Fibrinogen Genes and Myocardial Infarction
A Haplotype Analysis

Werner Koch, Petra Hoppmann, Janita Biele, Jakob C. Mueller, Albert Schömig, Adnan Kastrati

Objective—Fibrinogen has a role in inflammatory processes and participates in atherosclerotic plaque formation. Despite intensive investigation, there is no clear evidence for a role of variations in the genes coding for the fibrinogen-α, fibrinogen-β, and fibrinogen-γ polypeptide chains in myocardial infarction. We examined the association of haplotypes in the 50-kb fibrinogen gene region with myocardial infarction in 2 large case-control samples.

Methods and Results—Study sample 1 consisted of 3657 patients with myocardial infarction and 1211 control individuals and sample 2 comprised 1392 patients and 1392 controls. Haplotypes were inferred from genotype analyses of tagging single nucleotide polymorphisms dispersed among the fibrinogen genes. The frequencies of these haplotypes were not significantly different between the case and control groups in either sample (P=0.07). In addition, haplotypes specific for individual fibrinogen genes were analyzed. No substantial differences in the frequencies of these haplotypes were observed between the groups (P=0.13). Finally, haplotypes composed of SNPs that exhibited relatively low pairwise allelic associations among each other were examined. The proportions of the haplotypes were not significantly different between cases and controls (P=0.12).

Conclusion—A haplotype analysis did not reveal a link between genetic variations in the fibrinogen gene region and myocardial infarction. (Arterioscler Thromb Vase Biol. 2008;28:000-000.)

Key Words: fibrinogen ■ myocardial infarction ■ risk factor ■ genetics ■ haplotype

Fibrinogen participates in atherosclerotic plaque formation by modulation of endothelial function and promotion of smooth muscle cell proliferation and migration. It is an important component of the coagulation cascade and a major determinant of blood viscosity and platelet aggregation. Positive associations between plasma fibrinogen concentrations and the risk of coronary heart disease and myocardial infarction (MI) have been reported from prospective epidemiological studies. However, it is unclear whether the elevations in fibrinogen levels are a causal factor in the development of atherosclerosis or an epiphenomenon of the atherosclerotic process.

High molecular weight (340 kDa) fibrinogen is a glycoprotein containing 2 copies of each of 3 polypeptide chains (Aα, Bβ, and γ) encoded by 3 distinct genes (FGA, FGB, and FGG) that are transcribed separately from each other. The genes are arranged in the order FGG-FGA-FGB within a 50-kb region on the long arm of chromosome 4, with the transcriptional direction of FGG and FGA opposite to that of FGB.

Single nucleotide polymorphisms (SNPs) in the FGG-FGA-FGB region have been examined for associations with coronary artery disease and MI, including rs1800792 (−647A/G) in FGG, rs6050 (Thr312Ala) in FGA, and rs1800790 (−455G/A) in FGB. In some studies, relationships between SNPs and MI were observed, whereas lack of association was reported from other investigations and meta-analyses. Recent evidence indicated that not individual SNPs but rather SNP-related haplotypes in the fibrinogen gene region were connected with the risk of MI.

We addressed the association of SNP-related haplotypes across the FGG-FGA-FGB region with MI in 2 large case-control samples. The SNPs used in this analysis represented the majority of genetic variation within the genes and some of them have been linked with gene expression, protein function, and plasma fibrinogen level.

Methods
Two case-control samples, sample 1 and sample 2, were examined at Deutsches Herzzentrum München or 1. Medizinische Klinik der Isar der Technischen Universität München. Sample 1 consisted of 3657 patients with MI and 1211 control individuals who were recruited from 1993 to 2002. Sample 2 comprised 1392 MI patients and 1392 control persons who were recruited from 2003 to 2006.

Haplotype-tagging SNPs of the fibrinogen genes were inferred from HapMap data: the rs2066864, rs1049636, and rs1800792 SNPs in FGG, the rs6050 and rs 2070011 SNPs in FGA, and the rs1800790 and rs1800788 SNPs in FGB (HapMap data release 21a/phase II Jan07, on National Center for Biotechnology Information B35 assembly, SNP database build 125; http://www.hapmap.org and http://www.ncbi.nlm.nih.gov/projects/SNP). In addition, the rs1800787, rs1800791, and rs4220 SNPs in FGB were included in...
the analysis because allele-associated functional differences of these SNPs have been reported. Figure 1 indicates the positions of the SNPs in the fibrinogen gene region selected for examination in this study. Table 1 provides information about the relative positions of the SNPs, major and minor SNP alleles, and alternative designations of the SNPs used in prior publications. TaqMan allelic discrimination assays were designed and used for SNP genotyping.

The statistical analysis consisted of comparing separately allele and haplotype frequencies between the control group and the MI group in sample 1 and sample 2. Discrete variables were compared with the use of the \( \chi^2 \) test. Hardy-Weinberg equilibrium was assessed with the use of the \( \chi^2 \) test. Pairwise measures of linkage disequilibrium (\( D' \) and \( r^2 \)) between the SNPs were calculated from primary genotype data with the software package Haploview. Haplotypes were reconstructed using the software package PHASE.

For more detailed Methods, please see the supplemental materials (available online at http://atvb.ahajournals.org).

Results

Main baseline characteristics of the control and MI groups in samples 1 and 2 are presented in Table 2. Mean age of the patients was higher than that of the control group, the proportion of women was lower in the patient group than in the control group, and history of arterial hypertension and hypercholesterolemia, present cigarette smoking, and diabetes mellitus were more prevalent in the patient group than in the control group (\( P<0.0001 \) for all comparisons; Table 2). The frequencies of the major alleles of SNPs in the fibrinogen gene region were not significantly different between the control and MI groups in samples 1 and 2 (Table 3). Genotype distributions in the study groups were consistent with those expected for samples in Hardy-Weinberg equilibrium (\( P>0.17 \)).

Associations among the alleles of the SNPs were calculated from genotype data. Pairwise measures of allelic association, expressed as linkage disequilibrium coefficients \( D' \) and \( r^2 \), are shown in Figure 2. Overall high \( D' \) values indicated low historical recombination within the fibrinogen gene region. Thus, haplotype phase estimation appeared to be reliable across the entire region. Relatively low \( r^2 \) values among most of the SNP pairs referred to a disparate evolutionary history of these markers and gave the reasons to perform haplotype analyses. SNP-related haplotypes were established and their frequencies determined in the control and MI groups of samples 1 and 2. Risk estimates showed that the 10-marker haplotypes with frequencies >1% in the groups of each sample (Hap1 to Hap12) were not associated

**Table 1. SNPs in the Genes for Fibrinogen-\( \gamma \) (FGG), Fibrinogen-\( \alpha \) (FGA), and Fibrinogen-\( \beta \) (FGB) Addressed in This Study**

<table>
<thead>
<tr>
<th>Gene</th>
<th>SNP ID</th>
<th>SNP Location</th>
<th>SNP Alleles*</th>
<th>SNP Alias(es) (Reference)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FGG</td>
<td>rs1800792</td>
<td>5’ upstream</td>
<td>A&gt;G–</td>
<td>647A&gt;G (33)</td>
</tr>
<tr>
<td>FGG</td>
<td>rs1049636</td>
<td>intron 9</td>
<td>T&gt;C</td>
<td>7843C→T (47), 7792C/T (48), 1299+79T&gt;C (33), 9340 T/C (52)</td>
</tr>
<tr>
<td>FGG</td>
<td>rs2066864</td>
<td>intron 9</td>
<td>C&gt;T</td>
<td>1300→189C&gt;T (33)</td>
</tr>
<tr>
<td>FGA</td>
<td>rs2070011</td>
<td>exon 1</td>
<td>G&gt;A</td>
<td>−586G/A (48)</td>
</tr>
<tr>
<td>FGA</td>
<td>rs6050</td>
<td>exon 5</td>
<td>A&gt;G</td>
<td>Aα312 (Thr/Ala) (40), Rsfl RFLP (56)</td>
</tr>
<tr>
<td>FGB</td>
<td>rs4220</td>
<td>exon 8</td>
<td>C&gt;T</td>
<td>Arg448Lys (38), Bg448 (Arg/Lys) (40), Mnl1 RFLP (56), G8059A (29)</td>
</tr>
<tr>
<td>FGB</td>
<td>rs1800787</td>
<td>5’ upstream</td>
<td>G&gt;A</td>
<td>HindII RFLP (41), Alu RFLP (56), C/T (42), −156C&gt;T (33)</td>
</tr>
<tr>
<td>FGB</td>
<td>rs1800788</td>
<td>5’ upstream</td>
<td>G&gt;A</td>
<td>β−249 C→T (9), −257C&gt;T (33)</td>
</tr>
<tr>
<td>FG</td>
<td>Brs1800790</td>
<td>5’ upstream</td>
<td>C&gt;T</td>
<td>−453 HaeIII RFLP (39), G/A (49) (16), −463G&gt;A (33)</td>
</tr>
<tr>
<td>FGB</td>
<td>rs1800791</td>
<td>5’ upstream</td>
<td>C&gt;T</td>
<td>β−854G→A (9), −862G&gt;A (33)</td>
</tr>
</tbody>
</table>

RFLP indicates restriction fragment length polymorphism.

*Alleles are depicted from the same DNA strand, the coding strand of FGG and FGA, and the noncoding strand of FGB.

**Figure 1. Positions of SNPs in the fibrinogen gene region genotyped in the study samples.** See Table 1 for alternative SNP designations. FGG indicates fibrinogen \( \gamma \) gene; FGA, fibrinogen \( \alpha \) gene; FGB, fibrinogen \( \beta \) gene.
with MI (Table 4). Together, these 12 10-marker haplotypes represented the fibrinogen gene region of approximately 95% of the haploid genomes in the study population.

Gene-specific haplotypes were established on the basis of the 12 most frequent 10-marker haplotypes. The proportions of haplotypes related to $FGG$ (rs1800792-rs1049636-rs2066864), $FGA$ (rs2070011-rs6050), and $FGB$ (rs4220-rs1800787-rs1800788-rs1800789-rs1800791) were not significantly different between the control and MI groups in both study samples (supplemental Table I, available online at http://atvb.ahajournals.org).

Finally, intergenic 2- and 3-marker haplotypes of SNPs exhibiting relatively low allelic associations among each other (Figure 2) were inferred from the 12 most frequent 10-marker haplotypes. Proportions of such haplotypes were not significantly different between the control and MI groups in both study samples (supplemental Table I, available online at http://atvb.ahajournals.org).

Table 3. Major Allele Frequencies of the $FGG$, $FGA$, and $FGB$ SNPs in the Control and MI Groups of Sample 1 and Sample 2

<table>
<thead>
<tr>
<th>Gene*</th>
<th>SNP</th>
<th>Major Allele†</th>
<th>Control Group (2422 Alleles)</th>
<th>MI Group (7314 Alleles)</th>
<th>Sample 1</th>
<th>Sample 2</th>
<th>Control Group (2784 Alleles)</th>
<th>MI Group (2784 Alleles)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>$FGG$</td>
<td>rs1800792</td>
<td>A</td>
<td>1357 (56.0)</td>
<td>3980 (54.4)</td>
<td>0.17</td>
<td>1538 (55.2)</td>
<td>1536 (55.2)</td>
<td>0.96</td>
<td></td>
</tr>
<tr>
<td>$FGG$</td>
<td>rs1049636</td>
<td>T</td>
<td>1692 (69.9)</td>
<td>5170 (70.7)</td>
<td>0.44</td>
<td>1987 (71.4)</td>
<td>1938 (69.6)</td>
<td>0.15</td>
<td></td>
</tr>
<tr>
<td>$FGG$</td>
<td>rs2066864</td>
<td>C</td>
<td>1811 (74.8)</td>
<td>5538 (75.7)</td>
<td>0.35</td>
<td>2058 (73.9)</td>
<td>2106 (75.6)</td>
<td>0.14</td>
<td></td>
</tr>
<tr>
<td>$FGA$</td>
<td>rs2070011</td>
<td>G</td>
<td>1517 (62.6)</td>
<td>4630 (63.3)</td>
<td>0.55</td>
<td>1696 (60.9)</td>
<td>1723 (61.9)</td>
<td>0.46</td>
<td></td>
</tr>
<tr>
<td>$FGA$</td>
<td>rs6050</td>
<td>A</td>
<td>1790 (73.9)</td>
<td>5451 (74.5)</td>
<td>0.54</td>
<td>2028 (72.8)</td>
<td>2075 (74.5)</td>
<td>0.15</td>
<td></td>
</tr>
<tr>
<td>$FGB$</td>
<td>rs4220</td>
<td>C</td>
<td>1904 (78.6)</td>
<td>5788 (79.1)</td>
<td>0.58</td>
<td>2192 (78.7)</td>
<td>2145 (77.0)</td>
<td>0.13</td>
<td></td>
</tr>
<tr>
<td>$FGB$</td>
<td>rs1800787</td>
<td>G</td>
<td>1863 (76.9)</td>
<td>5648 (77.2)</td>
<td>0.76</td>
<td>2150 (77.0)</td>
<td>2086 (74.9)</td>
<td>0.06</td>
<td></td>
</tr>
<tr>
<td>$FGB$</td>
<td>rs1800788</td>
<td>G</td>
<td>1938 (80.0)</td>
<td>5871 (80.3)</td>
<td>0.79</td>
<td>2188 (78.6)</td>
<td>2243 (80.6)</td>
<td>0.07</td>
<td></td>
</tr>
<tr>
<td>$FGB$</td>
<td>rs1800790</td>
<td>C</td>
<td>1863 (76.9)</td>
<td>5651 (77.3)</td>
<td>0.72</td>
<td>2152 (77.3)</td>
<td>2090 (75.1)</td>
<td>0.05</td>
<td></td>
</tr>
<tr>
<td>$FGB$</td>
<td>rs1800791</td>
<td>C</td>
<td>2034 (84.0)</td>
<td>6253 (85.5)</td>
<td>0.07</td>
<td>2431 (87.3)</td>
<td>2402 (86.3)</td>
<td>0.25</td>
<td></td>
</tr>
</tbody>
</table>

Variables are presented as n (%) of control individuals and MI patients. *$FGG$, $FGA$, $FGB$; genes for fibrinogen-$g$, fibrinogen-$a$, and fibrinogen-$b$, respectively. †Alleles are depicted from the same DNA strand, the coding strand of $FGG$ and $FGA$, and the noncoding strand of $FGB$.  

Age is mean±SD; other variables are presented as n (%) of controls and patients.

Discussion

The present results strongly suggest that genetic variations in the fibrinogen gene region are not associated with myocardial infarction. This conclusion was reached on evaluation of alleles and haplotypes in 2 case-control samples which included large numbers of participants.

Systematic examinations, including electrocardiography and left ventricular and coronary angiography, enabled us to safely define case and control status of the study participants. The allele frequencies in the control groups were not significantly different from those observed in other control groups that consisted predominantly (>92%) or completely of white individual, and in a European population sample used as a reference group for genomewide haplotype mapping (HapMap CEU; http://www.ncbi.nlm.nih.gov/projects/SNP).55 Pairwise allelic associations among SNPs corresponded well with those determined in different other populations or established by the International HapMap Consortium (http://www.hapmap.org),9,33,42,55,56 The sample size provided the analysis with 99% power to detect a 20% increase in the risk of MI among the carriers of the Hap1 haplotype and 72% power to detect a 20% increase in the risk of MI among the carriers of the Hap12 haplotype (2-sided α-error 0.05).

In prior studies of fibrinogen genes, SNPs were usually examined one by one, and the results suggested a lack of association with coronary artery disease and MI in most...
instances. Individual SNPs are considered to make at most a small contribution to disease risk, and their potential effects may escape detection when examined separately. Therefore, combined analysis of a series of SNPs, together capturing a major portion of the total genetic variation of the chromosomal region in question, may be more suitable than separate calculations to identify an existing relationship with disease. Mannila et al were the first to undertake such an extensive analysis in the fibrinogen gene region, when they studied the association of haplotypes with MI in a sample of 377 patients and 387 healthy individuals from Sweden. In their analysis, 8 of the SNPs were used that were also examined in the present study, not included were the rs4220 and rs1800787 SNPs. Among the 8-marker haplotypes,
Mannila et al observed associations of 3 different haplotypes, named FGG-FGA-FGB*1b, 4b, and 5b in their report, with MI. In terms of allelic composition, these haplotypes were entirely equivalent to the 10-marker haplotypes Hap1, HapIII, and Hap5 in the present samples, respectively, because inclusion of the rs4220 and rs1800787 SNPs did not result in altered haplotype diversity. Among the haplotypes that were also addressed here, Mannila et al found higher risks of MI linked to the TG (rs1049636-rs2070011) and TGC (rs1049636-rs2070011-rs1800790) haplotypes and lower risks connected with the ACC (rs1800792-rs1049636-rs2066864), AA (rs2070011-rs6050), Calif (rs1049636-rs2070011) and CAC (rs1049636-rs2070011-rs1800790) haplotypes. Obviously, the association data reported by Mannila et al are different from the results of the present study in which no evidence for a relationship of fibrinogen gene haplotypes with MI was obtained. Differences in particular characteristics between the study samples may have accounted for the opposite results. Two case-control samples were examined in the present study each of which was much larger than the sample investigated by Mannila et al. Mean ages of cases and controls were higher in the present investigation than in the prior study. All participants of the present study underwent coronary angiography, whereas in the study conducted by Mannila et al, coronary angiography was incomplete in the patient group and not performed in the control group. Similar to the present results, Uitte de Młnchen (KKF 1.4-05) to W.K.

The work was funded by a grant from Deutsches Herzzentrum München (KKF 1.4-05) to W.K.

Acknowledgments

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Sources of Funding

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Disclosures

None.

References


40. Thomas A, Lamplum H, Humphries S, Green F. Linkage disequilibrium across the fibrinogen locus as shown by five genetic polymorphisms, G/α A–355 (HrIII), C/T –145 (HindiIII/Ala), T/G –169 (Avall), and B/α (β-fibrinogen) and TaqI (α-fibrinogen), and their detection by PCR. *Hum Mutat*. 1994;3:79–81.


Online Data Supplement

Fibrinogen Genes and Myocardial Infarction: a Haplotype Analysis

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The supplemental materials have the following sections in order:

1. Supplemental Methods
2. Supplemental Table I
3. Supplemental Table II
1. Supplemental Methods

Patients and Controls

Two case-control samples, sample 1 and sample 2, were examined at Deutsches Herzzentrum München or 1. Medizinische Klinik rechts der Isar der Technischen Universität München. Sample 1 consisted of 3657 patients with MI and 1211 control individuals who were recruited from 1993 to 2002. Sample 2 comprised 1392 MI patients and 1392 control persons who were recruited from 2003 to 2006. Written informed consent was obtained from all study participants. The study protocol was approved by the institutional ethics committee and the reported investigations were in accordance with the principles of the current version of the Declaration of Helsinki (http://www.wma.net/e/policy/b3.htm).

Definitions

The diagnosis of MI was established in the presence of chest pain lasting >20 min combined with ST-segment elevation or pathological Q waves on a surface electrocardiogram. Patients with MI had to show either an angiographically occluded infarct-related artery or regional wall motion abnormalities corresponding to the electrocardiographic infarct localization, or both. Individuals were considered disease free and, therefore, eligible as controls when their coronary arteries were angiographically normal and when they had no history of MI, no symptoms suggestive of MI, no electrocardiographic signs of MI, and no regional wall motion abnormalities. Coronary angiography in the control individuals was performed for the evaluation of chest pain. Systemic arterial hypertension was defined as a systolic blood pressure of ≥140 mm Hg and/or a diastolic blood pressure of ≥90 mm Hg (1), at least on two separate occasions, or antihypertensive treatment. Hypercholesterolemia was defined as a documented total cholesterol value ≥240 mg/dL (≥6.2 mmol/L) or current treatment with
cholesterol-lowering medication. Persons reporting regular smoking in the previous 6 months were considered as current smokers. Diabetes mellitus was defined as the presence of an active treatment with insulin or an oral antidiabetic agent; for patients on dietary treatment, documentation of an abnormal fasting blood glucose or glucose tolerance test based on the World Health Organisation criteria (2) was required for establishing this diagnosis.

**SNP selection**

Haplotype-tagging SNPs were inferred from HapMap data on the basis of the CEU population sample and with cut offs for pairwise \( r^2 \) values set at 0.8 (HapMap data release 21a/phase II Jan07, on National Center for Biotechnology Information B35 assembly, SNP database build 125; http://www.hapmap.org and http://www.ncbi.nlm.nih.gov/projects/SNP) (3). Variation in the fibrinogen genes was represented by the rs2066864, rs1049636, and rs1800792 SNPs (FGG region: positions 155,881,000 to 155,940,000 on chromosome 4), rs6050 and rs 2070011 SNPs (FGA region: 155,860,000 to 155,870,000), and by the rs1800790 and rs1800788 SNPs (FGB region: 155,840,000 to 155,850,000). In addition, the rs1800787, rs1800791, and rs4220 SNPs in FGB were included in the analysis because they have been associated with nuclear protein binding to the FGB promoter (rs1800787), transcriptional activity (rs1800791), and plasma fibrinogen level and clot structure (rs4220) (4-7).

**Genetic analysis**

TaqMan allelic discrimination assays were designed and used for SNP genotyping (8,9). The sequences of oligonucleotide primers and TaqMan probes and reaction protocols are available upon request. About 100 different PCR products obtained with each TaqMan system were sequenced to test whether one or more additional polymorphisms were present in the probe-
binding section of the amplicons, because they may interfere with TaqMan reactions and result in wrong genotype assignments. The known SNPs were identified as the only sequence variants in the probe-binding regions, which implicated that the probability of genotyping errors because of possible further sequence variations was relatively low. In addition, the genotype results obtained with sequence analyses and the corresponding TaqMan reactions were in full agreement. With each SNP, re-typing of 20% of the DNA samples was done to control for correct sample handling and data acquisition. Clinicians responsible for diagnosis were not aware of the genetic data. All genetic analyses were blinded.

Statistical analysis

The analysis consisted of comparing separately allele and haplotype frequencies between the control group and the MI group in sample 1 and sample 2. Discrete variables were compared with the use of the $\chi^2$ test. Continuous variables are expressed as mean±SD and were compared by means of the unpaired 2-sided $t$ test. Hardy-Weinberg equilibrium was assessed with the use of the $\chi^2$ test. Pairwise measures of linkage disequilibrium ($D'$ and $r^2$) between the SNPs were calculated from primary genotype data with the software package Haploview (10). Haplotypes were reconstructed using the software package PHASE (11).

References


5. Thomas A, Lamllum H, Humphries S, Green F. Linkage disequilibrium across the fibrinogen locus as shown by five genetic polymorphisms, G/A\textsuperscript{−455} (*HaeIII*), C/T\textsuperscript{−148} (*HindIII/Alu*I), T/G\textsuperscript{+1689} (*AvaII*), and *BclI* (β-fibrinogen) and *TaqI* (α-fibrinogen), and their detection by PCR. *Hum Mutat*. 1994;3:79-81.


### 2. Supplemental Table I. Haplotype Frequencies, ORs, and 95% CIs for Myocardial Infarction in Relation to Fibrinogen Gene-specific Haplotypes. Haplotypes were Inferred From the 12 Most Frequent 10-marker Haplotypes of the FGG-FGA-FGB Region.

<table>
<thead>
<tr>
<th>Gene</th>
<th>Haplotype*</th>
<th>Sample 1</th>
<th>Sample 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Frequencies†</td>
<td>OR (95% CI)</td>
<td>P</td>
</tr>
<tr>
<td>FGG</td>
<td>GTC</td>
<td>44.9/46.8</td>
<td>1.08 (0.94 to 1.23)</td>
</tr>
<tr>
<td></td>
<td>ACC</td>
<td>29.9/28.7</td>
<td>0.89 (0.77 to 1.33)</td>
</tr>
<tr>
<td></td>
<td>ATT</td>
<td>25.3/24.6</td>
<td>0.96 (0.83 to 1.12)</td>
</tr>
<tr>
<td>FGA</td>
<td>GA</td>
<td>62.9/63.8</td>
<td>1.04 (0.90 to 1.19)</td>
</tr>
<tr>
<td></td>
<td>AG</td>
<td>26.6/25.8</td>
<td>0.96 (0.83 to 1.12)</td>
</tr>
<tr>
<td></td>
<td>AA</td>
<td>10.5/10.4</td>
<td>0.99 (0.80 to 1.24)</td>
</tr>
<tr>
<td>FGB</td>
<td>CGGCC</td>
<td>41.5/43.7</td>
<td>1.10 (0.96 to 1.25)</td>
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<td></td>
<td>TAGTC</td>
<td>21.5/20.5</td>
<td>0.94 (0.80 to 1.11)</td>
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<td></td>
<td>CGACC</td>
<td>20.1/19.7</td>
<td>0.98 (0.83 to 1.16)</td>
</tr>
<tr>
<td></td>
<td>CGGCT</td>
<td>15.3/14.3</td>
<td>0.92 (0.76 to 1.11)</td>
</tr>
<tr>
<td></td>
<td>CAGTC</td>
<td>1.7/1.8</td>
<td>1.10 (0.65 to 1.84)</td>
</tr>
</tbody>
</table>

*The order of the alleles in the haplotypes is in accordance with the relative chromosomal positions of the SNPs (from left to right): FGG: rs1800792, rs1049636, rs2066864; FGA: rs2070011, rs6050; FGB: rs4220, rs1800787, rs1800788, rs1800790, rs1800791.

Alleles are depicted from the same DNA strand, the coding strand of FGG and FGA and the non-coding strand of FGB.

†Haplotype frequencies (%) in the control and MI groups.
3. Supplemental Table II. Haplotype Frequencies, ORs, and 95% CIs for Myocardial Infarction in Relation to Haplotypes of SNPs with Relatively low Allelic Associations. Haplotypes Were Inferred From the 12 Most Frequent 10-marker Haplotypes of the *FGG-FGA-FGB* Region.

<table>
<thead>
<tr>
<th>SNP (gene)</th>
<th>Haplotype*</th>
<th>Sample 1</th>
<th>Sample 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Frequency†</td>
<td>OR (95% CI)</td>
<td>P</td>
</tr>
<tr>
<td>rs1049636-rs2070011</td>
<td>TG</td>
<td>43.6/45.5</td>
<td>1.08 (0.95 to 1.24)</td>
</tr>
<tr>
<td>(FGG-FGA)</td>
<td>TA</td>
<td>26.6/25.8</td>
<td>0.96 (0.83 to 1.12)</td>
</tr>
<tr>
<td></td>
<td>CG</td>
<td>19.4/18.2</td>
<td>0.93 (0.78 to 1.10)</td>
</tr>
<tr>
<td></td>
<td>CA</td>
<td>10.5/10.4</td>
<td>0.99 (0.80 to 1.24)</td>
</tr>
<tr>
<td>rs1049636-rs2070011-rs1800790</td>
<td>TGC</td>
<td>27.7/30.1</td>
<td>1.13 (0.97 to 1.31)</td>
</tr>
<tr>
<td>(FGG-FGA-FGB)</td>
<td>TAC</td>
<td>22.3/22.2</td>
<td>0.99 (0.85 to 1.17)</td>
</tr>
<tr>
<td></td>
<td>CGC</td>
<td>18.1/16.8</td>
<td>0.91 (0.77 to 1.09)</td>
</tr>
<tr>
<td></td>
<td>TGT</td>
<td>15.9/15.4</td>
<td>0.96 (0.80 to 1.16)</td>
</tr>
<tr>
<td></td>
<td>CAC</td>
<td>8.8/8.6</td>
<td>0.97 (0.77 to 1.23)</td>
</tr>
<tr>
<td></td>
<td>TAT</td>
<td>4.3/3.6</td>
<td>0.84 (0.60 to 1.18)</td>
</tr>
<tr>
<td></td>
<td>CAT</td>
<td>1.7/1.8</td>
<td>1.10 (0.65 to 1.84)</td>
</tr>
<tr>
<td></td>
<td>CGT</td>
<td>1.3/1.5</td>
<td>1.18 (0.65 to 2.14)</td>
</tr>
</tbody>
</table>

*The order of the alleles in the haplotypes is in accordance with the relative chromosomal positions of the SNPs.

Haplotype bases are depicted from the same DNA strand, the coding strand of *FGG* and *FGA* and the non-coding strand of *FGB*.

†Haplotype frequencies (%) in the control and MI groups.