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Original Article

Interleukin-6 receptor (IL6R) rs7529229 polymorphism and coronary heart disease risk

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Abstract: Some studies investigated the association of IL6R rs7529229 polymorphism with CHD. However, the result was still inconsistent. The aim of this study was to investigate whether there is an association between the IL6R rs7529229 polymorphism and CHD risk. Electronic databases, such as PubMed, EMBASE, and China National Knowledge Infrastructure (CNKI) databases, were searched for identification of the studies. The strength of association between IL6R rs7529229 polymorphism and CHD risk was assessed by calculating OR with 95% CI. In this current study, 77349 cases and 237357 controls were included. IL6R rs7529229 polymorphism was associated with a significantly decreased risk of CHD (OR=0.96; 95% CI, 0.94-0.97; I^2=6%). We also found that this polymorphism decreased CHD risk in Caucasians (OR=0.96; 95% CI, 0.94-0.97; I^2=10%). In the subgroup analysis according to gender, both women and men were significantly associated with the decreased risk of CHD (OR=0.96; 95% CI, 0.92-1.00; I^2=9% and OR=0.97; 95% CI, 0.94-1.00; I^2=3%). In the subgroup analysis by age, IL6R rs7529229 polymorphism showed no significant results. However, this polymorphism influenced CHD risk in subjects without diabetes (OR=0.97; 95% CI, 0.94-1.00; I^2=0%). In conclusion, this meta-analysis suggested that IL6R rs7529229 polymorphism was associated with CHD risk.

Keywords: Coronary heart disease, IL-6R, meta-analysis, polymorphism

Introduction

Coronary heart disease (CHD) is a complex polygenic disease. CHD involves complex interactions among multiple genetic and environmental conditions [1]. There are several risk factors for CHD, such as hypertension, diabetes mellitus, hyperlipidaemia, smoking, family history of CHD, and obesity. However, studies indicate that cardiovascular risk stratification may be improved through the concurrent evaluation of novel genetic risk factors in addition to conventional risk criteria [2].

Mounting evidence highlights the role of a systemic inflammatory state in cardiovascular risk. Interleukin-6 is one of the inflammatory cytokines. Su et al. found that serum IL-6 is significantly associated with all-cause and cardiovascular mortality in hospitalized patients with CHD [3]. Li et al. indicated that the carriers of -572G allele of IL6 gene might be predisposed to CHD risk [4]. Danesh et al. found that long-term IL-6 levels were associated with CHD risk about as strongly as are some major established risk factors [5]. Anderson et al. suggested that there was a decrease in IL-6R (0.374-fold, P<0.01) as compared to CHD and controls [6]. These findings highlight the potential relevance of IL-6-mediated pathways to CHD. Some studies investigated the association of IL6R rs7529229 polymorphism with CHD [7-10]. However, the result was still inconsistent. The aim of this study was to investigate whether there is an association between the IL6R rs7529229 polymorphism and CHD risk.

Methods

Publication search

Electronic databases, such as PubMed, EMBASE, and China National Knowledge Infrastructure (CNKI) databases, were searched for identification of the studies. The last search was up to October 10, 2015. Search terms included

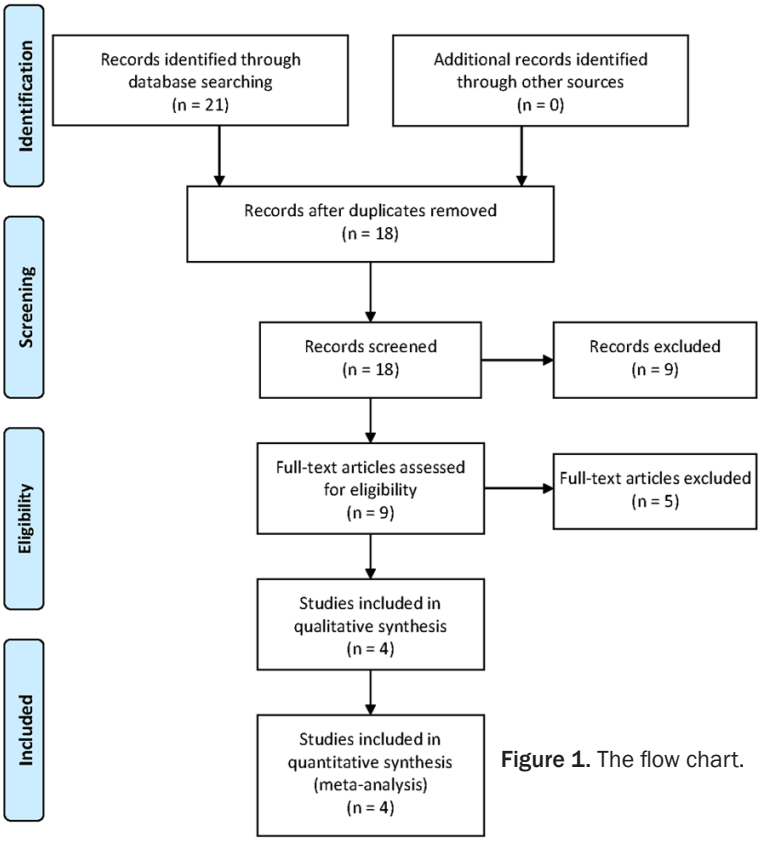

Figure 1. The flow chart.

"coronary heart disease or CHD or CAD or coronary artery disease" and "IL6R or Interleukin-6 receptor". All searched studies were retrieved and the bibliographies were checked for other relevant publications.

Inclusion criteria

The following criteria were used to select the eligible studies: (a) evaluation of the association between IL6R rs7529229 polymorphism and CHD risk; (b) an unrelated case–control study in which family members were excluded; (c) sufficient published data for estimating an odds ratio (OR) with 95% confidence interval (CI). When authors reported two or more publications on the same patient population, only the largest study was selected. Additionally, when a study reported the results on different subpopulations, we treated them as a separate study.

Data extraction

Data were extracted by two authors independently. If encountered the conflicting evaluations, an agreement was reached following a discussion; if could not reached agreement, another author was consulted to resolve the debate. The following information was extracted from each study: first author, year of publication, ethnicity, age, gender, sample size, and Hardy-Weinberg equilibrium (HWE) results.

Quality assessment

Quality assessment was conducted for each article according to strengthening the Reporting of Genetic Association studies (STREGA) containing eleven items associated with valid data reported in the study. For each item, there are three degrees, "yes" (scored 2), "can't tell" (scored 1) or "no" (scored 0), after evaluating each item, a total score from 0 to 22 was reported for each article. Studies would be divided into 3 grades: Grade A (scored 15-22, high quality), Grade B (scored 8-14, medium quality), or Grade C (scored 0-7, inferior quality). Only the studies of Grade A or B would be included in the final analysis.

Statistical analysis

The strength of association between IL6R rs7529229 polymorphism and CHD risk was assessed by calculating OR with 95% CI. The pooled ORs were performed in additive model. A statistical test for heterogeneity was performed based on the Q statistic. The $P>0.10$ of the Q-test indicated a lack of heterogeneity among studies. The summary OR estimate of each study was calculated by the random-effects model (the DerSimonian and Laird method). Stratified analysis was performed by race, age, gender, and diabetes. Cumulative meta-analysis and sensitivity analysis were also conducted. Potential publication bias was examined by Egger's test. All statistical tests were performed with the Revman 5.1 software (Nordic Cochrane Center, Copenhagen, Denmark) and STATA version 11.0 (Stata Corporation, College station, TX, USA). A P value <0.05 was considered statistically significant.

Table 1. Characteristics of the studies included in this meta-analysis

Study	Year	Ethnicity	Age	Gender	No. of case	No. of control	Quality grade	Hardy-Weinberg equilibrium
Swerdlow (AAA)	2012	Caucasian	Adult	Mixed	95	2137	A (scored 21)	Yes
Swerdlow (MESA)	2012	Caucasian	Adult	Mixed	100	2195	A (scored 20)	Yes
Swerdlow (INCHINATI)	2012	Caucasian	Adult	Mixed	115	1158	A (scored 21)	Yes
Swerdlow (CHS)	2012	Caucasian	Adult	Mixed	128	3632	A (scored 19)	Yes
Swerdlow (ET2DS)	2012	Caucasian	Adult	Mixed	145	908	A (scored 17)	Yes
Swerdlow (FHS)	2012	Caucasian	Adult	Mixed	159	1176	A (scored 19)	Yes
Swerdlow (NPHS-II)	2012	Caucasian	Adult	Male	269	2398	A (scored 21)	Yes
Swerdlow (CAPS)	2012	Caucasian	Adult	Male	277	1127	A (scored 20)	Yes
Swerdlow (PREVEND)	2012	Caucasian	Adult	Mixed	289	3578	A (scored 18)	Yes
Swerdlow (TPT)	2012	Caucasian	Adult	Male	299	3475	A (scored 19)	Yes
Swerdlow (IMPROVE)	2012	Caucasian	Adult	Mixed	301	3164	A (scored 20)	Yes
Swerdlow (EAS)	2012	Caucasian	Adult	Mixed	312	578	A (scored 19)	Yes
Swerdlow (MEDSTAR)	2012	Caucasian	Adult	Mixed	410	441	A (scored 21)	Yes
Swerdlow (WHITEHAII)	2012	Caucasian	Adult	Mixed	418	4624	A (scored 20)	Yes
Swerdlow (HAPIEE-CZ)	2012	Caucasian	Adult	Mixed	435	6265	A (scored 18)	Yes
Swerdlow (PROSPER)	2012	Caucasian	Adult	Mixed	589	4654	A (scored 19)	Yes
Swerdlow (BWHHS)	2012	Caucasian	Adult	Female	617	2657	A (scored 1)	Yes
Swerdlow (HAPIEE-RU)	2012	Caucasian	Adult	Mixed	648	6437	A (scored 19)	Yes
Swerdlow (BRHS)	2012	Caucasian	Adult	Male	668	3206	A (scored 21)	Yes
Swerdlow (HAPIEE-LT)	2012	Caucasian	Adult	Mixed	676	6238	A (scored 20)	Yes
Swerdlow (HAPIEE-PL)	2012	Caucasian	Adult	Mixed	737	8021	A (scored 21)	Yes
Swerdlow (LOLOPOP)	2012	Caucasian	Adult	Mixed	896	5761	A (scored 19)	Yes
Swerdlow (EPIC-NL)	2012	Caucasian	Adult	Mixed	1303	3880	A (scored 20)	Yes
Swerdlow (ARIC)	2012	Caucasian	Adult	Mixed	1837	7692	A (scored 19)	Yes
Swerdlow (WHI)	2012	Caucasian	Adult	Female	2396	2094	A (scored 21)	Yes
Swerdlow (EDS)	2012	Caucasian	Adult	Mixed	51	252	A (scored 20)	Yes
Swerdlow (UDACS)	2012	Caucasian	Adult	Mixed	60	522	A (scored 18)	Yes
Swerdlow (HIFMECH)	2012	Caucasian	Adult	Male	509	553	A (scored 19)	Yes
Swerdlow (UCP)	2012	Caucasian	Adult	Mixed	632	1000	A (scored 21)	Yes
Swerdlow (INTERHEART E)	2012	Caucasian	Adult	Mixed	796	895	A (scored 19)	Yes
Swerdlow (GERMIFS II)	2012	Caucasian	Adult	Mixed	1222	1298	A (scored 21)	Yes
Swerdlow (WTCCC)	2012	Caucasian	Adult	Mixed	1926	2937	A (scored 20)	Yes
Swerdlow (ISIS)	2012	Caucasian	Adult	Mixed	2073	1493	A (scored 18)	Yes
Swerdlow (PROCARDIS)	2012	Caucasian	Adult	Mixed	4070	4258	A (scored 19)	Yes
Sarwar	2012	Caucasian	Adult	Mixed	51441	136226	A (scored 20)	Yes
Chen	2013	Asian	Adult	Mixed	187	231	A (scored 18)	Yes
Zhou	2014	Asian	Adult	Mixed	263	196	A (scored 17)	Yes

NA, not available.

Results

Study characteristics

The flow chart in **Figure 1** summarizes this literature review process. In this current study, a total of 4 eligible studies met the inclusion criteria. One study reported 35 cohorts, and each cohort was considered as a case-control study. Finally, a total of 38 case-control studies involving 77349 cases and 237-357 controls were included in this meta-analysis. There were 2 studies performed using Asians and 36 studies using Caucasians. Characteristics of studies are presented in **Table 1**.

Table 2. Results of this meta-analysis

	Test of association		Heterogeneity	
	OR (95% CI)	*P* Value	I^2 (%)	*P* Value
Overall	0.96 (0.94-0.97)	<0.00001	6	0.36
Caucasian	0.96 (0.94-0.97)	<0.00001	10	0.29
Asian	0.90 (0.74-1.09)	0.27	61	0.02
Old	1.00 (0.94-1.06)	1.00	29	0.14
Young	0.98 (0.94-1.07)	0.64	33	0.11
Male	0.97 (0.94-1.00)	0.05	3	0.39
Female	0.96 (0.92-1.00)	0.05	9	0.35
Diabetes	1.00 (0.93-1.07)	1.00	22	0.19
No Diabetes	0.97 (0.94-1.00)	0.05	0	0.69

Results of meta-analysis

The results of the association between IL6R rs7529229 polymorphism and CHD risk are listed in **Table 2**. IL6R rs7529229 polymorphism was associated with a significantly decreased risk of CHD (OR=0.96; 95% CI, 0.94-0.97; I^2=6%; **Figure 2**). We also found that this polymorphism decreased CHD risk in Caucasians (OR=0.96; 95% CI, 0.94-0.97; I^2=10%). In the subgroup analysis according to gender, both women and men were significantly associated with the decreased risk of CHD (OR=0.96; 95% CI, 0.92-1.00; I^2=9% and OR=0.97; 95% CI, 0.94-1.00; I^2=3%). In the subgroup analysis by age, IL6R rs7529229 polymorphism showed no significant results. However, this polymorphism influenced CHD risk in subjects without diabetes (OR=0.97; 95% CI, 0.94-1.00; I^2=0%).

Significant associations were evident with each addition of more data over time (data not shown). A single study involved in the meta-analysis was deleted each time to reflect the influence of the individual data set to the pooled ORs, and the corresponding pooled ORs were not materially altered (data not shown).

The shape of the funnel plots did not reveal any evidence of obvious asymmetry (**Figure 3**). The Egger test also did not displayed any evidence of publication bias (*P*=0.990).

Discussion

This present meta-analysis investigating the relationship between IL6R rs7529229 polymorphism and CHD risk. Thirty seven studies with a total of 77349 cases and 237357 controls were included. At the overall analysis, the IL6R rs7529229 polymorphism was significantly associated with CHD risk. In the subgroup analysis by ethnicity, we noted that Caucasians carrying IL6R rs7529229 polymorphism had a decreased CHD risk. Only two studies investigated the association between IL6R rs7529229 polymorphism and CHD risk in Asians. Therefore, more studies are needed to investigate this issue. In the stratified analysis by age, no significant results were found. The positive association could not be ruled out, because studies with small sample size may have insufficient statistical power to detect a slight effect. The subgroup analysis based on gender found that this polymorphism showed decreased CAD risk in female subjects. When subgroup analysis was performed according to diabetes status, significant association was showed in non-diabetes subjects. This result suggested that diabetes might change the effect of IL6R rs7529229 polymorphism on CHD.

The association between the IL6R polymorphisms and the serum levels of soluble IL-6 receptor (sIL-6R) was investigated. Galicia and colleagues found that IL6R rs7529229 polymorphism carriers had higher sIL-6R level [11]. High levels of IL-6 have been reported in several chronic inflammatory diseases as well as in CHD. The sIL-6R is likewise able to bind to IL-6. Thus, IL6R rs7529229 polymorphism carriers might have lower CHD risk. Recently, He and colleagues found that IL6R rs7529229 polymorphism may contribute to the risk of left main CHD in a Chinese population [12]. Meta-analysis of five studies demonstrated that rs7529229 was associated with a lower risk of abdominal aortic aneurysm [13].

There are several limitations in this current study. First of all, although the subgroup analysis on Asian population showed no decreases risk of CHD, this result was based on only 2 studies. Consequently, the lack of power due to the small number of studies leaves it an open field for Asians. Second, due to the lack of original information of the entire data, we did not evaluate interactions of gene and environmental factors in all pooled studies. As a result, further assessment of potential interactions which might be an important element of the association of the polymorphism and CD risk was not conducted.

In conclusion, this meta-analysis suggested that IL6R rs7529229 polymorphism is associated with CHD risk.

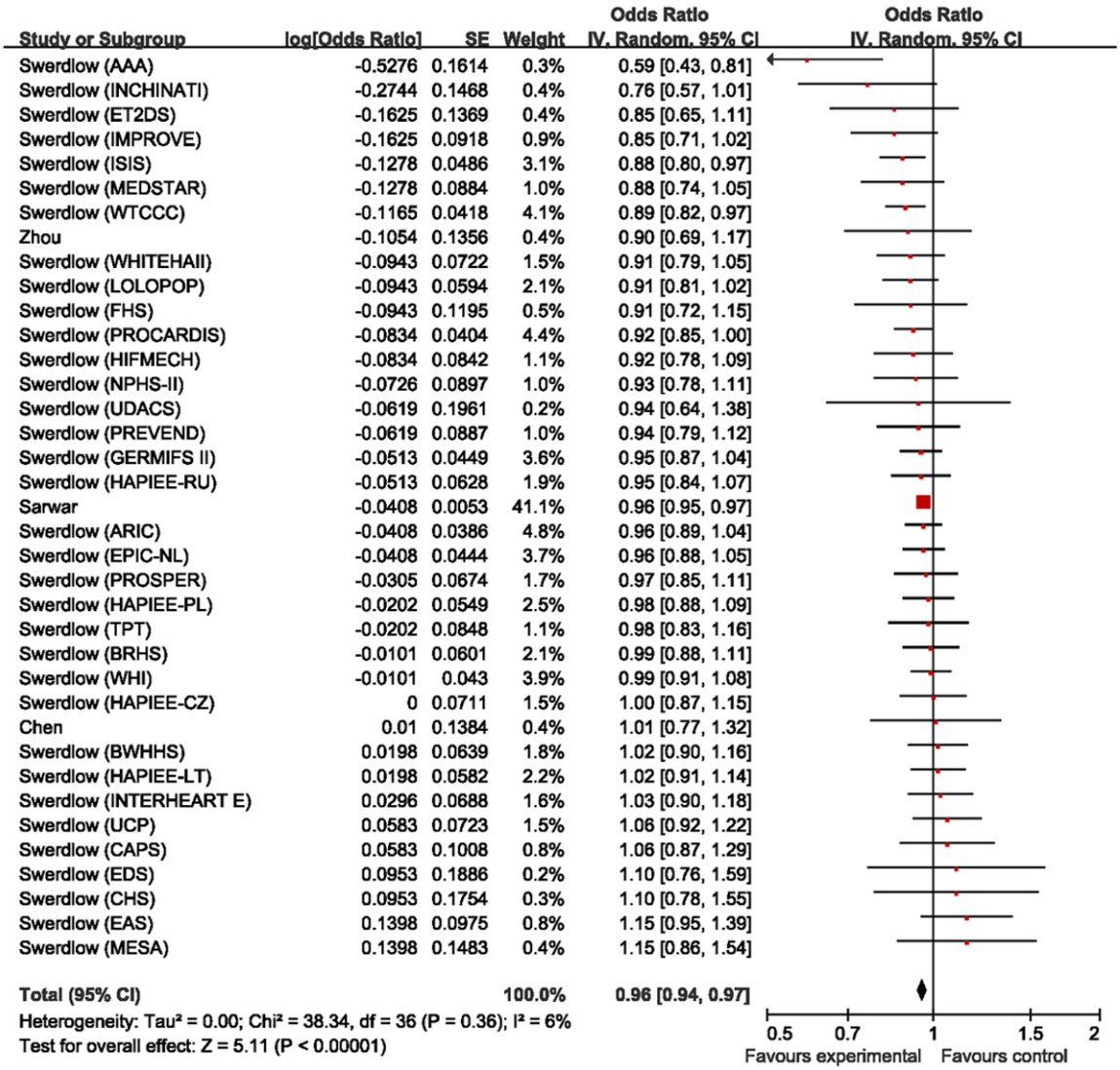

Figure 2. Meta-analysis for the association between IL6R rs7529229 polymorphism and CHD risk.

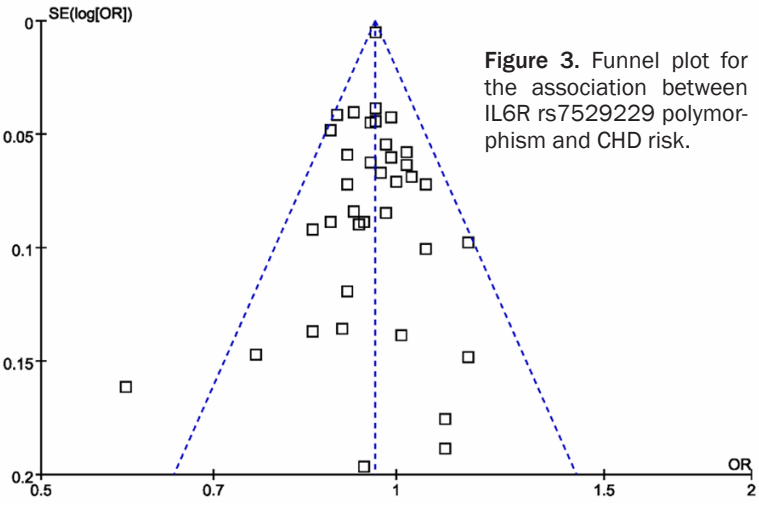

Figure 3. Funnel plot for the association between IL6R rs7529229 polymorphism and CHD risk.

Disclosure of conflict of interest

None.

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