominant model, the overall odds ratio was 1.34 (95% confidence interval, 1.10-1.64, P = 0.004). For the recessive model, the overall odds ratio was 1.46 (95% confidence interval, 1.15-1.86, P = 0.002). For the homozygote comparison, the overall odds ratio was 1.67 (95% confidence interval, 1.20-2.32, P = 0.002). In the subgroup analysis by ethnicity, significantly elevated risks were found in Asians and Americans, but not in Africans and Europeans. We also used the Begg and Egger tests to examine publication bias, and no major publication bias was detected. Our results indicate that there is an association between the *MCP-1* -2518A/G polymorphism and human TB susceptibility.

Key words: Meta-analysis; Monocyte chemoattractant protein-1; Tuberculosis

INTRODUCTION

Tuberculosis (TB) is an infectious disease caused by the bacillus *Mycobacterium tuberculosis* (Mtb). Although the treatment is inexpensive and has existed for more than 50 years, Mtb remains a global public health problem (Marais et al., 2010). Approximately 1/3 of the world's population is latently infected and at risk of developing this disease. Approximately 90% of people infected with Mtb never develop TB. It is not known why some individuals exposed to Mtb resist infection more successfully than others. Heritable factors are thought to play an important role in determining the inter-individual variation that leads to higher susceptibility (Singh et al., 2014). The susceptibility of developing TB disease after exposure is a complex multifactorial trait; disease expression is influenced by complex interactions between the host and pathogen, as well as between genetic and environmental factors (Möller and Hoal, 2010). Numerous studies have confirmed that various genetic factors affect the susceptibility to TB. An increasing number of studies have been focused on identifying genetic factors causing TB, including the monocyte chemoattractant protein 1 (*MCP-1*) gene.

MCP-1, also referred as chemokine C-C motif ligand 2 (CCL2), is a member of the small inducible gene family. It plays an essential role in the innate immune response against microbial infection and contributes to adaptive immune defense and long-term immunity (Serbina et al., 2008). MCP-1/CCL2 shows the highest potential as a chemoattractant and activator for monocytes and plays an important role in the host-pathogen interaction. Increased expression of MCP-1 has been shown to be associated with disease severity of TB (Hasan et al., 2009). Genetic variations within the *MCP-1* gene have also been suggested to be associated with disease susceptibility and manifestation. MCP-1 expression levels are highly variable among individuals, which may contribute to differential susceptibility to the progress of various inflammatory diseases (Frahm et al., 2011).

Previous studies have identified that polymorphisms in the regulatory regions of the *MCP-1* gene were associated with variability in MCP-1 expression levels (Berrahmoune et al., 2007; Pham et al., 2012). The gene encoding MCP-1 is located in the 17q11.2-q12 chromosomal region; single-nucleotide polymorphisms such as -2518A/G (rs1024611) and -362G/C (rs2857656) have been identified. These polymorphisms may influence MCP-1 secretion, impacting TB susceptibility (Mishra et al., 2012).

Several studies have investigated the association between these polymorphisms and TB susceptibility; however, the results are inconsistent and inconclusive. Zhang et al. (2012) showed that significantly elevated risks were observed in Asians and Latinos, but not in Africans between the -2518A/G polymorphism in the *MCP-1* gene and TB. Another group reported that the CCL2-2518G allele increased the risk of developing TB in Asians and Hispanics (Feng et al., 2012). Another recent study showed that the G allele of the *MCP-1* -2518 polymorphism was a risk factor for TB in Asians and Americans, but not in Africans (Gong et al., 2013). In this study, we performed a meta-analysis to more comprehensively estimate the association between the -2518A/G polymorphism and human TB susceptibility.

MATERIAL AND METHODS

Study selection

Multiple electronic databases were searched for data collection. For first-round exclusion, studies were searched with National Center of Biotechnology Information Global Cross Database, including PubMed, PMC, Gene, PubChem, etc., using the search terms "tuberculosis", "monocyte chemoattractant protein-1", "MCP-1", "CCL2", and "-2518A/G polymorphism". Search results were limited to studies in English. We excluded books and other literature that were not case-control studies. For second-round selection, we excluded articles that did not investigate the association between *MCP-1* -2518A/G polymorphisms and human TB susceptibility. Duplicated studies were eliminated. When data overlapped between studies, we retained those showing the most extensive results.

Statistical methods

To obtain a reasonable statistical conclusion, the association between the *MCP*-1 -2518A/G polymorphism and TB was evaluated using the odds ratio (OR) derived from different analysis models. Subjects were placed into 4 subgroups based on the region of the case-control study. Subgroup A included 5 studies in Africans. Subgroup B included 4 studies in Americans. Subgroup C included 3 studies in Europeans. Subgroup D included 10 studies in Asians. Three different methods were used: dominant model (GG+GA *vs* AA), recessive model (GG *vs* GA+AA), and homozygote comparison (GG *vs* AA). For each study, the number of subjects with the 3 genotypes in the case and control groups were used as pooled data. When examining studies with large sample sizes, Peto's method (Brockhaus et al., 2014) may be misleading. However, the inverse variance method is only effective for continuous data. Another key factor in choosing an analysis model is to test the heterogeneity in the studies. The Mantel-Haenszel (M-H) fixed-effect model should be applied for analyzing datasets without significant heterogeneity and the DerSimonian and Laird random-effects model should be applied for datasets showing obvious heterogeneity. In our analysis, the heterogeneity between studies was tested using the I^2 index, using an equation in which Q was the statistical data and df was the degrees of freedom. A higher value of I^2 indicated more significant heterogeneity. Values of I^2 = 25, 50, and 75% represented low, medium, and high heterogeneity, respectively. When $I^2 \leq 25$, 50, and 75%, there was no significant heterogeneity among pooled data. In this meta-analysis, 22 studies were included in the final analysis for -2518A/G. For each analysis, we first used the M-H fixed-effect model to test the heterogeneity, and then used different

models based on these results. ORs were calculated for each model with 95% confidence intervals (95%CIs). Available polymorphism data were analyzed using STATA 12 (StataCorp, College Station, TX, USA). Forest plots were generated to summarize the results. To evaluate publication bias, Begg's funnel plots were generated based on the analysis results and database size. Funnel plots showing higher asymmetry indicated higher publication bias. In addition, the Egger test was also performed for publication bias evaluation.

RESULTS

Data collection

A total of 149 results were identified in the selected electronic databases. We excluded books and other studies that were not case-control studies, resulting in 67 articles. After excluding the articles that did not investigate the association between *MCP-1* -2518A/G polymorphisms and human TB susceptibility, 24 articles remained. Duplicated studies were eliminated and only those with the most extensive results were retained. A total of 18 articles, including 22 case-control studies, were included in the final meta-analysis. The data collection flow chart is shown in Figure 1.

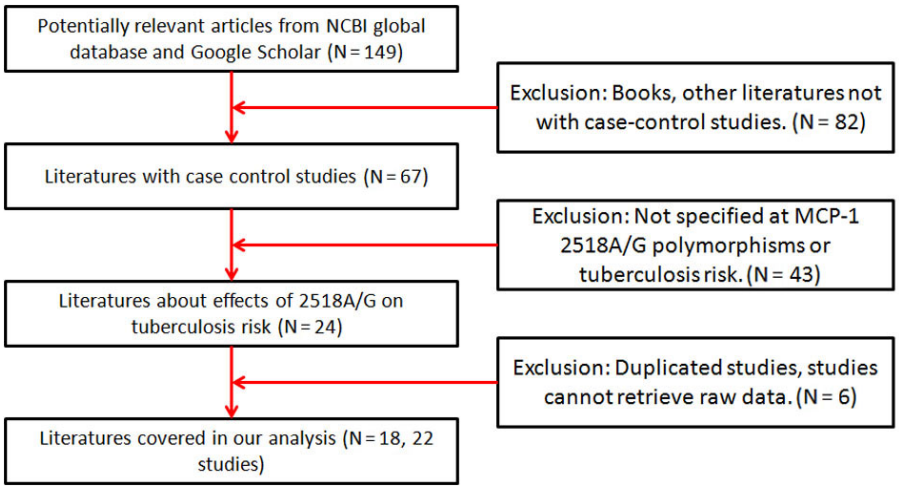

Figure 1. Data collection procedure. A total of 149 articles were searched for first-round exclusion. Eighteen articles including 22 studies were included in the final meta-analysis.

Characteristics of studies included

In this meta-analysis, we included 22 studies divided into 4 subgroups. The African group included 5 studies [Buijtels et al., 2008; Möller et al., 2009; Thye et al., 2009; Velez Edwards et al., 2012 (2 case-control studies)]. The American group included 4 studies [Flores-Villaneuva et al., 2005; Ganachari et al., 2010 (2 case-control studies); Velez Edwards et al., 2012]. The Europeans group included 3 studies (Ben-Selma et al., 2011; Hussain et al., 2011; Arji et al., 2012). The Asian group included 10 studies (Flores-Villanueva et al., 2005; Chu et al., 2007; Alagarasu et al., 2009; Xu et al., 2009; Yang et al., 2009; Feng et al., 2011; Naderi et al., 2011; Mishra et al.,

2012; Zhang et al., 2012; Singh et al., 2014). All studies analyzed the association between *MCP-1* -2518A/G polymorphisms and human TB susceptibility. The characteristics of all studies are shown in Table 1.

Table 1. Pooled data for *MCP-1* 2518A/G analysis.

Study	Case				Control				HWE P value
	GG	GA	AA	Total	GG	GA	AA	Total	
African									
Buijets, 2008	1	23	22	46	4	30	81	115	0.560
Thye, 2008	63	546	1355	1964	92	748	1472	2312	0.803
Velez, 2012	17	123	174	314	21	103	217	341	0.163
Velez, 2012	18	80	138	236	15	93	144	252	0.991
Moller, 2009	26	142	263	431	38	173	270	481	0.170
American									
Ganachari, 2010	93	77	23	193	70	127	46	243	0.386
Ganachari, 2010	354	273	74	701	327	371	98	796	0.646
Flores, 2005	229	168	38	435	137	249	124	510	0.605
Velez, 2012	8	91	189	288	4	49	123	176	0.243
Caucasian									
Arji, 2012	10	128	199	337	14	80	110	204	NA
Hussian, 2011	19	43	48	110	3	44	39	86	0.515
Ben-Selma, 2011	26	87	110	223	8	49	93	150	0.645
Asian									
Chu, 2007	110	200	93	403	113	233	115	461	0.816
Yang, 2009	84	62	21	167	42	83	42	167	0.938
Xu, 2009	36	49	15	100	14	45	41	100	0.770
Naderi, 2011	17	50	75	142	15	68	83	166	0.493
Feng, 2011	106	157	38	301	117	170	51	338	0.400
Flores, 2005	46	63	20	129	22	74	66	162	0.862
Zhang, 2009	49	76	16	141	35	77	40	152	0.860
Singh, 2013	36	116	151	303	40	117	138	295	0.420
Alagarasu, 2009	21	54	78	153	29	81	93	203	0.105
Mishra, 2012	18	72	125	215	20	112	162	294	0.011

NA = not available.

Analysis of *MCP-1* -2518A/G polymorphism and TB susceptibility

First, we performed the analysis for the entire data set. Three analysis methods (dominant, recessive, and homozygote comparison) were applied. Based on the heterogeneity observed in the data, the DerSimonian and Laird random-effect model was applied with all 3 analysis methods. Final results are shown in Table 2. Corresponding forest plots and funnel plots for each model are shown in Figures 2 and 3. For the dominant model, the overall OR was 1.34 (95%CI = 1.10-1.64, P = 0.004), and minor publication bias was observed. For the recessive model, the overall OR was 1.46 (95%CI = 1.15-1.86, P = 0.002), and no significant publication bias was observed. For the homozygote comparison, the overall OR was 1.67 (95%CI = 1.20-2.32, P = 0.002), and no significant publication bias was observed.

Similarly, for subgroup analysis, the M-H fixed-effects model was applied for each subgroup dataset using 3 different analysis models (dominant, recessive, and homozygote) to examine heterogeneity. Based on the results, we selected different methods (M-H fixed-effects model or DerSimonian and Laird random-effects model) for analysis. We then continued with the final analysis to derive the OR as well as its P value. In the subgroup analysis by ethnicity, a significantly increased risk of TB because of the *MCP-1* -2518A/G polymorphism was observed among the American population (dominant model: OR = 1.694, 95%CI = 1.019-

Table 2. Meta-analysis for entire database with dominant model (GG+GA *vs* AA), recessive model (GG *vs* GG+AA), and homozygote comparison (GG *vs* AA).

Analysis model	Analysis method	Heterogeneity		OR (95%CI)				Publication bias	
		I^2 (%)	P value	Overall	Lower	Upper	P value	Begger	Egger
Dominant	Random	84.20	0.000	1.342	1.101	1.635	0.004	0.003	0.000
Recessive	Random	80.60	0.000	1.460	1.148	1.856	0.002	0.955	0.856
Homozygote	Random	84.80	0.000	1.668	1.199	2.321	0.002	0.143	0.318

OR = odds ratio; 95%CI = 95% confidence interval.

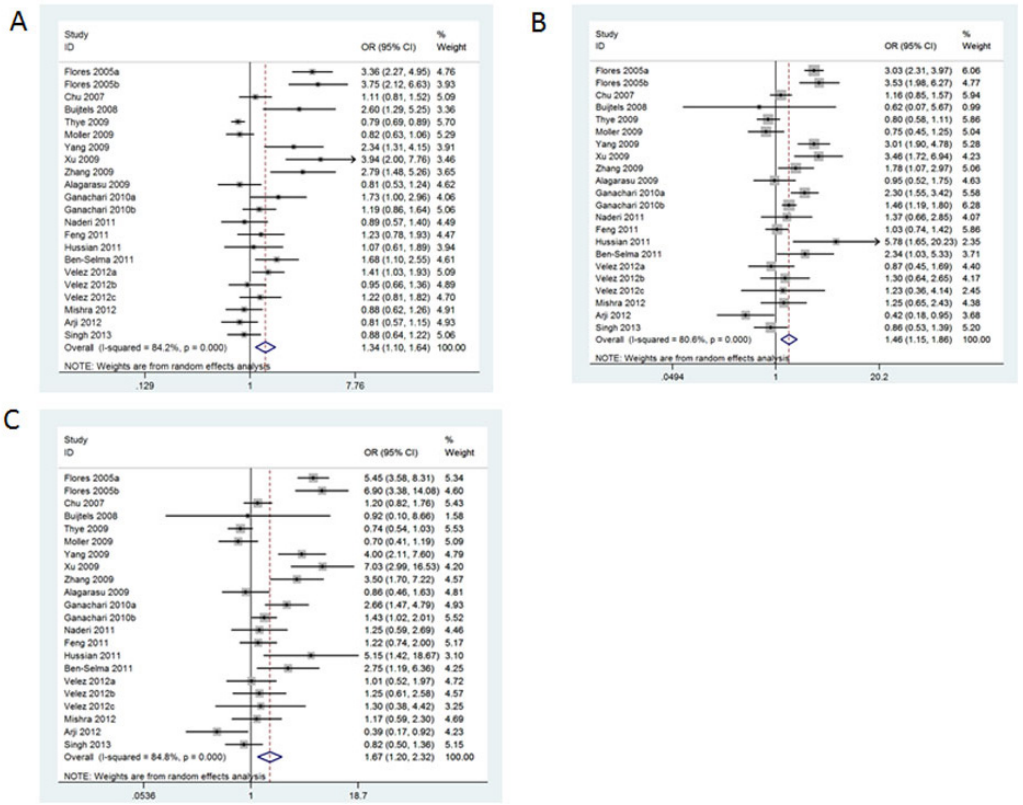

Figure 2. Forest plot for the entire database including 22 studies. (**A**) Dominant model (GG+GA *vs* AA), (**B**) recessive model (GG *vs* GA+AA), and (**C**) homozygote comparison (GG *vs* AA) were applied in these analyses.

2.817, P = 0.042; recessive model: OR = 2.032, 95%CI = 1.292-3.197, P = 0.002; homozygote model: OR = 2.406, 95%CI = 1.123-5.517, P = 0.024) and Asian population (dominant model: OR = 1.929, 95%CI = 1.203-3.094, P = 0.006; recessive model: OR = 1.566, 95%CI = 1.1332-2.164, P = 0.007; homozygote model: OR = 1.929, 95%CI = 1.203-3.094, P = 0.006), but not for the Europeans (dominant model: OR = 1.126, 95%CI = 0.707-1.791, P = 0.618; recessive model: OR = 1.692, 95%CI = 0.382-7.495, P = 0.489; homozygote model: OR = 1.696, 95%CI = 0.364-7.892, P = 0.501) and African populations (dominant model: OR = 1.059, 95%CI = 0.786-1.428, P = 0.706; recessive model: OR = 0.84, 95%CI = 0.662-1.065, P

= 0.149; homozygote model: OR = 0.812, 95%CI = 0.638-1.032, P = 0.089). The summarized results obtained using the different models are shown in Table 3. To test for publication bias, both the Begger and Egger tests were performed. Forest plots and funnel plots for the American and Asian subgroups are summarized in Figures 4 and 5.

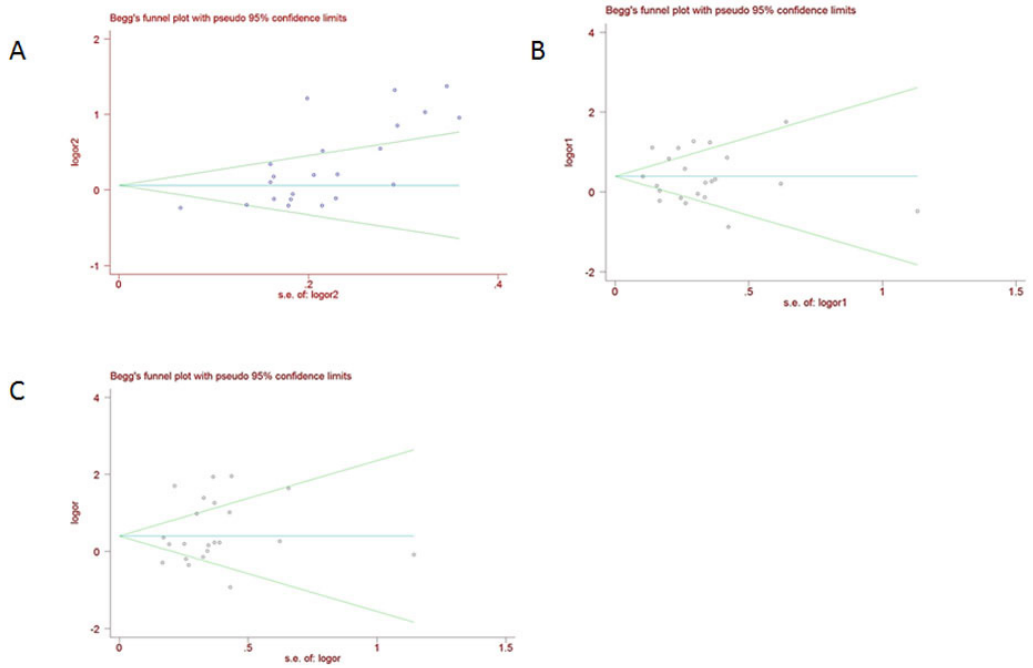

Figure 3. Funnel plot for the entire database including 22 studies. (**A**) Dominant model (GG+GA *vs* AA), (**B**) recessive model (GG *vs* GA+AA), and (**C**) homozygote comparison (GG *vs* AA) were applied in these analyses.

Table 3. Meta-analysis for subgroups using 3 analysis models.

Analysis model	Analysis method	Heterogeneity		OR (95%CI)				Publication bias	
		I^2 (%)	P value	Overall	Lower	Upper	P value	Begger	Egger
African									
Dominant	Random	81.00	0.000	1.059	0.786	1.428	0.706	0.221	0.079
Recessive	Fixed	0.00	0.764	0.840	0.662	1.065	0.149	0.462	0.708
Homozygote	Fixed	0.00	0.670	0.812	0.638	1.032	0.089	0.221	0.339
American									
Dominant	Random	84.20	0.000	1.694	1.019	2.817	0.042	0.734	0.726
Recessive	Random	84.10	0.000	2.032	1.292	3.197	0.002	1.000	0.852
Homozygote	Random	87.90	0.000	2.406	1.123	5.157	0.024	1.000	0.948
European									
Dominant	Random	70.30	0.035	1.126	0.707	1.791	0.618	1.000	0.755
Recessive	Random	86.50	0.001	1.692	0.382	7.495	0.489	1.000	0.566
Homozygote	Random	86.80	0.001	1.696	0.364	7.892	0.501	1.000	0.625
Asian									
Dominant	Random	82.20	0.000	1.929	1.203	3.094	0.006	0.049	0.068
Recessive	Random	76.50	0.000	1.566	1.133	2.164	0.007	0.371	0.213
Homozygote	Random	83.60	0.000	1.929	1.203	3.094	0.006	0.049	0.068

OR = odds ratio; 95%CI = 95% confidence interval.

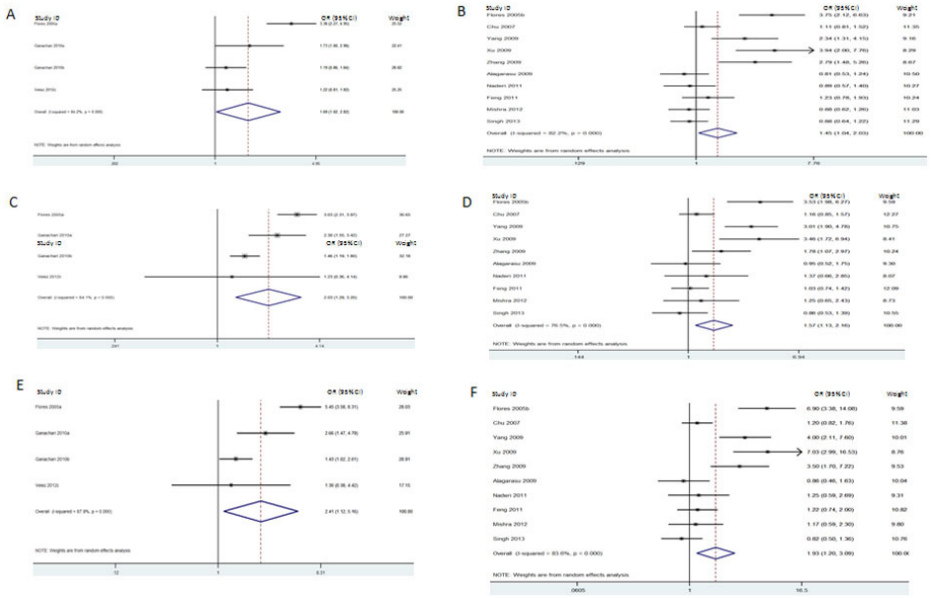

Figure 4. Forest plots for the American subgroup (A, C, and E) and Asian subgroup (B, D, and F) were generated with the dominant model (GG+GA *vs* AA), recessive model (GG *vs* GA+AA), and homozygote model.

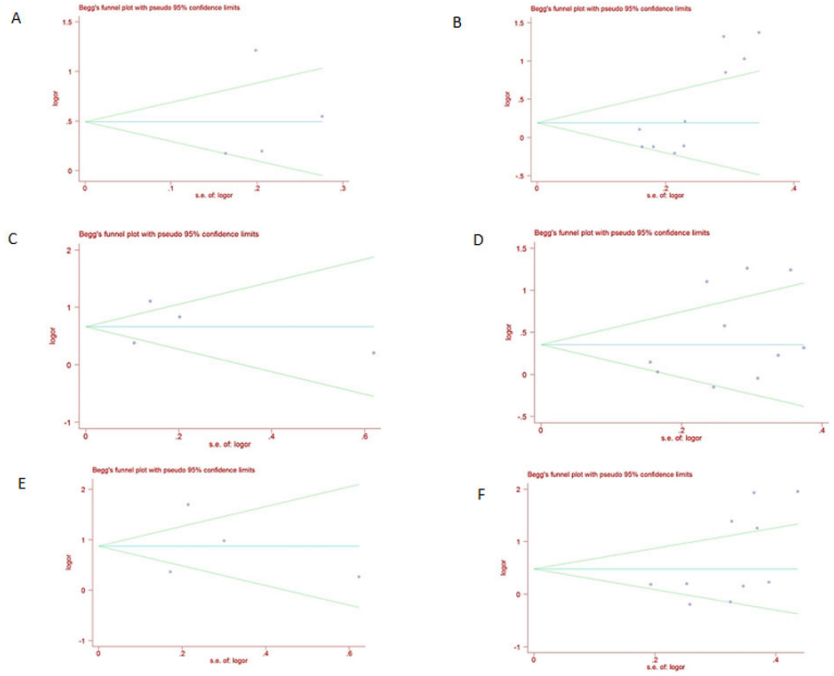

Figure 5. Funnel plots for the American subgroup (**A**, **C**, and **E**) and Asian subgroup (**B**, **D**, and **F**) were generated with the dominant model (GG+GA *vs* AA), recessive model (GG *vs* GA+AA), and homozygote model.

DISCUSSION

Our results revealed an association between the *MCP-1* -2518A/G polymorphism and human TB susceptibility using all 3 analysis models for all data. The studies included contained data from African, American, Europeans, and Asian populations. Because the same nucleotide polymorphism can function differently in different genetic backgrounds, the results for these 4 ethnicities should be interpreted with caution. Therefore, we further investigated the susceptibility in 4 population subgroups. After stratification by ethnicity, significantly elevated risks were observed in Americans and Asians, but not in Africans and Europeans. This may be because of the relatively small size of the database and because the results were not very uniform. This may also be because of genetic differences among the populations.

In our meta-analysis of the *MCP-1* -2518A/G polymorphism, significant heterogeneity was found in the overall effect. Several factors may have affected this heterogeneity. First, the populations had different genetic backgrounds (Tian et al., 2011). Second, environmental factors in different case-control studies were not investigated, which may have influenced TB susceptibility. Third, the cases and controls included were not very homogenous in the analysis.

There were 3 previous meta-analyses that evaluated the association between the *MCP-1* -2518A/G polymorphism and TB susceptibility (Feng et al., 2011; Zhang et al., 2012; Gong et al., 2013). Compared with these reports, ours revealed some new insights. First, our dataset was much more comprehensive, and additional recently published studies were included when estimating the risk associated with the *MCP-1* -2518A/G polymorphism. Second, only high-quality studies were included in our analysis; we provided a more precise overview of the studies included through strict study selection and data extraction. Moreover, we used 3 different genetic models to analyze the association in subgroups and in the entire population.

There were several limitations to this study. First, because not all of the original data from each study were available, we could not analyze the effect of the polymorphism on various types of TB (pulmonary TB and extra-pulmonary TB). Second, genetic heterogeneity among different populations emphasizes the need to interpret the results with caution. Despite these limitations, our meta-analysis results suggest that the *MCP-1* -2518A/G polymorphism is significantly associated with an increased risk of TB. Future well-designed studies with a larger sample size and including different ethnicities are needed.

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