Genetic Variation at the $\beta$-Fibrinogen Locus in Relation to Plasma Fibrinogen Concentrations and Risk of Myocardial Infarction

The ECTIM Study

Pierre-Yves Scarabin, Lucienne Bara, Sylvain Ricard, Odette Poirier, Jean Pierre Cambou, Dominique Arveiler, Gerald Luc, Alun E. Evans, Michel M. Samama, and François Cambien

Increased plasma fibrinogen concentration is a major cardiovascular risk factor. Conflicting results on genetic variations in plasma fibrinogen levels have been reported. Furthermore, whether fibrinogen genotype is associated with the risk of ischemic heart disease has not been studied so far. An $Hae$III restriction fragment length polymorphism of the $\beta$-fibrinogen gene was used in a case–control study to investigate the genetic variation at this locus in relation to plasma fibrinogen concentrations and the risk of myocardial infarction (MI). Five hundred thirty-three male patients aged 27–66 years and 648 control subjects were recruited from four World Health Organization MONICA centers in Northern Ireland and in France. The absence of the $Hae$III cutting site (H2 allele) was associated with a significant rise in fibrinogen concentrations in both patients and control subjects. The effect of the $Hae$III polymorphism on plasma fibrinogen levels did not significantly differ between centers. Fibrinogen levels were higher in smokers than in nonsmokers. The difference between the two groups was larger in subjects with the genotype H1H2 than in those with either genotype H1H1 or H1H2, regardless of the case–control status. However, there was no significant interaction between smoking status and genotype in their effects on fibrinogen levels. $Hae$III genotype accounted for $\sim$1% of the total variance in fibrinogen levels, whereas smoking and age together explained 7% and 5% in control subjects and patients, respectively. The frequency of the H2 allele was 0.21 in control subjects and 0.19 in patients. The relative risk estimate of MI associated with the presence of the H2 allele was 0.89 (95% confidence interval, 0.69–1.13). The results were consistent with respect to the centers. Multiple regression analysis showed that smoking and raised plasma fibrinogen made independent contributions to the increase in MI risk. There was no significant interaction between $Hae$III genotype and the effect of smoking on MI risk. These data provide further evidence for the role of the genetic variation at the $\beta$-fibrinogen locus in the determination of plasma fibrinogen concentrations. However, this study failed to detect an association between this genetic variation and MI risk. Further investigations are needed to assess the relative contribution of genetic and environmental determinants of plasma fibrinogen to the prediction of atherothrombotic diseases.

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KEY WORDS • fibrinogen • genetic • myocardial infarction

Several lines of evidence suggest that high levels of plasma fibrinogen may be involved in the pathogenesis of ischemic heart disease (IHD). Prospective studies have consistently shown a strong and positive association between fibrinogen concentration and the risk of IHD and stroke. Fibrinogen is an acute-phase protein that is synthesized in the liver, and its plasma concentration plays an important role in the potential rate of fibrin formation. Plasma fibrinogen is a major determinant of blood viscosity, and high levels within the physiological range may increase platelet aggregability. High concentrations of fibrinogen have been found in developing atherosclerotic lesions. Population-based studies have reported associations between plasma fibrinogen and risk factors for IHD. Plasma fibrinogen concentration is higher in smokers than in nonsmokers, and a substantial part of the relation between smoking and IHD may be mediated through a rise in fibrinogen level. Advancing age, obesity, diabetes mellitus, and oral contraceptive use are related to high fibrinogen levels. However, conventional IHD risk factors account for only a small proportion of the total variance of fibrinogen levels in the general population. The relative contribution of genetic and environmental determinants of plasma fibrinogen has been esti-
mated more recently, but it remains controversial.\textsuperscript{13,14} Several studies that used DNA polymorphisms at the fibrinogen gene locus produced conflicting results.\textsuperscript{14-16} In addition, whether fibrinogen genotype is associated with the IHD risk has not been studied so far. Therefore, we used an HaeIII restriction fragment length polymorphism (RFLP) of the b-fibrinogen gene\textsuperscript{17} to investigate the genetic variation at this locus in relation to plasma fibrinogen concentrations and the risk of myocardial infarction (MI) in a large case-control study (Etude Cas-Témoins sur l’Infarctus du Myocarde [the ECTIM Study]).

Methods

Study Population

Full details of the populations studied have already been given.\textsuperscript{18} Men aged 25–64 years were recruited between 1989 and 1991 from four MONICA registers, one in Northern Ireland (Belfast) and three in France (Toulouse, Lille, and Strasbourg). The subjects had to be residents of the region, and their parents and grandparents had to have been born in Europe (for the French centers) or the historical entity of Ulster (Northern Ireland). Cases were survivors of MI who were recruited into the study between 3 and 9 months after the event. Patients had to satisfy the World Health Organization criteria for definite acute MI (category I). For each patient, three control subjects from the same region were randomly selected from the electoral rolls in France and from the registers of general practitioners in Ireland. Stratification by age and community size was used. When the first control subject declined the investigation, the following one was asked to participate in the study. The subjects had to give informed consent, and they had to be fasting before blood sampling. The overall response rate was \(=50\%\) in control subjects and close to 100\% in patients. In Ireland, the patients and control subjects were invited to attend a clinic, whereas French participants were visited at home for clinical investigations and blood collection. All subjects completed a questionnaire on medical history, drug intake, smoking status, and alcohol consumption. This information was obtained at the time of MI in patients.

Blood Sampling and Fibrinogen Assay

Venous blood (9 volumes) was collected into siliconized Vacutainer tubes containing trisodium citrate (3.2\%, 1 volume). Platelet-poor plasma was obtained by centrifugation at 4,000g at room temperature for 30 minutes. Aliquots of plasma were prepared within 3 hours after venipuncture. Fibrinogen was assayed in batches on snap-frozen plasma samples that had been stored in liquid nitrogen. The thrombin time method described by Claus\textsuperscript{19} was used. Three different standards were used for the assays of fibrinogen, and each of them was tested against the next and expressed in terms of the first. The interassay coefficient of variation was \(=5\%\).

DNA Analysis

Genomic DNA was prepared from white blood cells by phenol extraction. DNA was amplified by the polymerase chain reaction (PCR) technique as previously described.\textsuperscript{17} Amplification products were blotted into nylon filters (Hybond N\textsuperscript{+}, Amersham), prehybridized for 4 hours in 0.9\% NaCl, 0.09 M EDTA, 0.1\% sodium dodecyl sulfate (SDS), and 250 mg/L salmon sperm DNA at 40°C. The sequences of the allele-specific oligonucleotides (ASOs) were as follows: for normal HI, 5' AAAGGGGCCAT-TAAAAT 3', and for mutant H2, 5' ATTTTAAT-AGCCCTTTT 3'. Each ASO was labeled with adenosine 5'-[\(\gamma\text{-}32\text{P}\)]triphosphate (3,000 Ci/mmol, Amersham), and hybridization was carried in the prehybridization solution for 1 hour at 40°C for each ASO. The filters were washed twice with 5\times saline–sodium citrate buffer and 0.1\% SDS at 46°C and autoradiographed by exposure to x-ray film (Hyperfilm, Amersham) for 4 hours at \(-80°C\).

Statistics

Statistical analysis used procedures available in the Statistical Analysis System software (SAS) (SAS Institute, Inc., Cary, N.C.). Because the distribution of fibrinogen was positively skewed, logarithmically transformed values were used. Mean fibrinogen levels are given in arithmetic form. The \(\chi^2\) test was used to compare the observed numbers of each genotype with

\begin{table}
\centering
\begin{tabular}{|c|cc|cc|cc|cc|cc|}
\hline
Parameter & \multicolumn{2}{c|}{Belfast} & \multicolumn{2}{c|}{Lille} & \multicolumn{2}{c|}{Strasbourg} & \multicolumn{2}{c|}{Toulouse} \\
 & Case & Control & Case & Control & Case & Control & Case & Control \\
\hline
Age (years) & 53.9 (8.1) & 54.2 (7.8) & 53.4 (8.9) & 54.2 (7.4) & 53.9 (7.9) & 53.1 (9.1) & 54.4 (8.1) & 51.5 (8.7) \\
BMI (kg/m\textsuperscript{2}) & 26.2 (3.6) & 25.7 (3.6) & 26.8 (4.4) & 25.8 (3.6) & 27.2 (3.6) & 27.3 (3.6) & 26.4 (3.3) & 26.6 (4.1) \\
Cigarettes (No/day) & 16.2 (20.1) & 5.1 (10.5) & 2.4 (5.6) & 7.6 (12.2) & 10.7 (14.6) & 5.6 (10.1) & 9.7 (14.0) & 5.1 (10.6) \\
Alcohol (g/day) & 34.7 (49.3) & 35.4 (48.7) & 44.1 (42.0) & 56.5 (46.1) & 29.0 (27.8) & 35.0 (35.5) & 33.2 (33.6) & 35.9 (33.2) \\
Fibrinogen (mg/dL) & 339 (76) & 312 (67) & 309 (75) & 303 (77) & 359 (111) & 302 (72) & 341 (90) & 264 (77) \\
\hline
\end{tabular}
\caption{General Characteristics and Plasma Fibrinogen by Center and Case–Control Status in the ECTIM Study}
\end{table}

\textit{Tests of effects* (F values and significance)}

\begin{tabular}{|c|c|c|c|}
\hline
Status Center Interaction & Case & Control & Case & Control \\
\hline
NS & NS & NS & NS \\
8§ & NS & NS & NS \\
21§ & 7† & 12§ & NS \\
NS & NS & NS & NS \\
\hline
\end{tabular}

BMI, body mass index. Values are mean and (SD).

*Two-way analysis of variance: NS, not significant; \(t p<0.05\); \(t p<0.01\); \(b p<0.001\).
those expected under Hardy-Weinberg equilibrium. Analysis of variance with grouping factors was used to compare the means of various parameters. Status (case or control), center (Belfast, Lille, Strasbourg, or Toulouse), and HaeIII genotype (H1H1, H1H2, or H2H2) were included in a model with fibrinogen as a dependent variable. All interactions between the effect of these factors on fibrinogen were tested to assess the homogeneity of associations. An additional analysis was performed to study differential effects of smoking on fibrinogen according to genotype. To estimate the relative contribution of HaeIII genotype, smoking, and other variables relevant to the prediction of fibrinogen, multiple regression analysis was used in both patients and control subjects. The χ² test was used to compare the distributions of genotypes between the various groups. Odds ratios for MI were computed according to smoking status and centers. The common relative risk was estimated by the method of Mantel-Haenszel, and the 95% confidence interval of the estimate was tested-based. The Breslow-Day test for homogeneity of the odds ratios was used. Finally, multivariate comparison of patients and control subjects was carried out by logistic regression analysis.

Results

The prevalence of IHD was about 6% in the control subjects, and therefore, these subjects were excluded. The results of this report are based on 533 patients and 648 control subjects.

General Characteristics and Plasma Fibrinogen by Case-Control Status and Center

The general characteristics and the mean fibrinogen values of the subjects by case-control status and center are shown in Table 1. As expected, the mean values of age were similar in the patients and control subjects, and they did not differ between centers. There were no significant differences between patients and control subjects in alcohol consumption and body mass index. Mean levels of cigarette use were significantly higher in patients than control subjects. The difference between the two groups was significantly larger in Belfast than in any of the French centers. The mean body mass index was greatest in Strasbourg, and alcohol consumption levels were highest in Lille than in the other three centers.

The patients had higher levels of fibrinogen concentration than did the control subjects within each center (Table 1). The unadjusted overall means for patients and control subjects were 344 and 300 mg/dL, respectively (p<0.0001). There was a significant difference between centers in fibrinogen levels. Control subjects in Belfast had the highest mean fibrinogen values, and the lowest mean control value was observed in Toulouse. Control subjects in both Lille and Strasbourg had a mean fibrinogen value intermediate to those of the other two centers. Patients did not significantly differ between centers with respect to fibrinogen levels. Two-way analysis of variance showed that the difference between patients and control subjects was significantly smaller in Belfast than in the other centers.

Allowance for confounding factors made no substantial difference in mean levels of fibrinogen between the different groups (Figure 1). After adjustment for age, body mass index, alcohol consumption, and smoking, the overall means of fibrinogen were 343 and 307 mg/dL in patients and control subjects, respectively (p<0.0001).

![Figure 1](image-url). Mean levels (and SEM) of fibrinogen by case-control status and center after adjustment for age, body mass index, alcohol consumption, and cigarette use (status effect, p<0.0001; center effect, p=0.03; center×status interaction effect, p<0.001).

TABLE 2. Plasma Fibrinogen by HaeIII Genotype, Center, and Case-Control Status in the ECTIM Study

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Case</th>
<th>Control</th>
<th>Case</th>
<th>Control</th>
<th>Case</th>
<th>Control</th>
<th>Case</th>
<th>Control</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Belfast</td>
<td>Lille</td>
<td>Strasbourg</td>
<td>Toulouse</td>
<td>All</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>H1H1</td>
<td>(n=129)</td>
<td>(n=107)</td>
<td>(n=118)</td>
<td>(n=116)</td>
<td>(n=72)</td>
<td>(n=103)</td>
<td>(n=352)</td>
<td>(n=410)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>331 (72)</td>
<td>305 (64)</td>
<td>300 (78)</td>
<td>298 (80)</td>
<td>358 (110)</td>
<td>301 (75)</td>
<td>333 (83)</td>
<td>282 (81)</td>
<td>338 (90)</td>
</tr>
<tr>
<td>H1H2</td>
<td>(n=129)</td>
<td>(n=107)</td>
<td>(n=118)</td>
<td>(n=116)</td>
<td>(n=72)</td>
<td>(n=103)</td>
<td>(n=352)</td>
<td>(n=410)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>344 (76)</td>
<td>315 (64)</td>
<td>335 (62)</td>
<td>317 (72)</td>
<td>358 (115)</td>
<td>306 (68)</td>
<td>355 (105)</td>
<td>284 (70)</td>
<td>351 (97)</td>
</tr>
<tr>
<td>H2H2</td>
<td>(n=54)</td>
<td>(n=10)</td>
<td>(n=55)</td>
<td>(n=54)</td>
<td>(n=40)</td>
<td>(n=51)</td>
<td>(n=159)</td>
<td>(n=203)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>410 (87)</td>
<td>371 (89)</td>
<td>350 (. )</td>
<td>288 (66)</td>
<td>369 (99)</td>
<td>276 (61)</td>
<td>352 (73)</td>
<td>310 (65)</td>
<td>380 (83)</td>
</tr>
</tbody>
</table>

Values are mean and (SD) in milligrams per deciliter. Three-way analysis of variance: genotype effect, p=0.006; center effect, p=0.006; group effect, p<0.0001; center×group interaction effect, p=0.007; status×genotype interaction effect, p=0.62; other interactions were not significant at p=0.05.
Relation of Genotype to Plasma Fibrinogen

Three-way analysis of variance showed no significant interactions between smoking status or center in their effects on fibrinogen levels. There was no significant trend toward higher fibrinogen levels according to Haelll genotype was not significant \( p=0.10 \); there was no evidence for significant interactions between Haelll genotype and either case-control status, and center are given in Table 2. The differential effect of smoking on fibrinogen levels. In a British study of three twins, the intraclass correlation coefficient was only close to 1, except for the nonsmokers in Lille. Summary statistics showed no significant association between Haelll genotype and MI risk. There were no significant differences in relative risks between the groups.

Multiple logistic regression showed that smoking and plasma fibrinogen made independent contributions to the increased risk of MI (Table 6). No other variables were significantly related to MI risk. There was no significant interaction between Haelll genotype and smoking effect on MI risk.

Discussion

The relative contribution of genetic and environmental factors in the determination of plasma fibrinogen concentrations is not well documented. Most of the studies were performed in small population samples, and confidence intervals of estimates were large. Heritability has been shown to account for \( \approx 50\% \) of the total phenotypic variance of plasma fibrinogen levels in Swedish nuclear families.13 In Norwegian monogygotic twins, the intraclass correlation coefficient was only 0.27.14 Several RFLPs at the \( \alpha \)- and \( \beta \)-fibrinogen loci have been used to investigate the genetic variations in plasma fibrinogen levels. In a British study of three RFLPs, the strongest association was found with the BeII polymorphism at the \( \beta \)-fibrinogen locus. Genetic variation at this locus accounted for 15% of the variance in fibrinogen values.15 By contrast, a Scottish study and

### Table 3: Plasma Fibrinogen by Haelll Genotype, Smoking Status, and Case-Control Status in the ECTIM Study

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Case Nonsmokers</th>
<th>Case Smokers</th>
<th>Control Nonsmokers</th>
<th>Control Smokers</th>
</tr>
</thead>
<tbody>
<tr>
<td>H1H1</td>
<td>337 (100)</td>
<td>339 (77)</td>
<td>288 (72)</td>
<td>319 (80)</td>
</tr>
<tr>
<td>(n=187)</td>
<td>(n=165)</td>
<td>(n=191)</td>
<td>(n=187)</td>
<td>(n=191)</td>
</tr>
<tr>
<td>H1H2</td>
<td>339 (99)</td>
<td>366 (93)</td>
<td>297 (62)</td>
<td>324 (80)</td>
</tr>
<tr>
<td>(n=87)</td>
<td>(n=76)</td>
<td>(n=61)</td>
<td>(n=87)</td>
<td>(n=76)</td>
</tr>
<tr>
<td>H2H2</td>
<td>338 (75)</td>
<td>399 (83)</td>
<td>292 (59)</td>
<td>353 (95)</td>
</tr>
<tr>
<td>(n=7)</td>
<td>(n=15)</td>
<td>(n=6)</td>
<td>(n=7)</td>
<td>(n=15)</td>
</tr>
</tbody>
</table>

Values are mean and (SD) in milligrams per deciliter.

### Table 4: Multiple Regression of Fibrinogen on Haelll Genotype and Smoking Status, Age, Body Mass Index, and Alcohol Consumption

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control Regression coefficients</th>
<th>Control SEM</th>
<th>Control Partial ( R^2 )</th>
<th>Case Regression coefficients</th>
<th>Case SEM</th>
<th>Case Partial ( R^2 )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smoking status</td>
<td>0.132*</td>
<td>0.020</td>
<td>0.04</td>
<td>0.068*</td>
<td>0.022</td>
<td>0.02</td>
</tr>
<tr>
<td>Age</td>
<td>0.005*</td>
<td>0.001</td>
<td>0.03</td>
<td>0.006*</td>
<td>0.001</td>
<td>0.03</td>
</tr>
<tr>
<td>Body mass index</td>
<td>0.004**</td>
<td>0.002</td>
<td>&lt;0.01</td>
<td>0.006**</td>
<td>0.003</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Alcohol consumption</td>
<td>-0.001**</td>
<td>&lt;0.001</td>
<td>0.01</td>
<td>-0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Genotype</td>
<td>0.034**</td>
<td>0.018</td>
<td>0.01</td>
<td>0.047**</td>
<td>0.019</td>
<td>0.01</td>
</tr>
<tr>
<td>( R^2 = 0.10 )</td>
<td></td>
<td></td>
<td></td>
<td>( R^2 = 0.07 )</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Genotypes are coded as follows: H1H1 = 1, H2H1 = 1, and H2H2 = 2.

*\( p<0.001 \), **\( p<0.05 \), *\( p<0.10 \).
a Norwegian study failed to detect any association between Bell polymorphism and plasma fibrinogen concentrations. In a subsequent British study, an HaeIII RFLP located in the promoter region of the β-fibrinogen gene was significantly associated with fibrinogen levels, and this genetic variation explained ~3% of the total phenotypic variance.

The ECTIM Study provides further evidence of a role for genetic variation at the fibrinogen locus in the determination of plasma fibrinogen concentrations. Multivariate analysis has shown that both smoking and HaeIII polymorphism are significantly associated with plasma fibrinogen levels in both control subjects and patients. Despite the substantial increase in fibrinogen concentrations in smokers who possessed two H2 alleles, there was no significant interaction between the effect of these two factors on fibrinogen concentrations. These results are consistent with those previously reported in a British study, although the associations are weaker in the ECTIM Study. The large within-subject variation in fibrinogen levels may result in a substantial underestimation of the size of the genetic contribution. Fibrinogen is an acute-phase protein that increases in a number of clinical situations. No attempt was made to adjust for orosomucoid levels, smoking status, and other proteins that may have been only partially taken into account. It is likely that some patients stopped smoking just after the acute phase of MI. The impact of this effect on fibrinogen levels about 6 months later is difficult to assess. However, prospective data indicate that smoking cessation results in a decrease of ~15 mg/100 mL in plasma fibrinogen after a 6-year follow-up. Accordingly, it can be assumed that the difference in fibrinogen levels between smokers and nonsmokers was reduced slightly. Our data support this hypothesis.

The strength of association between fibrinogen levels and MI in the ECTIM Study was close to those reported in cohort studies. A rise of 1 SD in plasma fibrinogen increased the MI risk by 65% in the ECTIM Study, whereas it increased by 74% the nonfatal IHD risk within 5 years in the Northwick Park Heart Study. Thus, our data suggest that high fibrinogen levels within a 3–9-month period after MI are not a consequence of the clinical event. No other acute-phase reactant proteins were measured in the ECTIM Study, and the possibility of an effect of MI per se on fibrinogen levels cannot be excluded. In a previous case–control study, survivors of MI had a significantly higher mean fibrinogen level than did control subjects, even after adjustment for orosomucoid levels, smoking status, and other relevant variables. The difference was no longer significant when orosomucoid alone was used as a covariate. Therefore, interpretation of high fibrinogen levels in MI remains unclear.

Geographic variation in fibrinogen levels was found in the control groups. In 1984–1986, the standardized mortality rates of coronary heart disease in men aged 25–64 years were 348, 105, 102, and 78 per 100,000 in Belfast, Lille, Strasbourg, and Toulouse, respectively. In 1984–1986, the standardized mortality rates of coronary heart disease in men aged 25–64 years were 348, 105, 102, and 78 per 100,000 in Belfast, Lille, Strasbourg, and Toulouse, respectively.22

Our results suggest that fibrinogen levels might partly explain these differences in the incidence of MI.

The ECTIM Study failed to detect any association between the HaeIII fibrinogen genotype and the risk of MI. Several reasons could explain this negative finding. First, biases in selection of subjects may have occurred, and these have been discussed in detail elsewhere. The case–control approach led us to select survivors of MI. It is quite conceivable that the association between HaeIII genotype and MI risk might differ in patients who experienced a fatal MI. Prospective data are clearly needed to explore this possibility. The overall response rate was relatively low in the control subjects, and the population samples may not be representative of healthy subjects in both France and Northern Ireland. No attempt was made to systematically study the characteristics of nonresponders. However, the frequency of the H2 allele (0.21) was very close to that observed (0.19) in the UK general population. Smoking was strongly related to MI risk, and, together with other information on plasma lipids, it is unlikely that the control subjects were selected on the basis of levels of cardiovascular risk factors. Second, the power of the

### Table 5. Associations Between HaeIII Genotype and Myocardial Infarction by Smoking Status and Center*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds ratio (95% confidence interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Univariate</td>
</tr>
<tr>
<td>HaeIII genotype (presence of H2 allele)</td>
<td>0.89 (0.69–1.13)</td>
</tr>
<tr>
<td>Fibrinogen ±1 SD</td>
<td>1.66 (1.48–1.83)*</td>
</tr>
<tr>
<td>Smoking (current smokers)</td>
<td>2.10 (1.64–2.66)*</td>
</tr>
</tbody>
</table>

SD, standard deviation. *p<0.0001.
study was such that the minimum significantly increased relative risk of MI associated with the presence of the H2 allele that could have been detected with 95% certainty was 1.38. Therefore, the ECTIM Study was adequately designed with respect to statistical power. Third, a weak association was detected between the HaeIII genotype and plasma fibrinogen concentrations. If one assumes a cause–effect relation between fibrinogen and MI, an increase of 10% in MI risk due to the genotype effect would be expected. Finally, the results of the ECTIM Study may merely indicate that fibrinogen is not relevant to the pathogenesis of MI. However, this latter hypothesis is unlikely in the light of current knowledge.

A Scottish case–control study has recently reported an association between genetic variation at the β-fibrinogen locus and an increased risk of peripheral atherosclerosis.23 No significant association was found between the polymorphisms at the α, β, and γ loci and fibrinogen concentrations. Structural changes in variant fibrinogen were suggested. However, the HaeIII genotype was not investigated in this study.

Further data are clearly needed to clarify the extent to which the genetic variations at the fibrinogen gene locus may be related to the risk of arterial disease as well as to changes in the structure and/or concentration of the protein. Prospective studies will be relevant to estimate the relative contribution of genetic and environmental determinants of plasma fibrinogen to the prediction of MI risk.

Acknowledgment

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References

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