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Genetic variations in the thrombin-activatable fibrinolysis inhibitor gene and risk of cardiovascular disease: A systematic review and meta-analysis

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ABSTRACT

Background: An imbalance between coagulation and fibrinolytic system plays an important role in the pathogenesis of arterial thrombosis. It has been identified that elevated plasma thrombin-activatable fibrinolysis inhibitor (TAFI) concentration, an anti-fibrinolytic factor, is associated with an increased risk of cardiovascular disease (CVD). But the effect of genetic variations in TAFI gene on the risk of CVD is inconclusive.
Objectives: To investigate the associations between two variants Ala147Thr(rs3742264) and Thr325Ile(rs1926447) in TAFI and the risk of CVD.
Methods: Systematic review and meta-analysis of eligible studies published before January 2014. Coronary heart disease(CHD) and stroke are regarded as end-points of CVD.
Results: A total of 18 articles including 23 studies were enrolled. Among these articles were 19 studies of Ala147Thr and 15 of Thr325Ile variants, comprising 4,977 CVD patients and 8,082 controls together with 4,890 cases and 8,311 controls, respectively. There were no significant associations between Ala147Thr variant and CVD under allele, dominant, recessive genetic models. Similar results were observed when end-point, ethnicity, sample size, genotyping method were taken into account. Likewise, meta-analysis of Thr325Ile variant did not show significant associations with CVD under three genetic models. Nevertheless, in sub-analysis based on end-point, the TT(Ile/Ile) genotype was associated with a 25% higher risk of coronary heart disease(CHD) (OR = 1.25, 95%CI, 1.02–1.54; $P = 0.03$) compared with TC + CC(Thr/Ile + Thr/Thr) genotype(recessive model).
Conclusions: The present meta-analysis failed to confirm the influence of Ala147Thr and Thr325Ile variants on the susceptibility to CVD. However, potentially increased risk of CHD was detected in Ile325 allele carriers under recessive model.

Introduction

Coronary heart disease(CHD) and stroke are leading causes of death and disability world-wide [1], which are both multifactorial diseases influenced by genetic and environmental factors and share the common pathophysiologic mechanism based on atherosclerosis and thrombosis in the artery. Downregulation of fibrinolytic system contributes to arterial thrombosis. Thrombin-activatable fibrinolysis inhibitor (TAFI), as an important anti-fibrinolytic factor, plays a critical role in fibrinolytic system [2]. The plasma TAFI is a zymogen consisting of 423 amino acids and can be activated by thrombin, plasmin and thrombin/thrombomodulin complex [3]. Activated TAFI (TAFIa) potently attenuates fibrinolysis through removal of the carboxyl-terminal lysine residues from partially degraded fibrin that are important for the development of positive feedback in the fibrinolytic cascade subsequent to plasminogen binding with its surface [3]. Because of its anti-fibrinolytic function, TAFI is thought to be involved in arterial thrombotic diseases and further illustrated by epidemiologic studies which recognized an association between high levels of plasma TAFI and increased risk of several end points of cardiovascular disease(CVD) such as acute coronary disease(ACS) [4], myocardial infarction(MI) [5], angina pectoris(AP) [6], ischemic stroke(IS) [7–9],coronary heart disease(CHD) [9]. TAFI genetic variants were reported to account for approximately 25% variability in plasma levels of TAFI [3,10–12]. Recently, two variants were identified in the coding region of the TAFI gene(CPB2): nucleotide substitution at positions 505(G → A) and 1040(C → T) leading to amino acid exchanges at positions 147(Ala → Thr) and 325 (Thr → Ile) of the TAFI protein [6]. Owing to their important roles in concentrations

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and activity of TAFI, they were extensively studied and anticipated to be involved in arterial thrombotic diseases. This is supported by several studies that observe an increased risk of CHD [6,13] and stroke [14,15] in Thr147 allele carriers. However, such associations could not be confirmed in other studies [7–9,16–22]. The associations between Thr325Ile variant and CVD were not conclusive as well [5,7,9,18–25]. Hence, we assessed the susceptibilities of TAFI gene variants to CVD risk using meta-analysis in the present study.

Methods

Search Strategy

We conducted a systematic literature search for studies evaluating the relationships between TAFI variants and the risk of CVD in 7 databases: PubMed (1865- January 2, 2014), Science Direct (1997- January 2, 2014), BIOSIS Previews (1950- January 2, 2014), Chinese Biomedical Database (1978- January 2, 2014), Chinese National Knowledge Infrastructure (1979- January 2, 2014), Wanfang Database (1982- January 2, 2014) and Cochrane Library (1999- January 2, 2014). Following search terms: ("thrombin activatable fibrinolytic inhibitor" or "TAFI" or "CPB2" or "carboxypeptidase U") and ("myocardial infarction" or "coronary artery disease" or "coronary heart disease" or " cardiovascular disease" or "stroke" or "cerebral ischemia" or "cerebral ischaemia" or "cerebral infarction" or "brain infarction") and ("polymorphism" or "variation" or "allele" or "genotype") were used without language restriction. Additionally, the references of retrieved articles and review articles of interest were manually screened for other articles that were not identified initially.

Study Selection

Two investigators(J. Shi and P. K. Zhi) independently assessed all potentially relevant articles for their eligibility according to the following inclusion criteria: 1) evaluation for the association between Ala147Thr/Thr325Ile variant and CVD; 2) original research in case-control or cohort design; 3) sufficient genotype distribution data for calculation of combined odds ratios (ORs) and 95%CI. If researches did not report detailed information regarding genotype distribution in each group, corresponding authors were contacted for unpublished data. When the study populations overlapped, only the most extensive dataset was chosen to avoid duplication. The quality of included studies was assessed using the Newcastle-Ottawa Scale (NOS) [26], which contains three main sections (selection, comparability and exposure). One star was reached through a satisfactory answer. Studies with stars equal to or higher than five were considered to be of high quality.

Data Extraction

To evaluate the specificity and characteristics of enrolled researches, following information was separately extracted by two reviewers (J. Chen and P. H. Wu): first author, year of publication, study design, number of cases and controls, the type of clinical outcome, study population characteristics (mean age, gender, country or ethnicity, body mass index(BMI)), genotyping method, genotype distribution in cases and controls. The end-points of our meta-analysis were defined as stroke and coronary heart disease (including myocardial infarction, angina pectoris and acute coronary syndrome). For data extraction, disagreements were checked until a consensus was reached.

Statistical Analysis

For each genetic variant study, summary ORs and 95% confidence intervals(CI) were calculated to assess the strength of association, using random-effect model (DerSimonian-Laird method) [27] in the presence of heterogeneity or fixed-effect model when free of heterogeneity(Mantel–Haenszel method) [28]. The significance of summary OR was checked by Z-test and $Pz < 0.05$ was considered as statistically significance. In order to refrain excessive comparisons, three genetic models were employed to compute global data: allele model (G vs. A allele for Ala147Thr and T vs. C allele for Thr325Ile), dominant model (GG + GA vs. AA for Ala147Thr as well as TT + TC vs. CC for Thr325Ile), recessive model (GG vs. GA + AA for Ala147Thr and TT vs. TC + CC for Thr325Ile). The degree of heterogeneity among studies was detected through Q-test and Higgins I^2 statistic, with a low $P_Q(<0.1)$ or high value of $I^2(\geq 50\%)$ being considered significant heterogeneity [29]. Sub-analysis were performed to explore the source of heterogeneity in light of clinical outcome (CHD, stroke), ethnicity of subjects (European, Asian, African), total sample size (≥ 1000, <1000) and genotyping method (PCR-RELP, TaqMan, other). Sensitivity analysis, in which single study was withdrew each time to appraise the influence of single study, was conducted in an effort to justify the reliability of our results. Publication bias was examined through the regression method of Egger [30]. For Egger test, P value < 0.1 was used as significant level. All data were analyzed using statistical package Stata 10 (Stata Corporation, College Station, TX,USA).

Results

As Fig. 1 shown, a total of 189 potentially relevant articles were identified after initial literature search, of which 148 were retrieved for detailed evaluation after duplicates removal. Then, 127 articles were excluded because did not meet our inclusion criteria. Of the remaining

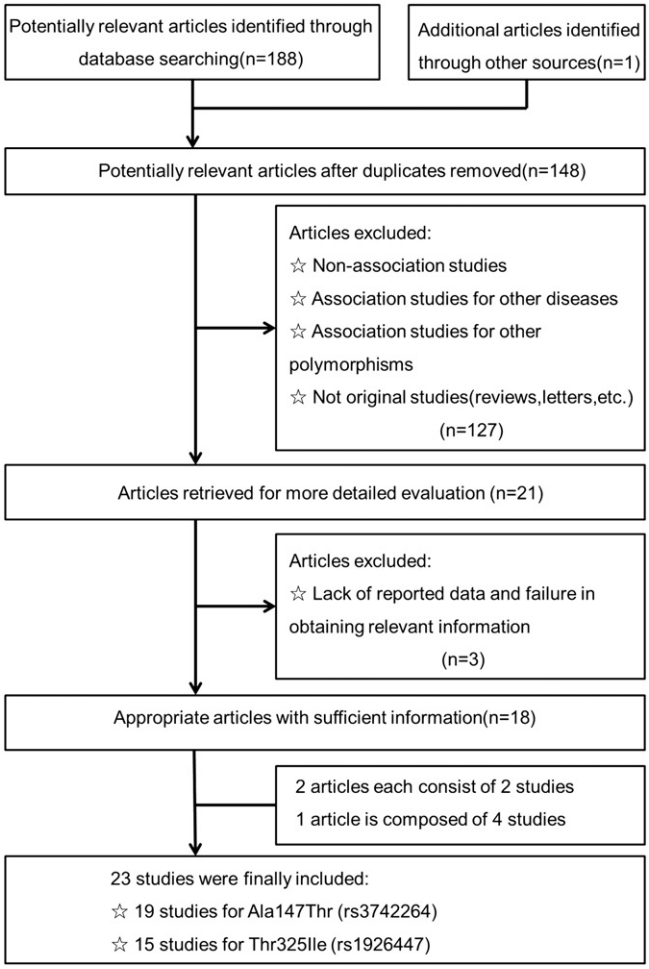

Fig. 1. Flow diagram of the selection of eligible studies.