Extended evidence for association between the melanoma inhibitory activity 3 gene and myocardial infarction

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Summary
In a genome-wide scan, isolated single nucleotide polymorphisms (SNPs), including rs17465637, in the melanoma inhibitory activity 3 gene (MIA3) on chromosome 1 were identified to be associated with coronary artery disease and myocardial infarction (MI). Because the role of common variation at the MIA3 locus has not yet been investigated, the aim of this case-control study was to determine the impact of haplotype-tagging SNPs and haplotypes in the MIA3 region on the risk of MI. In a set of nine haplotype-tagging SNPs, rs17465637, but none of the other SNPs, was associated with MI. After adjustments were made for age, gender, history of arterial hypertension, history of hypercholesterolaemia, current cigarette smoking and diabetes mellitus, multiple logistic regression analyses showed an increased risk in the carriers of one or two C alleles [adjusted odds ratio (OR) 1.17, 95% confidence interval (CI) 1.04–1.32, and 1.37, 95% CI 1.08–1.74, respectively]. Nine common haplotypes (frequency >1%) were established across the MIA3 region. Two of the haplotypes were associated with an increased risk of MI: the frequent (48%) TGACCAAAG haplotype and the rare (2%) CGACCAAAG haplotype (adjusted OR 1.102, 95% CI 1.002–1.212, and 1.574, 95% CI 1.077–2.298, respectively). Showing association between rs17465637 and MI, this work was consistent with results from the original detection study and most prior replication studies addressing this issue. In addition to correspond with such isolated evidence of association with MI, the present study identified specific haplotypes capturing the risk-related variation in the entire MIA3 region.

Keywords
Genetic risk, haplotype, melanoma inhibitory activity 3 gene, MIA3, myocardial infarction

Introduction
Specific single nucleotide polymorphisms (SNPs) at chromosome 1q41, rs17465637 and rs3008621, were shown to be associated with coronary artery disease (CAD) and myocardial infarction (MI) in a genome-wide association study (1). These SNPs reside in the melanoma inhibitory activity 3 gene (MIA3), also known as TANGO, which has a broad expression pattern and encodes a 14-kDa protein of so far unknown function (2). MIA3 is down-regulated in malignant melanoma and also colon and hepatocellular carcinoma suggesting that it may act as a tumour suppressor gene (3, 4). The MIA3 protein directly binds to the leukocyte-specific β2-integrin CD11c/CD18 which is involved in leukocyte adhesive interactions with vascular endothelium (5, 6). Experimental evidence suggests that the MIA3 protein reduces attachment and promotes migration of monocytes across the endothelium by modulating CD11c/CD18 activity (5). Upon transmigration, monocytes differentiate to macrophages, which advance to foam cells and form the fatty streak, an early indicator of atherosclerosis in the arterial intima (7). Thus, a functional link appears to exist between MIA3 and the formation of atherosclerotic plaques, which may become unstable and give rise to thrombotic complications such as MI.

Support for an association of rs17465637 with MI was obtained in a cohort from Japan and different other samples most of which were exclusively comprised of participants of European ancestry (8–10). Unlike these observations (8–10) and the discovery study (1), rs17465637 was not found to be associated with CAD and MI in an independent investigation combining different cohorts from Europe (11). Similar to the original report (1), association of rs3008621 with CAD was shown in the latter study (11).

Prior association studies including SNPs located at 1q41 were limited to rs17465637 or rs17465637 and rs3008621 (1, 8–11), and thus only partially captured the common variation in the MIA3 gene region. In a more comprehensive analysis, we now used a set of haplotype-tagging SNPs to examine the relation between MIA3 and MI in a case-control sample from Germany.

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Materials and methods

Study population

The study population consisted of white individuals, 3,657 patients with prior or acute MI and 1,211 control individuals, who were consecutively recruited from 1993 to 2002 and examined with coronary angiography at Deutsches Herzzentrum München and 1. Medizinische Klinik rechts der Isar der Technischen Universität München. The sample size provided the analysis with 87% power to detect a 50% increase in the risk of MI among the carriers of the rs17465637 C allele in comparison with the reference genotype AA (2-sided α-error 0.05). The probability of false association results due to population stratification is relatively low because cases and controls were recruited from a defined geographic area of southern Germany with limited recent immigration. 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).

The diagnosis of MI was established in the presence of chest pain lasting >20 minutes 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 localisation, or both. These criteria were applied for both prior and acute MI. Individuals were considered disease free and therefore eligible as controls when their coronary arteries were angiographically normal or showed wall irregularities resulting in less than 10% lumen narrowing, and when they had no history of MI, no symptoms suggestive of MI, no electrocardiographic signs of MI, and no regional wall motion abnormalities. In addition, control individuals had no history of CAD. Coronary angiography in the control individuals was performed for the evaluation of chest pain.

Systemic arterial hypertension was defined as a systolic blood pressure ≥140 mm Hg and/or a diastolic blood pressure ≥90 mm Hg (12), on at least two separate occasions, or antihypertensive treatment. Hypercholesterolaemia was defined as a documented total cholesterol value >240 mg dl⁻¹ (>6.2 mmol L⁻¹) or current treatment with cholesterol-lowering medication. Persons reporting regular smoking in the previous six months were considered 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 (13) was required for establishing this diagnosis.

Polymorphisms

Haplotype-tagging SNPs in and near MIA3 (between positions 220,850,000 and 220,920,000 on chromosome 1; genome build 36.3) were retrieved from HapMap data (phase III, release 2, Feb09, on National Center for Biotechnology Information B36 assembly, SNP database build 126) (http://www.hapmap.org). On the basis of the CEU population sample and with cut-offs for pairwise r² values ≥0.9 and minimum minor allele frequency ≤0.10, nine SNPs were captured (Fig. 1), including rs17465637, the original discovery SNP at the MIA3 locus (1). rs17011681, a SNP located at a relatively short distance from (r² = 1) rs17465637, was used as a replication SNP to assess genotyping accuracy. In addition to rs17465637, another SNP of the MIA3 region, rs3008621, not a tag SNP in this study, was found to be associated with CAD and MI (1). To identify a proxy for rs3008621 among the tag SNPs, allelic linkage was assessed between rs3008621 and each of the tag SNPs. Using DNA sequencing, the rs3008621 genotypes of 150 individuals were determined; otherwise genotyping was performed with TaqMan reactions as described below.

Genotyping

Genomic DNA was extracted from peripheral blood leukocytes with Nucleo-Spin Blood Quick Pure (Macherey-Nagel, Düren, Germany) or QIAamp DNA Blood Kit (Qiagen, Hilden, Germany) reagents. Genotyping was performed with allele-specific fluorogenic oligonucleotide probes in an assay combining the PCR and the 5' nuclease reaction (TaqMan technique) (14, 15). Probes with a conjugated minor groove binder group and a dark quencher were used (15). Primers and probes were designed in house and synthesised by Applied Biosystems (Foster City, CA, USA). The sequences of primers and probes are shown in Table 1 (available online at www.thrombosis-online.com). Reactions were performed in Q-PCR Mastermix (Thermo Fisher Scientific, Waltham, MA, USA), after cycling on a GeneAmp PCR System 9600 or 9700 (Applied Biosystems), or a MultiCycler PTC 220 Dyad (MJ Research, Waltham, MA, USA). The system for typing was a ABI PRISM 7000 Sequence Detection System (Applied Biosystems).

With the use of DNA separately prepared from the original blood sample, re-typing of 20% of the DNA samples was done to control for correct sample handling and data acquisition. The accuracy of genotyping with the new TaqMan systems was evaluated and confirmed by BigDye Terminator DNA sequencing of 100 randomly selected DNA samples using the ABI PRISM 3100 Genetic Analyzer (Applied Biosystems). In addition to demonstrating the usefulness of the TaqMan assays for genotyping, sequencing also showed that no variation in addition to the SNPs under examination was present in the probe-binding sections of the amplicons. This finding greatly reduced the probability of wrongful genotype assignments that might have occurred with a TaqMan assay if one or more additional variations had existed in the probe-binding region (16). The primers used in genotyping for rs3008621 by sequence analysis were 5' -TGGTTACATTCTGAAAAGG-GAAACTT-3' and 5' -GGCATGTAGCCTAAAGTTATT-
ACCAGTCAA-3'. Details of reaction protocols are available upon request. Genotyping was done by persons who were not aware of the clinical or laboratory data of the study individuals.

**Statistical analysis**

Discrete baseline variables of the case and control groups are expressed as counts (%) and compared by the Chi² test. Age is expressed as mean ± standard deviation (SD) and compared by means of the unpaired, two-sided t-test. Differences by genotype were tested for cases compared with controls using the Cochran-Armitage test for trend, assuming an additive genetic model. Deviation from Hardy-Weinberg equilibrium was assessed by the Chi² test. Independence of genetic association from potentially confounding effects was tested in a multiple logistic regression model of MI that included as covariates age, gender, history of arterial hypertension, history of hypercholesterolaemia, current cigarette smoking, and diabetes mellitus. The adjusted odds ratio (OR) and 95% Wald confidence intervals (CI) were calculated on the basis of this model. Haplotypes were reconstructed from genotype data using the software package PHASE (17). The resulting haplotype probabilities were used to test for association with MI in a logistic regression analysis (18) and to calculate haplotype frequencies. Haplotypic effects were determined both unadjusted for co-variates and after adjustments were made for age and gender.

**Results**

**Baseline characteristics of the case and control groups**

Mean age of the case group (n = 3,657) was higher than that of the control group (n = 1,211), the proportion of women was lower in the case group than in the control group, and history of arterial hypertension and hypercholesterolaemia, current cigarette smoking, and diabetes mellitus were encountered more often in the case group than in the control group (p < 0.0001 for all comparisons) (Table 1).

**Association between SNPs and MI**

Nine SNPs, together comprising a set of tag SNPs for a haplotype analysis, were employed in the analysis, including rs17465637, the original detection SNP (1). In addition, rs17011681, a SNP located at a relatively short distance from (Fig. 1) and tightly associated with rs17465637, was used as a replication SNP to assess genotyping accuracy. The frequencies of the genotypes in the case and control groups are shown in Table 2. No significant deviation of the genotype distributions from Hardy-Weinberg equilibrium was observed in the control group (Table 2). Among the tag SNPs, only rs17465637 was associated with MI in the present sample (Table 2). Adjusted for age and gender, the per-allele risk for the C allele of rs17465637 was 1.14 (95% CI 1.02–1.27). After adjust-

<table>
<thead>
<tr>
<th>Case group (n = 3,657)</th>
<th>Control group (n = 1,211)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>64.0 ± 12.0</td>
</tr>
<tr>
<td>Women</td>
<td>885 (24.2)</td>
</tr>
<tr>
<td>Arterial hypertension</td>
<td>2,246 (61.4)</td>
</tr>
<tr>
<td>Hypercholesterolaemia</td>
<td>2,067 (56.5)</td>
</tr>
<tr>
<td>Current cigarette smoking</td>
<td>1,849 (50.6)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>754 (20.6)</td>
</tr>
</tbody>
</table>

Age is mean ± SD; other variables are presented as number (%) of individuals in the case and control groups.
ments were made for conventional cardiovascular risk markers (age, gender, history of arterial hypertension, history of hypercholesterolaemia, current cigarette smoking and diabetes mellitus), multiple logistic regression analyses showed similar results: in comparison with the non-carriers of the C allele, an increased risk was present in the carriers of one (adjusted OR 1.19, 95% CI 1.04–1.36) or two (adjusted OR 1.42, 95% CI 1.09–1.84) C alleles remained in the carriers of one (adjusted OR 1.19, 95% CI 1.04–1.36) or two (adjusted OR 1.42, 95% CI 1.09–1.84) C alleles of rs17465637.

Association of replication SNP rs17011681 with MI was similar to that of rs17465637 (Table 2), as was expected from the tight correlation between these SNPs. An examination of allelic association between rs17011681 and rs17465637 revealed 10 mismatches which were validated by repeated genotyping. This result strongly suggested the accuracy of rs17465637 (and rs17011681) genotyping.

In addition to rs17465637, another SNP of the MIA3 region, rs3008621, not a tag SNP in this study, was found to be associated with CAD and MI in the original study (1). Using a fraction of the study population for a comparative genotyping analysis, we found rs3008621 to be in perfect allelic association with tag SNP rs3002145 (150 of 150 samples; 300 of 300 alleles). Because rs3002145 was not related to MI in the present study (Table 2), no support was obtained for an association of rs3008621.

Haplotypes of the MIA3 locus

Nine major haplotypes (frequency > 1%) were reconstructed from the genotypes. Table 3 shows the allelic compositions of the haplotypes, their frequencies in the case and control groups, allotted unadjusted and adjusted p-values, and ORs together with 95% CIs. A trend regression test did not reveal overall significant association of haplotypes with MI.

Table 2: SNP genotype distributions in the case and control groups.

<table>
<thead>
<tr>
<th>SNP Alleles</th>
<th>Maj (Min) Het (Min)</th>
<th>Pval HWEa</th>
<th>Pval Band</th>
</tr>
</thead>
<tbody>
<tr>
<td>rs3002142</td>
<td>T&gt;C</td>
<td>2,884 (78.9) 725 (19.8)</td>
<td>48 (1.3)</td>
</tr>
<tr>
<td>rs904323</td>
<td>G&gt;A</td>
<td>2,493 (68.2) 1,047 (28.6)</td>
<td>117 (3.2)</td>
</tr>
<tr>
<td>rs17011666</td>
<td>A&gt;G</td>
<td>2,348 (64.2) 1,169 (32.0)</td>
<td>140 (3.8)</td>
</tr>
<tr>
<td>rs3002145</td>
<td>C&gt;T</td>
<td>2,726 (74.5) 861 (23.5)</td>
<td>70 (1.9)</td>
</tr>
<tr>
<td>rs17465637b</td>
<td>C&gt;A</td>
<td>2,026 (55.4) 1,385 (37.9)</td>
<td>246 (6.7)</td>
</tr>
<tr>
<td>rs17011681c</td>
<td>G&gt;C</td>
<td>2,020 (55.2) 1,389 (38.0)</td>
<td>248 (6.8)</td>
</tr>
<tr>
<td>rs2088514</td>
<td>A&gt;G</td>
<td>2,575 (70.4) 993 (27.2)</td>
<td>89 (2.4)</td>
</tr>
<tr>
<td>rs35822937</td>
<td>A&gt;G</td>
<td>2,480 (67.8) 1,056 (28.9)</td>
<td>121 (3.3)</td>
</tr>
<tr>
<td>rs17163384</td>
<td>A&gt;C</td>
<td>3,143 (85.9) 491 (13.4)</td>
<td>23 (0.6)</td>
</tr>
<tr>
<td>rs1053316</td>
<td>G&gt;A</td>
<td>2,991 (81.8) 624 (17.1)</td>
<td>42 (1.1)</td>
</tr>
</tbody>
</table>

Data are presented as number (%) of cases and controls. Maj (Min)–frequency of subjects homozygous for the major (minor) allele; Het–frequency of heterozygous subjects. a Deviation from Hardy-Weinberg equilibrium (HWE) in the control group was assessed by the Chi² test. b Original discovery SNP in the MIA3 region (1).

Table 3: Association between haplotypes of MIA3 and myocardial infarction.

<table>
<thead>
<tr>
<th>Haplotypea</th>
<th>Frequency Case</th>
<th>Control</th>
<th>P1</th>
<th>P2</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>T G A C C A A G</td>
<td>0.490</td>
<td>0.469</td>
<td>0.072</td>
<td>0.046</td>
<td>1.102 (1.002–1.212)</td>
</tr>
<tr>
<td>T G A C C A G A G</td>
<td>0.171</td>
<td>0.173</td>
<td>0.820</td>
<td>0.922</td>
<td>0.994 (0.877–1.126)</td>
</tr>
<tr>
<td>T A G T A G A G</td>
<td>0.108</td>
<td>0.111</td>
<td>0.753</td>
<td>0.535</td>
<td>0.953 (0.819–1.109)</td>
</tr>
<tr>
<td>C G A C A A A A C</td>
<td>0.061</td>
<td>0.066</td>
<td>0.385</td>
<td>0.283</td>
<td>0.900 (0.743–1.091)</td>
</tr>
<tr>
<td>T A C C A A A A G</td>
<td>0.034</td>
<td>0.036</td>
<td>0.655</td>
<td>0.410</td>
<td>0.894 (0.684–1.168)</td>
</tr>
<tr>
<td>T G C A G A A C A</td>
<td>0.031</td>
<td>0.039</td>
<td>0.054</td>
<td>0.045</td>
<td>0.766 (0.591–0.999)</td>
</tr>
<tr>
<td>C G G C A A A A A A A</td>
<td>0.022</td>
<td>0.025</td>
<td>0.372</td>
<td>0.379</td>
<td>0.871 (0.640–1.185)</td>
</tr>
<tr>
<td>C G A C C A A A A A A</td>
<td>0.022</td>
<td>0.016</td>
<td>0.054</td>
<td>0.019</td>
<td>1.574 (1.077–2.298)</td>
</tr>
<tr>
<td>T A G T C A A A A</td>
<td>0.013</td>
<td>0.014</td>
<td>0.794</td>
<td>0.876</td>
<td>0.967 (0.637–1.468)</td>
</tr>
</tbody>
</table>

P1–P value unadjusted; P2–P value adjusted for age and gender; OR–odds ratio; CI–confidence interval. Conditional odds ratios are adjusted for age and gender and refer to an increment of a single haplotype in the diploid organism. The estimation of frequencies and conditional odds ratios and association tests are based on individual haplotype probabilities calculated with PHASE (17). a The order of the alleles in the haplotypes is in accordance with the relative chromosomal positions of the SNPs (from left to right): rs3002142, rs904323, rs17011666, rs3002145, rs17465637, rs2088514, rs35822937, rs17163384, rs1053316. Haplotype bases are depicted from the coding strand of MIA3.
of the haplotypes with MI, but indicated a trend (p = 0.085). The TGACCAAAG haplotype, accounting for 48% in the study sample, and the CGACCAAAG haplotype, which was quite rare (frequency 2%), were significantly more prevalent in the MI group than in the control group (Suppl. Table 3). None of the other haplotypes showed a relation with MI (Suppl. Table 3).

**Discussion**

Novel findings from a genome-wide association study connected MI with MIA3 (1), a gene that has been previously linked with malignant diseases (3, 4). Similar to the original study (1), we observed an association between the C allele of rs17465637 in MIA3 and the risk of MI. Different from a prior result (1), no evidence was obtained for an association of the MIA3 SNP rs3008621 with MI. Though genotyping for rs3008621 was not performed in the entire study sample, we deduced this estimation from the result of no association obtained with rs3002145, a SNP in perfect allelic association with rs3008621, as ascertained in this study.

Ample support has been provided for an association between rs17465637 and CAD or MI (see Suppl. Table 3 available online at www.thrombosis-online.com) (1, 8–10). Using cohorts with participants of European or Asian ancestry, statistical evidence was robust in most studies, with the same allele, the C allele, associated with an increased risk (1, 8–10). In the original genome-wide approach, association was observed in a sample containing patients with MI or coronary revascularisation (WTCCC), a sample including MI cases with a family record of CAD (GerMIFS I), and the combined samples (Suppl. Table 3 available online at www.thrombosis-online.com) (1). Similarly, rs17465637 was found to be associated with MI in a study from Japan (Suita Study) (8). Thus, association exists in populations of European and Asian ancestry, though genotype distributions and allele frequencies are significantly different between these distinct ethnic groups. For example, C allele frequency was 53.8% in the control group from Japan (8) and 72.2% in the control group of the present sample (p < 0.0001). In a genome-wide study consisting of four stages with the number of sequence variants tested reduced gradually from ∼2.5 million in stage 1 to 13 in stage 4, association of rs17465637 with MI was statistically significant in stages 1 (six samples) and 3 (six samples) but not in stages 2 (two samples) and 4 (one sample) (Suppl. Table 3 available online at www.thrombosis-online.com) (9). Because the direction of the effect was the same at all four stages, a strong association ensued from a combined analysis of stages 1 through 4, together comprising >12,000 cases and >12,000 controls of European (16 samples and subset of one sample) or South Asian (subset of one sample) ancestry (Suppl. Table 3 available online at www.thrombosis-online.com) (9). Association of rs17465637 with the history of MI was shown in a pooled sample consisting of 908 cases and 2,129 controls recruited from different areas in northern and Western Europe (Suppl. Table 3 available online at www.thrombosis-online.com) (10). Different from these results (1, 8–10), no relation of rs17465637 with CAD and MI was found in a combined study of nine separate samples amounting to >10,000 cases and >10,000 controls of white northern European origin (Suppl. Table 3 available online at www.thrombosis-online.com) (11).

The present sample showed an effect size of 1.14 for the C allele of rs17465637 which was similar or identical to effect sizes observed in prior studies: 1.15 in GerMIFS I (1), 1.13 in the combined analysis of stages 1 through 4 excluding the samples from the original study (9), and 1.14 in the combined analysis of stages 1 through 4 including the samples from the original study (Suppl. Table 3 available online at www.thrombosis-online.com) (9). Correspondence between the present and prior (1, 9) effect rates support the usefulness of the present sample, particularly the control group which did not represent a typical group of healthy controls, because individuals had some indication for coronary angiography. Although the association between the C allele and MI in the present sample was no longer statistically significant when the many comparisons drawn here were taken into consideration, the result is not a statistical fluke given the accordance with most of the prior data (Suppl. Table 3 available online at www.thrombosis-online.com) (1, 8–10).

Besides rs17011681, used here as a replication SNP for rs17465637, another SNP, rs2133189, was found to be in perfect allelic association with rs17465637 and associated with MI (1). Thus, the MI-associated SNPs rs17011681, rs17465637, and rs17011681 together define a linkage disequilibrium block which extends, at least, from within intron 6 into intron 10 across a region of >9,000 bp (Fig. 1). This block, rather than any other parts of MIA3, may conceal a functional link related to MI.

Though only one of the nine tag SNPs showed a relation with MI on an individual level and not even a trend was seen with most of the others, the TGACCAAAG haplotype, by far the most abundant haplotype in the study sample (frequency 48%), was associated with MI, but the effect was rather small (10% increase of risk compared with the other haplotypes combined) and statistical significance was borderline (adjusted p = 0.046). The CGACCAAAG haplotype also showed association with MI, but it was quite rare (frequency 2%) and the estimation of its effect (57% increase of risk) was affected by a large imprecision. Note of the fact should be taken that the associations of the TGACCAAAG and CGACCAAAG haplotypes with MI were not statistically significant after a correction was made for the number of SNPs and haplotypes tested. Further studies are therefore required to pinpoint the association of MIA3 haplotypes with MI.

**Limitation of the study**

Several lines of evidence suggested that approximately 20–30% of patients who develop an acute coronary event die before arrival at the hospital (19). For this reason, a considerable number of potentially eligible patients with acute MI were probably not included in the study. Consequently, underrepresentation of potential risk alleles or genotypes constituted a selection bias that could have af-
What is known about this topic?
- Specific single nucleotide polymorphisms (SNPs) in the melanoma inhibitory activity 3 gene (MIA3) at chromosome 1q41, including rs17465637, were shown to be associated with coronary artery disease (CAD) and myocardial infarction (MI) in a genome-wide association study.
- Support for an association of rs17465637 with MI was obtained in a cohort from Japan and different other samples most of which were exclusively comprised of participants of European ancestry. Unlike these observations and the discovery study, rs17465637 was not found to be associated with CAD and MI in an independent investigation combining different cohorts from Europe.

What does this paper add?
- In an effort to determine the impact of common variation at the MIA3 locus on the risk of MI, a set of nine haplotype-tagging SNPs was examined in a case-control study. Except rs17465637, none of the other haplotype-tagging SNPs were associated with MI.
- Nine common haplotypes (frequency >1%) were established across the MIA3 region. Two of the haplotypes were associated with an increased risk of MI: the frequent (48%) TGACCAAAG haplotype and the rare (2%) CGACCAAAG haplotype.

Conclusions
Following an original genome-wide approach and subsequent studies (1, 8–10), this work was consistent with the association of an individual SNP, rs17465637, with MI and extends prior knowledge by also linking to MI specific haplotypes capturing the majority of risk-related variation at the MIA3 locus.

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References