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Genetic polymorphisms of interleukin-6 gene and susceptibility to coronary artery disease in Chinese population: Evidence based on 4582 subjects ☆

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ABSTRACT

The aim of this study was to explore whether interleukin-6 (IL-6) gene (−174 G/C and −572 C/G) polymorphisms are associated with susceptibility to coronary artery disease (CAD) risk in Chinese population. All the statistical tests were performed using Stata version 11.0. Twelve articles involving 16 studies were included in this meta-analysis, covering a total of 2309 CAD cases and 2273 controls. For IL-6 gene −572 C/G polymorphism, the results showed evidence for significant association between IL-6 gene −572 C/G polymorphism and CAD risk (for G allele vs. C allele: OR = 1.48, 95% CI = 1.26–1.74, $p < 0.001$; for G/G vs. C/C: OR = 2.60, 95% CI = 1.54–4.39, $p < 0.001$; for G/G vs. G/C + C/C: OR = 2.15, 95% CI = 1.35–3.42, $p = 0.001$; for G/G + G/C vs. C/C: OR = 1.55, 95% CI = 1.29–1.85, $p < 0.001$). However, for IL-6 gene −174 G/C polymorphism, no significant association was found between this variation and CAD risk. In summary, our meta-analysis showed evidence that IL-6 gene −572 C/G polymorphism may be a risk factor for CAD susceptibility. For IL-6 gene −174 G/C polymorphism, no significant association was found between this variation and CAD risk.

1. Introduction

Coronary artery disease (CAD) is the most common cardiovascular disease that causes significant morbidity and mortality worldwide [1]. The World Health Organization (WHO) estimates that 17.3 million people died from this disease worldwide per year and most of these deaths occur in the developing countries, and this number will increase to 23.6 million by 2030 [1]. Despite it is well established that a poor diet, advanced age, smoking, diabetes, hypertension, and dyslipidemia are associated with increased risk of CAD, a detailed etiology underlying CAD is still obscure. It is well known that inflammatory response is an essential part of the pathogenesis of atherosclerosis [2–4], and inflammatory response has been implicated in increasing the risk of CAD [5,6]. In addition, several epidemiological studies have demonstrated that increased serum levels of inflammatory markers, such as interleukin-6 (IL-6) and interleukin-1 (IL-1), being associated with increased risk of CAD [7,8], suggesting genetic factors involved in cytokines may play an important role in the development of CAD.

IL-6 is an important proinflammatory cytokine produced by many different cells, such as adipocytes, fibroblasts, myocytes, lymphocytes, monocytes and endothelial cells. The human IL-6 gene, located on chromosome 7p21, the common single nucleotide polymorphisms (SNPs) at position −174 and −572 of the IL-6 promoter regions have been identified [9,10], and consequent evidences demonstrated that these SNPs in the promoter regions could affect IL-6 gene transcription and its secretion [10–12]. To date, a variety of molecular epidemiological studies have focused on the associations between IL-6 gene polymorphisms and CAD risk. However, results of different studies have been inconsistent. In 2012, Zheng et al. performed a meta-analysis of worldwide studies including 27 studies showed that no significant association between IL-6 gene −174 G/C polymorphism and CAD risk [13]. In addition, they also found significant association between IL-6 gene

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−572 C/G polymorphism and CAD risk. Considering that potential ethnic difference might be associated with the distribution of genotypes, we conducted a meta-analysis by collecting and sorting the previously published studies in Chinese population.

2. Materials and methods

2.1. Publication search

We performed this meta-analysis in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) criteria [14]. A computerized literature search was conducted for the relevant available studies from PubMed, Embase, Web of Science, Cochrane database, Clinicaltrials.gov, Current Controlled Trials, Chinese Clinical Trial Registry, CBMdisc, CNKI and Google Scholar (updated to February 12, 2014). These computer searches were limited to English and Chinese language articles. The following keywords and subject terms were used for searching: "interleukin-6" OR "IL-6" AND "polymorphism" OR "mutation" OR "variant" OR "genotype" AND "coronary artery disease" OR "CAD" OR "coronary heart disease" OR "CHD". The equivalent Chinese terms were used in the Chinese databases. Additionally, we also screened references of the retrieved articles and review articles by a hand search.

2.2. Inclusion criteria

The studies included in the meta-analysis must meet all the following inclusion criteria: (1) human studies; (2) studies on the relationships between IL-6 gene (−174 G/C and −572 C/G) polymorphisms and CAD; (3) published case-control studies; (4) studies with full text articles; (5) sufficient data for estimating an odds ratio (OR) with 95% confidence interval (CI); (6) at least two comparison groups (CAD group vs. control group), and (7) not republished data.

2.3. Data extraction

Data was carefully extracted from all eligible publications independently by two authors (Yin YW and Sun QQ) of this article. In case of disagreement, a third author (Hu AM) examined such articles, and the disagreement was resolved until consensus was reached. For each study, data was extracted including (1) name of the first author; (2) date of publication; (3) country of origin; (4) ethnicity of the studied population; (5) source of controls; (6) sample size; (7) genotype number in cases and controls and (8) evidence of Hardy–Weinberg equilibrium (HWE, $p < 0.05$ was considered significant deviation from HWE).

2.4. Quality score assessment

The quality of included studies were assessed independently by two authors (Hu AM and Sun QQ) using the Newcastle–Ottawa Scale (NOS) [15]. The NOS ranges between zero (worst) up to nine stars (best). Studies with a score of seven stars or greater were considered to be of high quality. Disagreement was settled as described above.

2.5. Statistical analysis

All of the statistical tests used in the present study were performed by Stata version 11.0, which has been widely used in the meta-analysis [16,17]. The strength of associations between IL-6 gene polymorphisms and CAD risk was measured by ORs with 95% CIs. For IL-6 gene −572 C/G polymorphism, the combined ORs were respectively calculated for four genetic models (allelic model: G allele vs. C allele, additive model: G/G vs. C/C, recessive model: G/G vs. G/C + C/C, and dominant model: G/G + G/C vs. C/C). For IL-6 gene −174 G/C polymorphism, only two genetic models (allelic model: C allele vs. G allele, and codominant model: G/C vs. G/G) were used to calculate the combined ORs due to the fact that no C/C genotype was found in Chinese population. Cochran's Q statistic and the I^2 statistic were used to assess

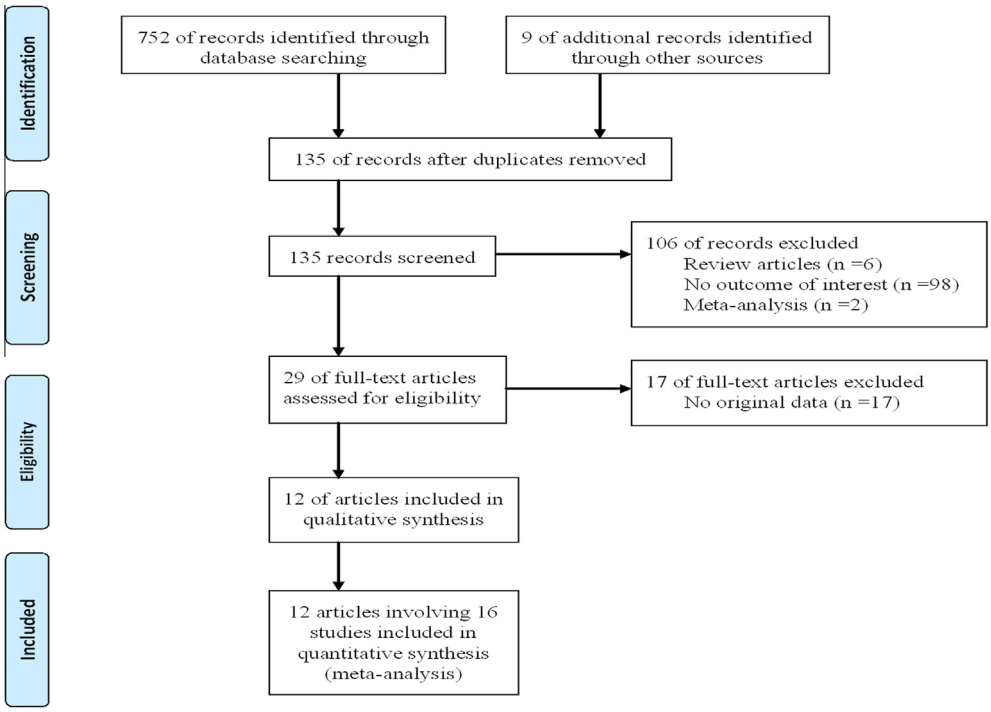

Fig. 1. Flow diagram of the study selection process.