Platelet Glycoprotein Ibα HPA-2 Met/VNTR B Haplotype as a Genetic Predictor of Myocardial Infarction and Sudden Cardiac Death

Jussi Mikkelsson, MD, PhD; Markus Perola, MD, PhD; Antti Penttilä, MD, PhD; Pekka J. Karhunen, MD, PhD

Background—Sudden cardiac death (SCD) is one of the leading manifestations of coronary heart disease in early middle age. Platelet glycoprotein (GP) Ib-IX-V receptor complexes play a key role in the initial adhesion of platelets to collagen during the formation of a coronary thrombus. The HPA-2 (Thr145 Met) and VNTR polymorphisms of the gene for GP Ibα have been studied previously in hospitalized patients with acute coronary syndromes. The significance of these polymorphisms in victims of sudden cardiac death is not known.

Methods and Results—The association of these 2 polymorphisms with coronary atherosclerosis, coronary artery stenosis, coronary thrombosis, myocardial infarction (MI), and SCD was studied in the Helsinki Sudden Death Study, which comprised 2 large autopsy series, collected 10 years apart during 1981 to 1982 and 1991 to 1992, of 700 middle-aged white Finnish men who suffered sudden or violent out-of-hospital death. The 2 polymorphisms showed an almost complete linkage disequilibrium. Men with acute MI (n = 80) and coronary thrombosis (n = 65) were more likely to be carriers of the HPA-2 Met allele (OR 2.0 and 2.6, respectively, P < 0.005 for both) than were control subjects who died of noncardiac causes (n = 367). In men <55 years old, the Met allele was overrepresented (OR 2.2) among victims of SCD (n = 98) compared with control subjects (n = 249). In men <55 years old, 17 of 29 men with acute MI (58.6%) and 16 of 23 men with coronary thrombosis (69.6%) were carriers of the HPA-2 Met allele compared with the 49 of 249 (19.7%) who had died of noncardiac causes (ORs 5.6 and 9.2, respectively). Similar associations were observed in the separate analyses of both autopsy series.

Conclusions—Our results suggest that the HPA-2 Met/VNTR B haplotype of the platelet von Willebrand factor and thrombin receptor protein GP Ib-V-IX may be considered to be a major risk factor of coronary thrombosis, fatal MI, and SCD in early middle age. (Circulation. 2001;104:876-880.)

Key Words: genetics • myocardial infarction • platelets • risk factors • thrombosis

Sudden cardiac death (SCD) is one of the main complications of coronary heart disease (CHD). Approximately 50% of deaths caused by CHD are sudden and take place outside a hospital. SCD is often the first manifestation of the underlying disease, being by far the leading first symptom of CHD in early middle age. As much as 90% of CHD mortality in individuals <55 years old occurs out-of-hospital. Factors most likely to increase the risk of dying suddenly of CHD as opposed to nonfatal coronary events are cigarette smoking and family history.

Erosion or disruption of the fibrous cap of an atheromatous plaque, subsequent platelet adhesion, aggregation, and thrombus formation are main events in the development of acute myocardial infarction (AMI) and SCD in patients with CHD. The primary event after rupture or fissuring of coronary plaques, eventually resulting in platelet aggregation and thrombus formation, is the activation of platelet GP Ib-IX-V receptors by high shear stress and/or thrombin and the subsequent receptor binding to subendothelial collagen via von Willebrand factor.

The altered amino acid sequence (C to T nucleotide substitution resulting in Thr to Met transition) responsible for the HPA-2 polymorphism is located in the leucine-rich region responsible for the ligand binding of GP Ibα. The HPA-2 polymorphism is in nearly complete linkage disequilibrium with a size polymorphism in the same gene. The Met allele of the HPA-2 polymorphism is associated with tandem repeats of the size polymorphism. All individuals with the Met allele have been reported to carry the B allele, but 1% to 5% of B allele carriers are Thr homozygotes. Thus, any association of the Met allele with CHD may also be due to an effect of the VNTR polymorphism on platelet function.

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876
Body mass index, kg/m² 25.9

out-of-hospital deaths.

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Characteristics and Phenotypes of MI

The presence of MI in the series was confirmed by macroscopic and

Thus far, HPA-2 polymorphism of the gene for GP Ibβ has not been found to affect the receptor binding to von Willebrand factor,12,13 but in a study using agonist-induced aggregation under high shear, the B allele carriers of the VNTR polymorphism (Met carriers of the HPA-2 polymorphism) had increased platelet activity, even though the study population was on aspirin.14 Previous studies on CHD patients15–17 have not unanimously supported an association between the Met allele and CHD. Only 2 studies, however, focused on acute coronary events, but they have reported controversial results.18,19 The HPA-2 polymorphism has been found to be associated with ischemic cerebrovascular disease20 and ischemic stroke.21

In the present study, we investigated the association of the GP Ibβ HPA-2 and VNTR polymorphisms with coronary atherosclerosis and the degree of coronary stenosis, coronary thrombosis, MI, and SCD in 2 large autopsy series of sudden, out-of-hospital deaths.

Methods

Autopsy Series of Middle-Aged Men

The Helsinki Sudden Death Study (HSDS) was designed to study the risk factors for sudden out-of-hospital cardiac death. The HSDS study comprised 2 consecutive series of a total of 700 white Finnish men who were subjected to medicolegal autopsy at the Department of Forensic Medicine, University of Helsinki, in 1981 to 1982, and 10 years later, in 1991 to 1992. The mean age of subjects in both series was 53 years (range 33 to 70 years). Causes of deaths were cardiac in 41.1% (n = 55); 14.1% (n = 11); and 8.9% (n = 6). Characteristics of the study population are given in Table 1. The study was approved by the Ethics Committee of the Department of Forensic Medicine, University of Helsinki.

DNA Extraction, HPA-2, and VNTR Genotyping

In the 1981 to 1982 series, DNA was extracted from paraffin-embedded samples of cardiac muscle, and in the 1991 to 1992 series, DNA was isolated from frozen (−70°C) cardiac muscle samples.22 Genotyping for the HPA-2 polymorphism was performed with restriction enzyme analysis with slight modifications from Kekomaki et al23 and VNTR polymorphism just as described previously by Kekomaki et al. Genotyping was successful for both HPA-2 and VNTR polymorphisms in 626 cases (HPA-2 630 and VNTR 643).

Risk Factors for Coronary Artery Disease and Sudden Death

A spouse, relative, or close friend of the deceased could be interviewed in 500 cases (71.4%). Questions delineated past and recent smoking and drinking habits as well as previous illnesses. On

<table>
<thead>
<tr>
<th>Variable</th>
<th>All (n=288)</th>
<th>Violent Death (n=272)</th>
<th>Other Disease (n=140)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>65.6 ± 8.6</td>
<td>49.2 ± 9.4</td>
<td>53.5 ± 8.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>25.9 ± 5.1</td>
<td>23.8 ± 4.0</td>
<td>23.5 ± 5.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Smokers</td>
<td>139/177 (78.5%)</td>
<td>125/164 (76.2%)</td>
<td>87/100 (87.0%)</td>
<td>&gt;0.1</td>
</tr>
<tr>
<td>Average alcohol consumption, drinks/d</td>
<td>5</td>
<td>10</td>
<td>9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypertension</td>
<td>64/206 (31.1%)</td>
<td>23/173 (13.3%)</td>
<td>20/98 (20.4%)</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>Diabetes</td>
<td>57/206 (27.7%)</td>
<td>31/173 (17.9%)</td>
<td>25/98 (25.5%)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>AMI</td>
<td>80 (27.8%)</td>
<td>8 (0.4%)</td>
<td>4 (2.9%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Old infarct scar</td>
<td>121 (42.0%)</td>
<td>15 (5.5%)</td>
<td>13 (9.3%)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Values are mean ± SD or n (%).

Thus far, HPA-2 polymorphism of the gene for GP Ibβ has not been found to affect the receptor binding to von Willebrand factor,12,13 but in a study using agonist-induced aggregation under high shear, the B allele carriers of the VNTR polymorphism (Met carriers of the HPA-2 polymorphism) had increased platelet activity, even though the study population was on aspirin.14 Previous studies on CHD patients15–17 have not unanimously supported an association between the Met allele and CHD. Only 2 studies, however, focused on acute coronary events, but they have reported controversial results.18,19 The HPA-2 polymorphism has been found to be associated with ischemic cerebrovascular disease20 and ischemic stroke.21

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Characteristics and Phenotypes of MI

The presence of MI in the series was confirmed by macroscopic and histological examination of the myocardium. The presence/absence of neutrophil granulocytes was considered diagnostic of an AMI and the presence/absence of fibrous scar tissue diagnostic of an old MI. On the basis of the autopsy findings and nitro blue tetrazolium staining, the MI was classified as either transmural or nontransmural. Of the entire series of 700 men, 184 were found to have had MI. Eighty-five men had died of AMI with or without an old MI. Of the

AMI cases, 39 were associated with coronary thrombosis, of which 24 were acute. Old nonfatal MI scar without AMI was found in an additional 99 cases, of which a macroscopic organizing thrombus was observed in 14 cases. AMI was transmural in 52% of men <55 years old (n=29) and in 42% of men >55 years old (n=55). Macroscopic coronary thrombosis was found in 89.5% of cases with transmural AMI whereas the corresponding figure in nontransmural AMI was only 11%.

Measuring the Percentage of Stenosis in Silicone Rubber Casts of the Coronary Arteries

At autopsy, coronary angiography was performed, with vulcanizing liquid silicone rubber mixed with lead oxide used as the contrast medium. The proximal, middle, and distal stenoses of the main trunks of the 3 main epicardial coronary arteries (left anterior descending, left circumflex, and right coronary arteries) were measured from the rubber cast model. The percentage of the stenosis was obtained by dividing the diameter (millimeters) of the greatest stenosis by the diameter of the nearest proximal undamaged part of the cast model of the artery, resulting in 9 measurements of the degree of stenosis for each individual. These measurements were available in 670 men.

Measuring the Area of Atherosclerosis by Morphometry of Coronary Arteries

The coronary arteries were fixed in 10% buffered formalin and stained for fat by the Sudan IV staining method. The following atherosclerotic changes were evaluated for all arteries: fatty streaks, elevated plaques, and complicated lesions. The proportional area of each particular atherosclerotic change in the most affected coronary artery was used for statistical analyses. Data on the atherosclerotic changes of coronary arteries were available in 512 men from both series.

DNA Extraction, HPA-2, and VNTR Genotyping

In the 1981 to 1982 series, DNA was extracted from paraffin-embedded samples of cardiac muscle, and in the 1991 to 1992 series, DNA was isolated from frozen (−70°C) cardiac muscle samples.22 Genotyping for the HPA-2 polymorphism was performed with restriction enzyme analysis with slight modifications from Kekomaki et al23 and VNTR polymorphism just as described previously by Kekomaki et al. Genotyping was successful for both polymorphisms in 626 cases (HPA-2 630 and VNTR 643).

Risk Factors for Coronary Artery Disease and Sudden Death

A spouse, relative, or close friend of the deceased could be interviewed in 500 cases (71.4%). Questions delineated past and recent smoking and drinking habits as well as previous illnesses. On
the basis of these interviews, men were classified as smokers (n=353) or nonsmokers (n=88). Ex-smokers (n=67) were included in the class of smokers for statistical analysis. Average daily alcohol consumption of the deceased was calculated from information given by the interviewed persons. Questions on previous illnesses showed that 107 men had suffered from hypertension and 113 from diabetes. The validity of the risk factor data and their collection method have been discussed previously.24

Statistical Analysis
Characteristic differences between causes of deaths were analyzed bivariately with Student’s t tests. Analyses of the effect of genotype on MI with/without thrombosis and comparisons between acute thrombosis cases and other SCD victims were based on logistic regression with the risk factor data. We also analyzed for the interaction between genotypes and age groups and groups of causes of deaths using logistic regression. Analyses of atherosclerotic variables and stenosis percentage are based on ANOVA/MANOVA with Bonferroni adjustments. All data analyses were performed both with and without the interview data. The computation was carried out with STATISTICA/WIN (version 5.0, Statsoft Inc) and SPSS for Windows (version 10.0, SPSS).

Results
Prevalence and Linkage Disequilibrium of HPA-2 and VNTR Alleles
Allele frequencies of Thr and Met in the HPA-2 genotyped population of 630 men were 0.88 and 0.12, respectively. Genotype frequencies were 77.1% for ThrThr, 21.3% for ThrMet, and 1.6% for MetMet. The frequency of the Met allele carriers among men in our study population (22.9%) is comparable to the frequency on a population basis in Finland (between 16% and 24%).10,23 The allele frequencies for the 643 men genotyped for the VNTR polymorphism were 0.083 for D allele, 0.78 for C allele, 0.13 for B allele, and 0.008 for A allele. Corresponding genotype frequencies were 2.2%, 12.6%, 61.6%, 20.5%, 2.3%, 0.6%, and 0.2% for DD, DC, CC, CB, BB, BD, and AC genotypes, respectively. The HPA-2 and VNTR polymorphisms showed an anticipated and strong linkage disequilibrium (Table 2). The 2 polymorphisms showed significant interaction for all the significant associations reported in this article, indicating a haplotype effect confined to the HPA-2 Met/VNTR B haplotype in comparison with the Met-negative/B-negative haplotype. Because of a very strong linkage disequilibrium, we were unable to distinguish independent effects of the 2 polymorphisms. Thus, all results are presented only for the HPA-2 polymorphism. Allele and genotype frequencies did not differ between the 1981 to 1982 and 1991 to 1992 autopsy series or between men with and those without interview data (data not shown). Genotypes were in Hardy-Weinberg equilibrium in both autopsy series and in the subgroups by interview data availability.

SCD and HPA-2 Polymorphism
The frequency of the HPA-2 Met allele was similar among cases of SCD, violent deaths, and deaths due to other diseases (P>0.3). Men with the Met genotype, however, were more frequently (OR 2.2; 95% CI 1.3 to 3.7, P<0.001 for age group–haplotype interaction) found among young (<55 years old) victims of SCD (n=98) compared with those (n=249) who died of noncardiac causes without significant coronary disease or MI at autopsy (referred to as controls later in this section) (34.7% versus 19.7%). Genotype distribution is given in Tables 3 and 4.

Coronary Thrombosis, MI, and the HPA-2 Polymorphism
The frequency of the HPA-2 Met allele carriers among men with AMI (n=80) was higher (OR 2.0; 95% CI 1.1 to 3.7, P<0.005) than in controls (n=367) (26.2% versus 21.3%), and the HPA-2 Met allele was found more often (OR 2.6; 95% CI 1.3 to 5.3, P<0.005) among men with coronary thrombosis (n=65) (36.9%) than in controls (adjusted analyses).

TABLE 2. Linkage Disequilibrium Between the VNTR and HPA-2 Polymorphisms of GP Ib

<table>
<thead>
<tr>
<th></th>
<th>DD</th>
<th>CD</th>
<th>CC</th>
<th>BC</th>
<th>BB</th>
<th>BD</th>
<th>AC</th>
</tr>
</thead>
<tbody>
<tr>
<td>ThrThr</td>
<td>13</td>
<td>79</td>
<td>381</td>
<td>6</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>ThrMet</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>125</td>
<td>4</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>MetMet</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>10</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

TABLE 3. Distribution of HPA-2 Genotypes in Men With SCD, Coronary Thrombosis, Fatal AMI, or Either Old or Recent MI and Men Who Had Died of Noncardiac Causes

<table>
<thead>
<tr>
<th></th>
<th>Overall &lt;55 Years Old</th>
<th>&gt;55 Years Old</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Thr/Thr</td>
<td>Met+</td>
</tr>
<tr>
<td>SCD</td>
<td>189</td>
<td>66 (25.9)</td>
</tr>
<tr>
<td>Coronary thrombosis</td>
<td>41</td>
<td>24 (36.9)</td>
</tr>
<tr>
<td>AMI</td>
<td>55</td>
<td>25 (31.3)</td>
</tr>
<tr>
<td>All MI</td>
<td>127</td>
<td>45 (26.2)</td>
</tr>
<tr>
<td>Controls</td>
<td>289</td>
<td>78 (21.3)</td>
</tr>
</tbody>
</table>

Values are n (%).
Significant ORs of adjusted analyses compared with controls are shown. Number of cases differs from that of the entire study population reported in Methods because of genotype being unavailable from all cases.
TABLE 4. Mean Age (y) of Men With Different HPA-2 Genotypes Among Men With SCD, Coronary Thrombosis, and Fatal AMI and Men Who Had Died of Noncardiac Causes

<table>
<thead>
<tr>
<th>Genotype</th>
<th>SCD</th>
<th>AMI</th>
<th>Thrombosis</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>MetThr + MetMet</td>
<td>52.6±9.2</td>
<td>51.0±9.4</td>
<td>50.5±10.1</td>
<td>49.9±8.6</td>
</tr>
<tr>
<td>ThrThr</td>
<td>57.7±8.2</td>
<td>58.6±8.3</td>
<td>60.0±6.3</td>
<td>49.5±9.3</td>
</tr>
</tbody>
</table>

*P<0.01 for comparison in age at SCD between genotypes; *P<0.005 for comparison in age at AMI and age at thrombosis.

Age group (<55 versus >55 years old) showed a significant interaction with the HPA-2 polymorphism on AMI and coronary thrombosis (P<0.001 for all). In men <55 years old, 69.6% of the 23 men with coronary thrombosis had the HPA-2 Met allele, compared with 19.7% in 249 controls (OR 9.2; 95% CI 2.4 to 35.0). This allele was found in 58.6% of the 29 men with AMI (OR 5.6; 95% CI 1.8 to 17.3, compared with controls) (Tables 3 and 4). The HPA-2 Met allele was found more frequently in individuals with SCD due to an acute coronary/myocardial lesion in men <55 years old compared with men with SCD due to CHD but without an acute lesion, men with SCD not due to CHD, and controls (ORs 3.5, 8.8, and 5.4; *P<0.005, *P<0.01, and *P<0.005, respectively). No statistically significant differences were observed between the 3 latter groups (data not shown) (Table 5).

In men <55 years old in the 1981 to 1982 series, 77.0% of men with AMI carried the HPA-2 Met allele, and it was found in 66.7% of men with coronary thrombosis compared with 19.6% among controls. In the 1991 to 1992 series, the respective frequencies in men <55 years old were 43.8% for men with AMI, 75.0% for men with coronary thrombosis, and 19.7% for controls. These differences were independently significant in both series (analysis not shown). The above associations were significant both in men with risk factor data and in those who lacked these data.

Coronary Disease and HPA-2 Polymorphism

The degree of coronary stenosis as well as the areas of atherosclerotic lesions failed to show an association with the HPA-2 Met allele in the entire series. Age group (<55 versus >55 years), however, showed a significant interaction with the HPA-2 polymorphism, with effect on coronary stenosis (5p<0.005) and elevated coronary lesions (5p=0.05). In men <55 years old, the average degree of coronary stenosis was significantly more severe and the average vessel wall area covered by elevated lesions larger in Met allele carriers than in noncarriers. In addition, the cause of death interacted with genotype and age group (*P<0.05), showing in post hoc analysis that the difference in coronary stenosis was most pronounced among young (<55 years old) victims of SCD with the Met allele compared with the low-MI-risk genotype (Table 3). This may be because CHD was the cause of SCD in this age group in 85% of the carriers of the Met allele but in only 60% of the carriers of the low-MI-risk genotype, of whom more individuals had died of cardiomyopathy or other cardiac causes and showed only mild atherosclerosis at the autopsy.

Discussion

We found that the haplotype defined by the carriernesship of the HPA-2 Met allele and the VNTR B allele of 2 polymorphisms of the gene for platelet glycoprotein Ibα was associated with coronary thrombosis, AMI, and SCD in early middle age. The association of this haplotype with elevated coronary lesions and severe vessel stenosis among young SCD victims is likely to result from increased platelet adhesion and organization on coronary lesions. These results could be confirmed in both the 1981 to 1982 and 1991 to 1992 autopsy series in their separate, independent analyses. These findings suggest that the HPA-2 Met/VNTR B haplotype of GP Ibα may be a predictor of fatal complications of atherosclerosis in early middle age. Because of an almost complete linkage between the 2 polymorphisms, this may be due to an effect of one or both of these variants on platelet function or this may serve as a surrogate (linkage) marker for an as yet unknown factor associated with platelet function.

The role of genetic factors is considered to be very important in SCD and first MI; positive family history is an independent risk factor for primary cardiac arrest and sudden death.4,5 Our study population with relatively young Finnish men with fatal MI and SCD represents individuals with high environmental6 and familial 4,5 risk for coronary events. The Finnish population is also ethnically and culturally very homogenous and thus particularly suitable for genetic association studies.25

Possible explanations for differences in the results of association studies on MI include the fact that younger men more often suffer Q-wave infarctions. Transmural (often Q-wave) infarction is nearly always caused by an occluding fibrin-rich (red) coronary thrombus, whereas in most patients

TABLE 5. Distribution of Genotypes in Men With Different Major End Points

<table>
<thead>
<tr>
<th>Category</th>
<th>Overall</th>
<th>&lt;55 Years Old</th>
<th>&gt;55 Years Old</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Thr/Thr</td>
<td>Met+</td>
<td>Thr/Thr</td>
</tr>
<tr>
<td>SCD, acute MI/thrombus</td>
<td>64</td>
<td>29 (31.2) OR 1.6</td>
<td>14</td>
</tr>
<tr>
<td>SCD, CHD, no acute lesion</td>
<td>91</td>
<td>25 (21.6)</td>
<td>25</td>
</tr>
<tr>
<td>SCD, no CHD</td>
<td>41</td>
<td>9 (18.0)</td>
<td>27</td>
</tr>
<tr>
<td>Controls</td>
<td>289</td>
<td>78 (21.3)</td>
<td>200</td>
</tr>
</tbody>
</table>

Values are n (%).

Significant ORs for adjusted analyses compared with controls are shown. Number of cases differs from that of the entire study population reported in Methods because of genotype being unavailable from all cases.

*OR 3.5 for comparison between these 2 groups. †OR 8.8 for comparison between these 2 groups.
(75% to 80%) with unstable angina pectoris who develop nontransmural (usually non–Q-wave) infarction, occluding thrombi are absent and the thrombotic material present (in ~50% of the cases) is usually composed of platelets (white thrombus) adhered to preexisting stenotic lesions.26–28 Thus, cases of Q-wave infarction (younger men) may represent individuals in whom prothrombotic factors are more important than in older victims of non–Q-wave MI. It is also possible that factors related to platelet aggregation may be more important in Q-wave than in non–Q-wave infarction,22,28 whereas factors related to platelet adhesion may be important in both types of infarction. This is probably due to the importance of the glycoprotein receptors mediating platelet adhesion as the primary event of the clot formation after fissures/erosion of the coronary lesion surface. The subsequent evolution of this clot to vessel occlusion may be more dependent on other systemic/inherited factors affecting the activation of the coagulation cascade, thrombin generation, and binding of fibrinogen to platelets, which lead to the formation of the fibrin-rich (red) thrombus. Our current knowledge about the interplay between different platelet adhesion molecules is in a state of constant evolution, and the relative importance of individual elements in the time course of an evolving acute coronary event has not yet been sufficiently elucidated. We hope that the present findings may add a little piece to this puzzle.

Previous studies on the association of the HPA-2 polymorphism with coronary events have shown controversial results. Gonzalez-Concejero et al18 studied middle-aged individuals with various kinds of acute coronary events (Q-wave MI, non–Q-wave MI, and unstable angina pectoris) and found the Met allele/B allele of the VNTR polymorphism to be associated with an increased risk of these events, whereas Ardissino et al19 studied very young patients with Q-wave MI and could not find an association between the Met allele and Q-wave MI. These results imply that the HPA-2/VNTR polymorphisms could be more strongly associated with non–Q-wave MI, in which platelet adhesion, more than aggregation, is thought to be the main pathogenetic event. Both of these previous studies, however, are based on event survivors and thus contain a selection bias, if one assumes that a risk factor could affect case fatality, which is an important issue when studying factors that may be associated with an increased risk of SCD.

We conclude that the HPA-2 Met/VNTR B haplotype of GP Ibα is strongly associated with SCD due to coronary thrombosis and fatal AMI in early middle age and may thus serve as a useful marker for inherited risk of MI/SCD in individuals with a familial burden of premature coronary mortality.

Acknowledgments
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References
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