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A meta-analysis of interleukin-6 -572G>C polymorphism and coronary heart disease susceptibility

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Coronary heart disease (CHD) is one of the leading causes of disability and death worldwide, which includes angina pectoris, myocardial infarction, as well as arterial sclerosis of the coronary arteries [1]. It is widely accepted that CHD is a multifactorial disease. Several factors (hereditary, social-environmental factors, and their interactions) contribute to the onset of CHD.

The *interleukin-6 (IL-6)* gene locates on 7p21. Previous epidemiological studies revealed that plasma levels of IL-6 in people with cardiovascular disease (CVD) are quite different from those without CVD [2, 3]. Till now, many studies have investigated the association between *IL-6* gene *-572G>C* polymorphism and CHD risk. However, the results are inconsistent. In order to avoid the limitations of single case-control study and to provide renewed evidence, we performed this meta-analysis and tried to give a more comprehensive estimation of association between *IL-6* gene *-572G>C* polymorphism and CHD susceptibility.

We searched in PubMed, EMBASE, EBSCO, and Chinese National Knowledge Infrastructure (CNKI) to retrieve relevant studies until May 1, 2016. Studies were considered eligible if they met the following criteria: (1) it was a case-control study in design; (2) it evaluated the *IL-6* gene *-572G>C* polymorphism and CHD susceptibility; (3) the diagnosis of CHD was definite; (4) sample sizes and individual genotype frequencies were available. Two reviewers independently searched and selected literature, and extracted relevant data according to a data extraction form. Disagreements were solved by discussion until consensus was made.

For each included study, the quality assessment was conducted according to STREGA (STrengthening the REporting of Genetic Association studies). Data analysis was conducted using STATA 11.0 software (Stata Statistical software, USA, www.stata.com). Odds ratio (OR) and its corresponding 95% confidence intervals (95% CI) were used to evaluate the strength of association. Heterogeneity among included studies was tested using χ^2-based Q test and I^2 test. The Mantel-Haenszel method was used for fix-effect model if no heterogeneity was found. Otherwise, the DerSimonian-Laird random-effect model was used. Five comparisons of genetic models were conduced, including the dominant model (GG+GC vs. CC), the recessive model (GG vs. GC+CC), the allele contrast genetic model (G vs. C), the heterozygote comparison (GC vs. CC), and the homozygote comparison (GG vs. CC). Sensitivity analyses were conducted by omitting individual studies sequentially. Publication bias was quantitatively assessed by Begg's rank correlation test. Subgroup analyses stratified by ethnicity, source of control and deviation from Hardy-Weinberg equilibrium (HWE) were conducted. Meta-regression test was used for the assessment of heterogeneity, characteristics tested included ethnicity, source of control, deviation from HWE, and sample size. $P < 0.05$ showed statistical significance.

Finally, 19 case-control studies including 4,545 cases and 7,720 controls were included in this meta-analysis. Table 1 presents the main characteristics, genotype frequencies of included studies, deviation from HWE in control groups, and quality of each study. The combined results based on all

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Table 1. The main characteristics of studies included in this meta-analysis and the distribution of *IL-6* gene *-572G>C* genotypic frequency and allelic frequency among the cases and controls.

First author	Year	Ethnicity	Source of controls	Cases			Controls			Cases		Controls		Deviation from HWE	Quality grade
				GG	GC	CC	GG	GC	CC	G	C	G	C		
Georges JL	2001	Caucasian	PB	552	58	1	589	73	3	1162	60	1251	79	No	++
Humphries SE	2001	Caucasian	PB	135	19	0	2224	225	9	289	19	4673	243	No	++
Basso F	2002	Caucasian	PB	425	56	1	959	116	2	906	58	2034	120	No	++
Kelberman D	2004	Caucasian	PB	433	71	1	475	69	3	937	73	1019	75	No	++
Li Y	2005	Asian	PB	16	64	119	4	60	125	96	302	68	310	No	+
Wei YS	2006	Asian	PB	6	54	105	4	50	116	66	264	58	282	No	+
Fu HX	2006	Asian	PB	16	101	128	4	90	166	133	357	98	422	Yes	+
Liu YS	2007	Asian	PB	2	39	49	1	26	68	43	137	28	162	No	+
Park S	2007	Asian	PB	9	62	97	12	62	92	80	256	86	246	No	++
Gao CX	2008	Asian	PB	10	51	65	4	32	72	71	181	40	176	No	+
Maitra A	2008	Asian	PB	23	15	8	11	23	6	61	31	45	35	No	++
Jia XW	2010	Asian	PB	22	130	79	15	107	88	174	288	137	283	Yes	+
Fragoso JM	2010	Caucasian	PB	115	146	23	108	103	36	376	192	319	175	No	++
Liang ZY	2010	Asian	HB	14	161	259	8	126	283	189	679	142	692	No	+
Coker A	2011	Caucasian	HB	126	30	11	169	45	21	282	52	383	87	No	++
Fan WH	2011	Asian	PB	4	38	42	3	32	95	46	122	38	222	No	+
Liu YC	2011	Asian	HB	11	52	63	3	55	92	74	178	61	239	No	+
Tong Z	2013	Asian	HB	179	110	37	180	120	41	468	184	480	202	Yes	+
Zhang YJ	2013	Asian	HB	64	26	12	157	52	6	154	50	366	64	No	+

++: high quality; +: moderate quality; HB — hospital-based study; HWE — Hardy-Weinberg equilibrium; PB — population-based study

Table 2. Results of subgroup analyses of *IL-6* gene *-572G>C* polymorphism.

Stratified by	Comparison	Number of datasets	Dominant genetic model		Allele contrast	
			OR (95% CI)	P	OR (95% CI)	P
Ethnicity	Asian	13	1.168 (1.040–1.312)	0.009	1.223 (1.078–1.387)	0.002
	Caucasian	6	1.004 (0.994–1.015)	0.426	1.001 (0.990–1.012)	0.864
Source of control	PB	14	1.052 (1.007–1.098)	0.023	1.046 (1.003–1.091)	0.034
	HB	5	1.044 (0.944–1.155)	0.405	1.059 (0.947–1.185)	0.313
Deviation from HWE	Yes	3	1.127 (0.936–1.358)	0.207	1.167 (0.950–1.434)	1.47
	No	16	1.031 (0.994–1.069)	0.099	1.029 (0.992–1.067)	1.52

CI — confidence interval; HB — hospital-based study; HWE — Hardy-Weinberg equilibrium; OR — odds ratio; PB — population-based study

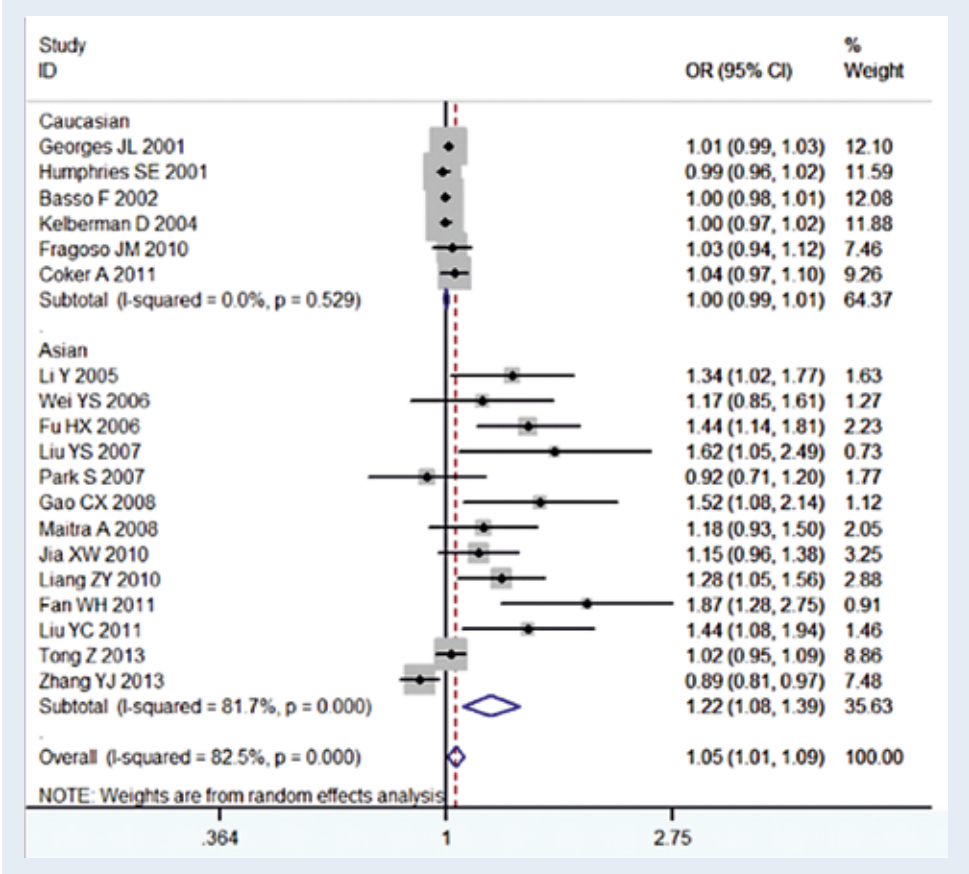

Figure 1. The association between *IL-6* gene *-572G>C* polymorphism and coronary heart disease susceptibility in the allele contrast genetic model stratified by ethnicity; CI — confidence interval; OR — odds ratio.

studies showed that a significant increase of CHD susceptibility was found in the dominant model (GG+GC vs. CC: OR = 1.044, 95% CI 1.006–1.084, p = 0.023), the heterozygote comparison (GC vs. CC: OR = 1.086, 95% CI 1.012–1.166, p = 0.021), and the allele contrast genetic model (G vs. C: OR = 1.046, 95% CI 1.007–1.086, p = 0.021), but not in the recessive model (GG vs. GC+CC: OR = 1.007, 95% CI 0.959–1.058, p = 0.770), or the homozygote comparison (GG vs. CC: OR = 1.009, 95% CI 0.980–1.039, p = 0.544). In the subgroup analysis stratified by ethnicity, significant increase of CHD susceptibility was found in Asians in the dominant model (GG+GC vs. CC: OR = 1.168, 95% CI 1.040–1.312, p = 0.009) and the allele contrast genetic model (C vs. G: OR = 1.223, 95% CI 1.078–1.387, p = 0.002). The detailed outcomes of subgroup analyses are shown in Table 2. Figure 1

shows the association between *IL-6* gene *-572G>C* polymorphism and CHD susceptibility in the allele contrast genetic model stratified by ethnicity.

Through Begg's rank correlation test, we identified heterogeneity in the dominant model, the allele contrast genetic model, and the homozygote comparison, but not for the other two genetic models. In the sensitivity analyses, the result did not change under any genetic model, which suggested that the results of main analysis were statistically robust. In meta-regression, the univariate regression test showed that ethnicity (I^2-residual = 40.1%, adj-R^2 = 41.8%, p = 0.04) were the significant source of heterogeneity among studies.

Cytokine genes have been supposed to be of crucial role in diseases susceptibility and host genetic polymorphisms. *IL-6* has a broad range of cellular and humoral properties in relation to the etiology and inflammatory response of CHD [4, 5]. Previous studies have demonstrated that plasma levels of IL-6 may be associated with CHD risk and that the *-572G* allele was associated with lower serum level of IL-6 concentrations compared with the *-572C* allele [6, 7]. Therefore, it is quite reasonable to deduce that *IL-6* gene *-572G>C* polymorphism is associated with CHD susceptibility.

Comparing with two previous meta-analyses focusing on association between *IL-6* gene *-572G>C* polymorphism [8, 9], our study has some important improvements. Firstly, some new studies were published and they were included in our meta-analysis. Moreover, in the present study, we conducted subgroup analyses and meta-regression test to identify the potential source of heterogeneity. Through subgroup analyses, we found that *G* allele of *-572G>C* polymorphism was significantly associated with increased CHD susceptibility in Asians, but the effect size was weak. Meta-regression test showed that ethnicity (I^2-residual = 40.1%, adj-R^2 = 41.8%, p = 0.04) was a significant source of heterogeneity among the studies. Therefore, the different ethnicity contributed to the overall heterogeneity. We also have to note the limitations of this study. Firstly, we only included published studies meeting our inclusion criteria from four databases, similar studies in other databases and unpublished researches may have been missed. Moreover, the possible pathogenesis of CHD is comprehensive, but due to insufficiency of included studies, we did not detect the interactions between genetic factors and other environmental or lifestyle factors.

In conclusion, from the combined results of currently included studies, our meta-analysis suggests that the *G* allele of *IL-6* gene *-572G>C* polymorphism is significantly associated with increased CHD susceptibility in Asians, but the effect size is weak. More studies with multiple ethnicities and different genders are needed to generalize the results.

Conflict of interest: None declared

References

1. Yoon SS, Dillon CF, Illoh K, Carroll M. Trends in the Prevalence of Coronary Heart Disease in the U.S.: National Health and Nutrition Examination Survey, 2001–2012. American Journal of Preventive Medicine, 2016.
2. Jenny NS, Tracy RP, Ogg MS et al. In the elderly, interleukin-6 plasma levels and the -174G>C polymorphism are associated with the development of cardiovascular disease. Arteriosclerosis Thrombosis Vascular Biol, 2002; 22: 2066–2071.
3. Cesari M, Penninx BW, Newman AB et al. Inflammatory markers and onset of cardiovascular events: results from the Health ABC study. Circulation, 2003; 108: 2317–2322.
4. Plutzky J. Inflammatory pathways in atherosclerosis and acute coronary syndromes. Am J Cardiol, 2001; 88: 10K–5K.
5. Woods A, Brull DJ, Humphries SE, Montgomery HE. Genetics of inflammation and risk of coronary artery disease: the central role of interleukin-6. Eur Heart J, 2000; 21: 1574–1583.
6. Danesh J, Kaptoge S, Mann AG et al. Long-term interleukin-6 levels and subsequent risk of coronary heart disease: Two new prospective studies and a systematic review. PLoS Med, 2008; 5: e78.
7. Malarstig A, Wallentin L, Siegbahn A. Genetic variation in the interleukin-6 gene in relation to risk and outcomes in acute coronary syndrome. Thrombosis Res, 2007; 119: 467–473.
8. Zheng GH, Chen HY, Xiong SQ. Polymorphisms of -174G>C and -572G>C in the interleukin 6 (IL-6) gene and coronary heart disease risk: a meta-analysis of 27 research studies. PloS One, 2012; 7: e34839.
9. Song C, Liu B, Yang D et al. Association between Interleukin-6 gene -572G>C polymorphism and coronary heart disease. Cell Bioch Biophysics, 2015; 71: 359–365.