Original Article
Plasminogen activator inhibitor-1 4G/5G polymorphism is associated with type 2 diabetes risk

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Abstract: A number of studies were performed to assess the association between plasminogen activator inhibitor-1 (PAI-1) 4G/5G polymorphism and susceptibility to type 2 diabetes (T2DM). However, the results were inconsistent and inconclusive. In the present study, the possible association was investigated by a meta-analysis. Eligible articles were identified for the period up to June 2013. Pooled odds ratios (OR) with 95% confidence intervals (CI) were appropriately derived from random-effects models or fixed-effects models. Fourteen case-control studies with a total of 2487 cases and 3538 controls were eligible. In recessive model, PAI-1 4G/5G polymorphism was associated with T2DM risk (OR = 1.23; 95% CI 1.07-1.41; P = 0.004). In the subgroup analysis by ethnicity, a significant association was found among Asians (OR = 1.27; 95% CI 1.08-1.51; P = 0.005). This meta-analysis suggested that PAI-1 4G/5G polymorphism may be associated with T2DM development.

Keywords: Type 2 diabetes, plasminogen activator inhibitor-1, meta-analysis, polymorphism

Introduction

Diabetes is a group of metabolic diseases that are characterized by glucose level chronically elevated above the normal range. More than 20 million Americans and over 170 million individuals worldwide suffer from diabetes mellitus [1]. Two main forms of disease are distinguished: type 1 and type 2. It is type 2 diabetes (T2DM), previously known as non-insulin dependent, much more prevalent form, responsible for 90% of the disease prevalence [2, 3]. T2DM is thought to develop from an interaction between environmental and genetic factors, indicating that there is a strong genetic basis for this disease.

The plasminogen activator inhibitor-1 (PAI-1), a 52 kDa glycoprotein belong to the serine proteinase inhibitor super family, is a multifaceted proteolytic factor. It is the principal inhibitor of tissue and urinary plasminogen activators, and therefore constitutes an important regulatory protein in fibrinolysis [4]. Elevated concentrations of PAI-1 have been observed consistently in blood from patients with diabetes, particularly those with T2DM [5]. In addition, Festa and coworkers found that progression of PAI-1 levels over time, in addition to high baseline PAI-1 levels, was associated with T2DM [6]. Therefore, PAI-1 may play an important role in the development of T2DM.

The PAI-1 gene, located in 7q21.3-22, spans 12.3 kb and contains 9 exons and 8 introns. The polymorphism of the 4G/5G gene is located in the PAI-1 gene promoter region. The most commonly studied functional variant in the PAI-1 gene is the guanine deletion polymorphism at position -675 nucleotides relative to the transcription start site (rs1799889). The PAI-1 -675 4G allele has higher transcriptional activity than the PAI-1 -675 5G allele and homozygous possession of -675 4G is associated with higher plasma PAI-1 levels [7]. A number of papers investigated the association between this polymorphism and T2DM risk. However, the results remained inconclusive [8-21]. Meta-analysis is a useful method for investigating associations between genetic factors and diseases, because a quantitative approach is used to combine the results from different studies on the same topic, thereby providing more reliable conclusions. Thus, we performed a
meta-analysis to clarify the association of PAI-1 4G/5G polymorphism with T2DM. To our knowledge, this is the first meta-analysis of the association between PAI-1 4G/5G polymorphism and the risk of T2DM.

Materials and methods

Search for publications

In our meta-analysis, we searched the articles using the search terms “plasminogen activator inhibitor-1”, “PAI-1”, “type 2 diabetes” and “polymorphism” in the PubMed, Embase and CNKI databases, and the last search updated on June 2013. Additional studies were identified by a hand search of references of original studies or review articles on the association between PAI-1 4G/5G polymorphism and T2DM. No publication date or language restriction were imposed.

Inclusion and exclusion criteria

The following inclusion criteria were used: (1) the study should have evaluated the association between the PAI-1 4G/5G polymorphism and T2DM risk; (2) the study should have had a case-control design; (3) sufficient data should have been provided in order to calculate odds ratios (OR) and 95% confidence intervals (CI). Studies were excluded if any of the following conditions applied: (1) irrelevant to T2DM, PAI-1, or PAI-1 4G/5G polymorphism and T2DM risk; (2) abstract or review; (3) genotype frequencies were not reported; (4) non-clinical study; (5) studies were repeated or publications overlapped.

Data extraction

Two investigators independently extracted data and reached consensus on the following characteristics of the selected studies: the first author’s name, year of publication, ethnicity of the study population, genotyping method, numbers of cases and controls with genotype numbers.

Statistical analysis

OR and 95% CI were employed to evaluate the strength of the association between 4G/5G polymorphism and the risk of T2DM. ORs were calculated for the genotypes: 4G/4G vs. 5G/5G (OR1), 4G/5G vs. 5G/5G (OR2), and 4G/4G vs.
Table 1. Characteristics of the case-control studies included in meta-analysis

<table>
<thead>
<tr>
<th>First author</th>
<th>Year</th>
<th>Ethnicity</th>
<th>Age group</th>
<th>Case number (n)</th>
<th>Control number (n)</th>
<th>Genotyping method</th>
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<td>Asian</td>
<td>Adult</td>
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<td>131</td>
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</table>

PCR, polymerase chain reaction.

Table 2. Distribution of PAI-1 4G/5G polymorphism among patients and controls

<table>
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<tr>
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<th>5G/5G</th>
<th>4G/4G</th>
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<td>4</td>
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<td>6</td>
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<tr>
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4G/5G (OR3) for the 4G/5G polymorphism. These pairwise differences were used to indicate the most appropriate genetic model as follows: if OR1 = OR3 ≠ 1 and OR2 = 1, then a recessive model was suggested; if OR1 = OR2 ≠ 1 and OR3 = 1, then a dominant model was suggested; if OR2 = 1/ OR3 ≠ 1 and OR1 = 1, then a complete overdominant model was suggested; if OR1 > OR2 > 1 and OR1 > OR3 > 1 (or OR1 < OR2 < 1 and OR1 < OR3 < 1), then a codominant model was suggested [22-24]. Once the best genetic model was identified, this model was used to collapse the three genotypes into two groups (except in the case of a codominant model) and to pool the results again.

Departure from Hardy-Weinberg equilibrium (HWE) in controls was tested by the chi-square test. The Q statistic and the I² statistic were used to assess the degree of heterogeneity among the studies included in the meta-analysis. If heterogeneity was observed among the studies, the random-effects model was used to estimate the pooled OR (the DerSimonian and Laird method). Otherwise, the fixed-effects model was adopted (the Mantel-Haenszel method). Subgroup analyses were carried out by ethnicity. Sensitivity analysis was performed.
through sequentially excluded individual studies to assess the stability of the results. The potential publication bias was examined visually in a funnel plot of log (OR) against its standard error (SE), and the degree of asymmetry was tested using Egger’s test [25].

All statistical tests were performed using Revman 5.1 software (Nordic Cochrane Center, Copenhagen, Denmark) and STATA 11.0 software (Stata Corporation, College Station, TX, USA). A P value < 0.05 was considered statistically significant, except for tests of heterogeneity where a level of 0.10 was used.

**Results**

**Characteristics of studies**

A total of 14 case-control studies (Figure 1) with 2487 cases and 3538 controls on the association between 4G/5G polymorphism and T2DM risk were included for this meta-analysis [8-21]. There were 2 studies of Caucasian pop-
PAI-1 polymorphism and T2DM risk

Figure 3. Cumulative meta-analysis of association between PAI-1 4G/5G and T2DM risk.

Figure 4. Sensitivity analysis of association between PAI-1 4G/5G and T2DM risk.
PAI-1 polymorphism and T2DM risk

Population and 12 studies of Asians. All studies suggested that the distribution of genotypes in the controls was consistent with HWE. The characteristics of each case-control study and the genotype in each study are presented in Tables 1 and 2.

Results of meta-analyses

Fourteen studies determined the association between 4G/5G polymorphism and T2DM risk [8-21]. The estimated OR1, OR2 and OR3 were 1.32 (P = 0.002), 1.10 (P = 0.25), and 1.19 (P = 0.02), respectively (Table 3). These estimates suggested a recessive genetic model, and therefore 4G/4G was compared with 4G/5G and 5G/5G. The pooled OR in this analysis was 1.23 (95% CI 1.07-1.41; P = 0.004) (Figure 2). This result suggested that the 4G/4G genotype was significantly associated with T2DM risk. In the subgroup analysis by ethnicity, a significant association was found among Asians (OR = 1.27; 95% CI 1.08-1.51; P = 0.005). No significant association was found between Caucasians and T2DM (OR = 1.13; 95% CI 0.88-1.44; P = 0.34).

With regard to the cumulative meta-analysis, the evidence was observed to support a significant association of the PAI-1 4G/5G polymorphism with the susceptibility to T2DM (Figure 3). As shown in Figure 4, sensitivity analysis did not influence the result excessively by omitting any single study.

Funnel plot and Egger’s test were both performed to access the publication bias of this meta-analysis. The shape of the funnel plot seemed asymmetrical (Figure 5). Egger’s test showed evidence of publication bias (P = 0.044).

Discussion

This present meta-analysis investigated the relationship between PAI-1 4G/5G polymorphism and risk of T2DM. Fourteen case-control studies with a total of 6025 subjects were eligible. At the overall analysis, the PAI-1 4G/5G polymorphism was significantly associated with T2DM risk. In the subgroup analysis by ethnicity, we noted that Asians carrying the 4G/4G genotype had an increased T2DM risk. Moreover, to investigate the stability of the result, we performed sensitivity analyses. Removal of each study did not alter the result, suggesting the reliability of our result. The cumulative meta-analysis showed a trend of significant association between this polymor-
PAI-1 polymorphism and T2DM risk

Obesity is an independent risk factor of T2DM [26]. Circulating PAI-1 level predicts development of T2DM, suggesting that it may be causally related to development of obesity. Morange et al. [27] found that the increase in plasma PAI-1 levels associated with visceral obesity. Additionally, studies conducted in mice also support the relationship of PAI-1 with development of obesity. Three groups found that fat accumulation was prevented in mice lacking PAI-1 in both a nutritionally induced and a genetic murine model of obesity [28-30]. Furthermore, Crandall et al. [31] indicated that pharmacological inhibition of PAI-1 can prevent development of diet-induced obesity. In a model of diet-induced obesity in mice, Lijnen and colleagues suggested that administration of the PAI-1 inhibitor tiplaxtinin resulted in impaired development of adipose tissue [32]. Therefore, in-vitro and in-vivo studies have indicated that PAI-1 might be involved in the development of obesity and T2DM. PAI-1 4G/5G polymorphism is one of the DNA sequence variations that plays a key role in regulating PAI-1 gene expression. Studies have shown that the PAI-1 activity of the 4G allele promoter is higher than that of 5G in a cytokine-stimulated state. PAI-1 4G/5G polymorphism also influences PAI-1 gene transcription similarly in non-stimulated cells [33]. Unlike the 5G allele that binds a transcription repressor protein, resulting in low PAI-1 expression, the 4G allele does not bind a transcription repressor, thus conferring a high PAI-1 expressor nature to the allele [7].

Some possible limitations in this meta-analysis should be acknowledged. First, only published studies that were included in the selected electronic databases were identified; it is possible that some relevant published or unpublished studies may have been missed. Second, the effect of gene-gene and gene-environment interactions was not addressed in this meta-analysis, because of limited available data. Third, our meta-analysis was based on unadjusted OR estimates because not all published studies presented adjusted ORs.

Conclusion

This meta-analysis suggests that PAI-1 4G/5G polymorphism may be associated with T2DM development. Further studies can assess the possible gene-environmental and gene-gene interactions in the association between this polymorphism and T2DM risk.

Disclosure of conflict of interest

None.

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References


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