Genetic Variation in Coagulation and Fibrinolytic Proteins and Their Relation With Acute Myocardial Infarction

A Systematic Review

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Background—It is pathophysiologically conceivable that genetic variations in coagulation and fibrinolytic proteins are associated with the risk of myocardial infarction.

Methods and Results—We performed a literature search to identify published case-control studies correlating the factor V Leiden or prothrombin G20210A mutations or fibrinogen G−455A or plasminogen activator inhibitor-1 (PAI-1) 4G/5G polymorphisms with the risk of myocardial infarction. Studies were included only if they used solid diagnostic criteria and complied with published methodological criteria. A common OR with corresponding 95% CI was calculated for the risk of myocardial infarction in a fixed-effect model according to Mantel-Haenszel. The factor V Leiden and prothrombin G20210A mutations did not significantly correlate with myocardial infarction (OR 1.26, 95% CI 0.94 to 1.67, \( P=0.12 \) and OR 0.89, 95% CI 0.59 to 1.35, \( P=0.6 \), respectively). Inclusion of the studies that investigated young patients (<55 years) made the association significant for factor V Leiden (OR 1.29, 95% CI 1.03 to 1.61, \( P=0.02 \)). Homozygosity for the fibrinogen −455A allele was significantly associated with a decreased risk of myocardial infarction (OR 0.66, 95% CI 0.44 to 0.99, \( P=0.04 \)), whereas the PAI-1 4G4G genotype was significantly associated with increased risk (OR 1.20, 95% CI 1.04 to 1.39, \( P=0.04 \)).

Conclusions—Associations between these genetic variations and myocardial infarction were weak or absent. In the absence of clinical implications, our results indicate that screening of patients with myocardial infarction for these genetic variations is not warranted. (Circulation. 2001;104:3063-3068.)

Key Words: myocardial infarction ■ genetics ■ coagulation

Methods

Literature Search

We identified all case-control studies correlating the factor V Leiden mutation, the prothrombin G20210A mutation, the fibrinogen β-chain G−455A polymorphism, or the PAI-1 4G/5G polymorphism with myocardial infarction. The literature was scanned by a formal search of MEDLINE and EMBASE electronic databases between 1990 and January 2001. Terms that were used for the search were both MeSH terms and (part of) the text words “acute coronary syndromes” or “myocardial infarction” in combination with “factor V,” “prothrombin,” “fibrinogen,” or “plasminogen activator inhibitor,” in combination with “polymorphism,” “mutation,” or “genetics.” The search results were limited to “human” and “English language.” Reference lists of identified articles were scanned for additional potentially relevant publications. In addition, for each identified publication, an electronic “cited reference search” was performed (Web of Science version 4.1.1, Institute for Scientific Information 2000), which identified all articles that cited the index publication.

Selection Criteria

Studies were included only if they were published as full-length articles in peer-reviewed journals and correlated the presence of a

Thrombosis, triggered by atherosclerotic plaque rupture, is generally accepted as the most common pathogenetic pathway of acute myocardial infarction. In recent years, several genetic variations in coagulation and fibrinolytic proteins have been described, and numerous case-control studies have sought to correlate these genetic variations with the risk of myocardial infarction. However, clear relationships have not been established, possibly owing to lack of statistical power of the individual studies or their heterogeneity in terms of methodological design, outcome definition, or selection of cases and controls. We hypothesized that a meta-analysis could provide stronger evidence in favor of the hypothesis that genetic variations in coagulation or fibrinolytic proteins are associated with the risk of myocardial infarction. We limited our analysis to 4 genetic variations that are common and on which sufficient published data were available, ie, the factor V Leiden and prothrombin G20210A mutations and the fibrinogen β-chain G−455A and plasminogen activator inhibitor-1 (PAI-1) 4G/5G polymorphisms.
genetic variation with the risk of myocardial infarction in a group of unrelated cases and an appropriate group of controls who were representative of the population from which the cases were recruited. We evaluated all studies for compliance with recently published criteria for methodological quality.2 Because none of the studies strictly fulfilled the criteria on objectivity and reproducibility, these were not used as a reason for exclusion. Studies were excluded if they did not comply with one or more of the criteria on delineation or spectrum of cases or controls. In addition, studies were excluded if they did not use at least 2 of the following 3 criteria for the diagnosis of myocardial infarction: chest pain, diagnostic ECG, and elevated cardiac enzymes. We also accepted studies that used angiographic or postmortem confirmation. All identified publications were independently evaluated by 2 investigators for compliance with these criteria. The results were compared and disagreements resolved by consensus. Studies investigating patients with a myocardial infarction before the age of 55 years were excluded from the main analysis because of failure to include an adequate spectrum of cases.2 Provided that they met all other inclusion criteria, these studies were included in a secondary analysis.

Data Extraction
Data were independently extracted and entered into separate databases by 2 investigators. The results were compared and disagreements resolved by consensus. One publication did not provide a quantitative summary of results,3 but complete data were subsequently obtained from the principal investigator. Authors were also contacted in case of a potential overlap between publications.

Data Analysis
Data were analyzed with Review Manager version 4.1 (The Cochrane Collaboration 2000). The raw data from each population were entered as a separate stratum. ORs with 95% CI for dichotomous data were calculated by the fixed-effects model according to Peto and Mantel-Haenszel. Tests for heterogeneity were performed with each meta-analysis.4 For the fibrinogen and PAI-1 polymorphisms, analyses were performed according to both a recessive model in which homozygotes for the rare allele were compared against homozygotes for the other allele, and a dominant model in which carriers of at least 1 rare allele were compared against homozygotes of the other allele.

Results

Factor V Leiden Mutation
A total of 18 studies were initially identified.5–22 From those, 12 studies were excluded because no solid diagnostic criteria for myocardial infarction were used,17–20 there was inadequate delineation of cases,21,22 or there was an inadequate spectrum of cases,11–16 leaving a total of 6 studies in the analysis.

The pooled analysis of the 6 qualifying studies included a total of 1302 patients and 2093 controls and indicated a nonsignificant association with myocardial infarction (OR 1.26, 95% CI 0.94 to 1.67, P = 0.12; Figure 1).5–10 Eight studies that investigated patients with myocardial infarction before the age of 55 years were initially identified.11–16 From those, 2 were excluded because of an inadequate spectrum of cases.21,22 Addition of the remaining 6 studies made the

Figure 1. Prevalence of factor V Leiden mutation in patients with myocardial infarction and controls. ORs for outcome of myocardial infarction in factor V Leiden carriers compared with noncarriers as reference group. Point estimates and corresponding 95% CIs are presented for individual studies and for pooled analyses. Square size is proportional to number of observations. Weight represents statistical weight of individual study in pooled analysis.

Figure 2. Prevalence of prothrombin G20210A mutation in patients with myocardial infarction and controls. ORs for outcome of myocardial infarction in prothrombin G20210A carriers compared with noncarriers as reference group. Point estimates and corresponding 95% CIs are presented for individual studies and for pooled analyses. Square size is proportional to number of observations. Weight represents statistical weight of individual study in pooled analysis.
association stronger and significant (OR 1.29, 95% CI 1.03 to 1.61, \(P = 0.02\)).\textsuperscript{11–16} All tests for heterogeneity were nonsignificant.

**Prothrombin G20210A Mutation**
A total of 13 studies were initially identified.\textsuperscript{5,10,13,14,19,23–30} From those, 9 studies were excluded because they did not use solid diagnostic criteria for myocardial infarction\textsuperscript{19,26} or because of inadequate delineation of cases\textsuperscript{27} or an inadequate spectrum of cases,\textsuperscript{13,14,25,28,29–30} leaving a total of 4 studies in the analysis.

A pooled analysis of the remaining 4 studies included a total of 1535 patients and 2943 controls and indicated no association with myocardial infarction (OR 0.89, 95% CI 0.59 to 1.35, \(P = 0.6\); Figure 2).\textsuperscript{5,10,23,24} Five studies that investigated patients with myocardial infarction before the age of 55 years were identified.\textsuperscript{13,14,25,27,30} From those, 2 were excluded because of inadequate delineation of cases\textsuperscript{27} or an inadequate spectrum of cases.\textsuperscript{30} Addition of the remaining 3 studies yielded an OR of 1.11 (95% CI 0.79 to 1.56, \(P = 0.6\)).\textsuperscript{13,14,25} All tests for heterogeneity were nonsignificant.

**Fibrinogen \(\beta\)-Chain G\textsuperscript{455}A Polymorphism**
Five studies were initially identified.\textsuperscript{3,31–34} From those, 3 studies were excluded because no solid diagnostic criteria for myocardial infarction were used\textsuperscript{3,31} or because of an inadequate spectrum of cases,\textsuperscript{34} leaving 2 studies in the analysis.

A total of 983 patients and 1121 controls from 3 distinct populations in 2 studies were included in the pooled analysis.\textsuperscript{32,33} The recessive model indicated a significant association between AA genotype and a lower risk of myocardial infarction (OR 0.67, 95% CI 0.45 to 0.98, \(P = 0.04\); Figure 3). The dominant model indicated a nonsignificant association between carriership of at least 1 A allele and the risk of myocardial infarction (OR 0.91, 95% CI 0.76 to 1.09, \(P = 0.3\)). In a secondary analysis, addition of the only study that investigated patients with myocardial infarction before the age of 55 years\textsuperscript{34} did not substantially change the results (recessive model: OR 0.68, 95% CI 0.46 to 0.99, \(P = 0.04\); dominant model: OR 0.92, 0.78 to 1.09, \(P = 0.3\)).\textsuperscript{34} All tests for heterogeneity were nonsignificant.

**PAI-1 4G/5G Polymorphism**
A total of 18 articles were initially identified.\textsuperscript{13,15,35–50} From those, 11 studies were excluded because they did not use solid diagnostic criteria for myocardial infarction\textsuperscript{43–49} or because of inadequate delineation of cases\textsuperscript{15,50} or an inadequate spectrum of cases,\textsuperscript{13,42} leaving 7 studies in the analysis.

The qualifying 7 studies described a total of 2813 patients and 3358 controls from 8 distinct populations.\textsuperscript{35–41} The pooled analysis indicated a significant association between the 4G allele and increased risk of myocardial infarction (recessive model: OR 1.20, 95% CI 1.04 to 1.39, \(P = 0.04\), Figure 4; dominant model: OR 1.18, 95% CI 1.04 to 1.37, \(P = 0.01\)). The test for heterogeneity was significant (\(P = 0.04\)). Exclusion of the only postmortem study\textsuperscript{35} resulted in nonsignificant heterogeneity without substantially chang-
ing the results. Three studies investigating patients with myocardial infarction occurring before the age of 55 years were identified.32,33,50 One study was excluded because of inadequate delineation of cases.50 Addition of the remaining 2 studies33,42 did not substantially change the results (recessive model: OR 1.20, 95% CI 1.04 to 1.37, \( P = 0.01 \); dominant model: OR 1.17, 95% CI 1.04 to 1.32, \( P = 0.009 \)).

**Discussion**

In our pooled analyses, the factor V Leiden and prothrombin G20210A mutations did not significantly correlate with the risk of myocardial infarction. Homozygosity for the fibrinogen \( \text{G} - 455 \text{A} \) allele and PAI-1 \( 4 \text{G} \) allele were significantly associated with decreased and increased risk of myocardial infarction, respectively.

The factor V Leiden mutation renders factor V relatively insensitive to proteolytic degradation by activated protein C, thus creating a procoagulant state, which increases the risk of venous thrombosis approximately 2- to 4-fold compared with noncarriers. Although pathophysiologically also conceivable in arterial atherothrombosis, we identified no significant association with myocardial infarction in our primary analysis. The addition of studies that investigated young patients (<55 years) resulted in a significant association. Several authors have reported that the observed association may be affected by interaction with other risk factors. For instance, Rosendaal et al12 observed that the risk of myocardial infarction was not elevated in nonsmoking factor V Leiden carriers, whereas factor V Leiden carriers who smoked had a 32-fold risk increase (95% CI 7.7 to 133) compared with a 9-fold increased risk in smokers without a factor V Leiden mutation. Thus, additional risk factors may amplify the risk associated with this prothrombotic genetic variation.

The prothrombin G20210A mutation has been associated with increased levels of prothrombin and is clearly associated with an increased risk of venous thrombosis.51 However, neither the individual studies or our pooled analysis showed a significant association with the risk of myocardial infarction.

Owing to the clear association between the fibrinogen \( \text{G} - 455 \text{A} \) polymorphism and fibrinogen plasma levels,3,52 many studies have focused on its association with myocardial infarction. The individual case-control studies show very consistently (although not significantly) that AA homozygosity, compared with GG homozygosity, is associated with decreased risk of myocardial infarction, and the pooled analysis confirms this finding. An association does not exist between carriership of at least 1 \( 4 \text{G} \) allele and the risk of myocardial infarction. If a cause-effect relation exists between the \( 4 \text{G} \) allele and risk of myocardial infarction, the effect may be present only in homozygotes.

The PAI-1 \( 4 \text{G}/5 \text{G} \) polymorphism has been associated with increased PAI-1 levels.44 Both alleles bind to a transcriptional activator, whereas the \( 5 \text{G} \) allele also binds a repressor protein to an overlapping binding site. In the absence of bound repressor, the basal level of PAI-1 transcription is increased. Compared with \( 5 \text{G} \) homozygosity, both \( 4 \text{G} \) homozygosity and \( 4 \text{G} \) carriership (\( 4 \text{G}4 \text{G} \) and \( 4 \text{G}5 \text{G} \) genotypes combined) were marginally significantly associated with increased risk of myocardial infarction. However, there is convergence to unity proportional to study size (Figure 4), which may indicate publication bias in favor of small studies with positive results. Therefore, the weak association must be interpreted with caution.

The results of studies correlating genetic variations with the risk of a disease are often too inconsistent to draw conclusions. This can be attributed to heterogeneity of the individual studies in terms of outcome definition, design, selection of cases and controls, study size, genetic makeup of the populations studied, and the interaction with acquired or environmental risk factors. In this review, we evaluated all identified studies for these confounders. Because none of the identified studies met the criteria for reproducibility and objectivity,2 these criteria were not applied. However, it is unlikely that nonconformity with these criteria would invalidate our findings. The included studies did fulfill the criteria for outcome definition and selection of cases and controls. However, several limitations remain. First, interaction between genetic variations and acquired or environmental risk factors could not be evaluated because data on these risk factors are not uniformly available. Second, the included studies differed substantially with regard to both the degree of matching between cases and controls and their racial background. Also, because of the retrospective design of most studies, people who died as a consequence of myocardial infarction were not included. We did, however, include studies investigating fatal myocardial infarction, because these belong to the full spectrum of disease, and exclusion would create a selection of less severe cases. Lastly, publication bias cannot be ruled out and is suggested in some of the analyses (eg, Figure 4). Importantly, the analyses represent associations between a genetic variation and the risk of acute myocardial infarction. Although tempting, conclusions on causality cannot be drawn.

The associations between the discussed genetic variations and myocardial infarction were, if significant at all, rather weak. The presence of additional risk factors may amplify these associations, but this does not have any clinical implications. Thus, in the absence of therapeutic consequences, our results suggest that screening of patients with myocardial infarction for the discussed genetic variations is not warranted.

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**References**

Boekholt et al  Genetic Variation in Hemostatic Proteins and MI 3067


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