Lack of Association Between the MEF2A Gene and Myocardial Infarction

Wolfgang Lieb, MD; Björn Mayer, MD; Inke R. König, PhD; Iris Borwitzky, MD; Anika Götz, PhD; Silke Kain, MD; Christian Hengstenberg, MD; Patrick Linsel-Nitschke, MD; Marcus Fischer, MD; Angela Döring, MD; H.-Erich Wichmann, MD; Thomas Meitinger, MD; Reinhold Kreutz, MD; Andreas Ziegler, PhD; Heribert Schunkert, MD; Jeanette Erdmann, PhD

Background—Coronary artery disease (CAD) and myocardial infarction (MI) are caused in part by genetic factors. Recently, the MEF2A gene was linked to MI/CAD in a single pedigree with autosomal-dominant pattern of inheritance. In addition, genetic variants within the gene have been associated with MI in case-control settings, producing inconsistent results.

Methods and Results—The MEF2A gene was sequenced in MI patients from 23 MI families (≥5 affected members per family), but no mutation was identified in any of these extended families. Moreover, the Pro279Leu variant in exon 7 was analyzed in 1181 unrelated MI patients with a positive family history for MI/CAD, in 533 patients with sporadic MI, and in 2 control populations (n=1021 and n=1055), showing no evidence for association with MI/CAD. In addition, a (CAG)n repeat in exon 11 was genotyped in 543 sporadic MI patients and in 1190 controls without evidence for association with MI. Finally, analyzing 11 single-nucleotide polymorphisms from the GeneChip Mapping 500K Array, genotyped in 1644 controls and 753 cases, failed to provide evidence for association (region-wide \( P=0.23 \)).

Conclusions—Studying independent samples of >1700 MI patients, 2 large control populations, and multiple families with apparently mendelian inheritance of the disease, we found no evidence for any linkage or association signal in the MEF2A gene. (Circulation. 2008;117:185-191.)

Key Words: coronary disease ■ epidemiology ■ genetics ■ myocardial infarction

The pathogenesis of coronary artery disease (CAD) and myocardial infarction (MI) is influenced by complex interactions of environmental and genetic factors. Genetic epidemiological approaches, including genome-wide linkage and molecular association studies, identified several chromosomal regions and polymorphisms related to MI and/or CAD. However, independent validations and mechanistic explanations of the underlying functional basis for many of these findings are still under investigation.

Clinical Perspective p 191

In addition to these studies, families with mutations in genes affecting classic cardiovascular risk factors such as lipid levels leading to abnormal lipid levels and therefore promoting the development of CAD have been described. Recently, Wang and coworkers reported an exceptional CAD family displaying an autosomal-dominant pattern of inheritance. Interestingly, this family is the first to suggest that MI or CAD may be inherited in a mendelian fashion regardless of classic risk factors. The family provided significant evidence of linkage to chromosome 15q26. Subsequently, the MEF2A gene, encoding the myocyte enhancer factor-2A, a transcription factor with high expression in vascular endothelium, was sequenced, and a 21-bp deletion was identified in all living affected family members but was absent in 119 controls with normal angiograms. Functional studies revealed that this deletion blocks the nuclear localization of the MEF2A protein and suppresses MEF2A-mediated transcription activation. These studies lead to the conclusion that this genetic variant is causative for MI/CAD in this particular family. The same group identified genetic variants in the MEF2A gene in 4 of 207 CAD/MI patients (1.9%), in part without a positive family history for CAD, suggesting that MEF2A may also play a role in the pathogenesis of MI/CAD in nonfamilial (sporadic) cases. The role of MEF2A was subsequently studied in a few small
molecular genetic association studies on sporadic MI patients, producing inconsistent results.12–15 Thus far, no families with autosomal-dominant inheritance of MI were available for genetic investigations, so the MEF2A gene was never analyzed in the specific context that initially allowed the identification of the genetic variant. To further clarify the role of MEF2A, we performed a comprehensive analysis in both familial and sporadic MI cases and in exceptional families with up to 22 affected members with MI.16

Methods

We sequenced the MEF2A gene in representative members of extended MI families with ≥5 affected family members. In addition, 2 previously associated genetic variants, P279L in exon 7 and (CAG)n repeat in exon 11, were investigated for association with MI using 2 large populations of patients with or without a positive family history for MI/CAD, respectively, and 2 control populations. Finally, we analyzed 11 single-nucleotide polymorphisms (SNPs), comprehensively covering the MEF2A gene from a large genome-wide association study conducted in 753 MI patients and 1644 controls.

MI Patients

Patients With Familial MI (German MI Family Study)

MI families were ascertained through index patients at 13 cardiac rehabilitation centers throughout Germany. All index patients had suffered an MI before 60 years of age.17 If at least 1 sibling presented with MI or severe CAD (defined as percutaneous coronary intervention or coronary artery bypass grafting) before 70 years of age, the nuclear family (index patient, available parents, and all affected and unaffected siblings) was contacted and invited to participate in the study. All study participants answered a standardized questionnaire about medical history, presence of coronary risk factors, clinical events, medication, anthropometric data, and socioeconomic background. This information was validated by retrospective analyses of medical records. Additionally, all patients underwent a medical examination during a visit scheduled at their primary care physician’s office.17 For the present study, 1181 unrelated MI patients with a positive family history for MI/CAD were genotyped for the P279L polymorphism.

Extended MI Families

As part of the German MI Family Study, 23 extended MI families were identified.16 Families were classified as extended MI families if they had at least 3 living MI siblings (index patient plus 2 affected siblings) and at least 2 additional second- or third-degree affected relatives. As a result, in addition to the index patient, these families included on average 3 first-degree affected relatives (range, 2 to 6), 2 second-degree affected relatives (range, 0 to 7), and 2 third-degree affected relatives (range, 0 to 11). Linkage analyses were carried out using a modified Weber 9 screening set with 402 markers. In our set, there was only 1 marker (D15S966) within the locus at 15q26 (markers D15S1014, D15S212, D15S120, D15S87) described by Wang et al.15 Because this marker was not informative in most of our families, we could not exclude linkage to this chromosomal region in our families. We therefore sequenced the MEF2A gene in representative members of all 23 extended families.

Patients With Sporadic (Nonfamilial) MI (Cooperative Research in the Region of Augsburg Heart Study)

A total of 609 patients suffering premature MI before 60 years of age were identified through the Augsburg Monitoring of Trends and Determinants in Cardiovascular Disease (MONICA) MI register,18 which is now continued in the framework of the Cooperative Research in the Region of Augsburg (KORA) study. The diagnosis of MI was established according to the MONICA diagnostic criteria. MI patients were studied by physical examination, blood testing, echocardiography, ECG, and a standardized interview that included medical history, physical activity, medication, and personal habits. Resting blood pressure was taken according to MONICA guidelines using the random-zero method and standard mercury sphygmomanometers after subjects had been resting in a seated position. For the present study, the P279L SNP was genotyped in 533 individuals, and the (CAG)n repeat was genotyped in 543 MI patients.

Control Populations

First Control Population (Married-In Spouses From the German MI Family Study)

Healthy married-in spouses served as a control group for the MI patients with a positive family history of MI. For the present study, 1021 controls were genotyped for the P279L polymorphism.

Second Control Population (Population-Based; MONICA/Cooperative Research in the Region of Augsburg Survey S3)

The controls for the sporadic MI cases came from the same geographical area (Augsburg, Bavaria, Germany) and participated in the echocardiographic substudy (total n=1674) of the MONICA/KORA survey S3 (1994–1995),19 which is now continued in the framework of KORA.20 S3 represents a gender- and age-stratified random sample of all German residents of the Augsburg area and consists of individuals 25 to 74 years of age, with ~500 participants for each 10-year increment. The population was studied by the same protocol as the sporadic MI patients. A total of 34 individuals with MI were excluded. For the present study, the P279L SNP was genotyped in 1055 individuals, and the (CAG)n repeat was genotyped in 1190 individuals.

Sequencing of the MEF2A Gene in Extended MI Families

Sequencing of polymerase chain reaction (PCR) products was performed on both strands by a commercial sequencing service (Geneart, Regensburg, Germany). Primer sequences can be obtained from the authors on request. From each extended family, 1 MI patient with a low PROCAM risk score was chosen for sequencing of the MEF2A gene. The PROCAM score estimates the risk for an acute coronary event (fatal or nonfatal myocardial infarction or acute coronary death) within 10 years based on results from the German PROCAM Münster Heart Study.21 By choosing MI patients with low PROCAM scores, we aimed to focus on patients with a low MI risk based on traditional risk factors and thus probably a high genetic susceptibility for MI.

Genotyping the P279L Polymorphism in Exon 7 and the (CAG)n Repeat in Exon 11

The Pro279Leu polymorphism was genotyped with a 5′-exonuclease activity (TaqMan) assay on an HT7900 (Applied Biosystems, Darmstadt, Germany). The SNP assay was ordered from Applied Biosystems as Custom TaqMan SNP genotyping assay. Probes were labeled with the fluorophores FAM or VIC. Genotyping was done on 384-well plates prepared with the GENESIS Freedom pipetting robot from TECAN (Crailsheim, Germany). The Universal PCR Master Mix from Applied Biosystems was used in a 5-μL total reaction volume with 10 ng DNA per reaction. Allelic discrimination was measured automatically on the ABI Prism HT7900 (Applied Biosystems) using the Sequence Detection Systems 2.1 software (auto callers confidence level, 95%).

Genetic determination of the (CAG)n repeat in exon 11 (rs3138597) was performed by amplification of genomic DNA with primers MEF-2A-F (5′-ATG AGC ATC AAG TCC GAA CC-3′) and MEF-2A-R (5′-AGA GCT GCC CAG ACT GCC CAC-3′) by PCR as previously described.22 In brief, the forward primer was labeled with (γ-32P)ATP by T4 polynucleotide kinase. PCR products were processed on PTC-100 Thermal Controllers (MJ Research, Watertown, Mass) according to the following protocol: initial denaturation at 94°C for 3 minutes, followed by 30 cycles of denaturation at 94°C for 15 seconds, annealing for 30 seconds with temperatures
between 61°C and 55°C using a touchdown protocol, extension periods at 72°C for 2 minutes, and a final extension step for 10 minutes. Subsequently, amplicons were analyzed by autoradiography after polyacrylamide gel electrophoresis. Twenty percent of all genotypes were repeated in independent PCR reactions to check for consistency and to ensure intraplate and interplate genotype quality control. No genotyping discrepancies were detected between the repeated samples.

**Genotyping SNPs Covering the MEF2A Gene From the GeneChip Mapping 500K Array**

A genome-wide association study was performed on 753 MI patients from the German MI Family Study and 1644 controls from the MONICA/KORA Survey S3 who participated in the follow-up examination F3 (2004–2005) (KORA 500K Study) using the GeneChip Mapping 500K Array from Affymetrix. The calling algorithm BRLMM was used to determine genotypes. For the present work, we analyzed SNPs covering the MEF2A gene for association with MI. Eleven SNPs covering the MEF2A gene were selected. A call rate (the percentage of successfully genotyped individuals for a given SNP) >97%, a minor allele frequency ≥0.01, and values of \( P > 0.001 \) for test of deviation from Hardy-Weinberg equilibrium were used as quality criteria. Two of these 11 SNPs (RS2290044, RS325410) that initially did not fulfill the quality criteria have been re-genotyped using 5′-exonuclease activity (TaqMan) assays.

All studies (German MI Family Study, KORA Heart Study, MONICA/KORA survey) were approved by local institutional review committees. All subjects gave written informed consent, and every attempt was made to ensure the anonymity of the participants.

**Statistical Analysis**

To determine whether the investigated genotypes deviated from Hardy-Weinberg equilibrium, actual and predicted genotype frequencies were compared by a \( \chi^2 \) goodness-of-fit test. Except for the P279L SNP, differences in genotype frequencies between MI cases and controls were tested with the Cochran-Armitage trend test. To account for the multiple testing of 11 SNPs covering the MEF2A gene, the resulting nominal probability values were adjusted according to the Sidak-Holm procedure. Associations with adjusted values of \( P \leq 0.05 \) were regarded as significant. Because the single SNPs are tightly linked, we also calculated an adjusted overall probability value for the 11 SNPs using a permutation procedure by Becker and Knapp. Because of the low number of individuals carrying the rare allele, genotype frequencies for the P279L polymorphism were compared using Fisher’s exact test. Odds ratios and 95% CIs are reported.

The authors had full access to and take responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

### Results

The baseline characteristics of all study populations are shown in Table 1.

#### Sequencing of the MEF2A Gene in Patients From Extended MI Families

All exons of the MEF2A gene with flanking intronic boundaries and the 5′ untranslated region and 3′ untranslated region were sequenced in 1 representative MI patient per extended family (n = 23). No mutation in the MEF2A gene was found in any of these MI patients. Accordingly, the 21-bp deletion in exon 11 described by Wang et al. [10] was not observed in any of the 23 representative MI patients.

Several polymorphisms in introns 1, 8, 9, and 11 and in the 3′ untranslated region and 1 synonymous point mutation in exon 10 were identified (Table 2).

#### Evaluation of Defined MEF2A Gene Variants in Patients With Familial and Sporadic MI and in Controls

The Pro279LLeu polymorphism was genotyped in 2 independent MI patient populations and in 2 control groups (Table 3). The genotype frequencies were not different between sporadic MI patients and population-based controls (OR for PL versus PP, 0.66; 95% CI, 0.01 to 8.23; \( P = 1.00 \)) or between MI cases with a positive family history for MI and controls (OR for PL versus PP, 0.86; 95% CI, 0.12 to 6.47; \( P = 1.00 \)).
The (CAG)n repeat in exon 11 was genotyped in 543 patients with sporadic (nonfamilial) MI and in 1190 population-based controls (Table 4). The frequencies of the different (CAG)n alleles were similar in MI patients and controls.

**Evaluation of SNPs Covering the MEF2A Gene From the GeneChip Mapping 500K Array**

A total of 11 SNPs within the MEF2A gene fulfilled our quality criteria (Table 5). The linkage disequilibrium structure of these SNPs is demonstrated in the Figure. After adjustment for multiple testing, none of the SNPs displayed evidence for association (Table 5). Moreover, the region-wide analysis of all 11 SNPs in the MEF2A gene displays no evidence for association ($P = 0.23$).

Power analyses revealed that we had a power of 73.7% in the sporadic sample and a power of 88.2% in our familial sample to detect effects similar to those described in the Spanish MI population (assuming the same genotype frequencies of 0.8% in controls and 2.3% in cases, as well as a 1-sided Pearson $\chi^2$ test at $\alpha=0.05$). Within our extended MI families, we had a power of 80% to detect at least 1 mutation in the MEF2A gene, which occurs with a frequency of 3.6% in comparable families.

**Discussion**

The present study on large independent samples of familial and sporadic MI patients displayed no evidence that either the Pro279Leu variant in exon 7 or the (CAG)n repeat in exon 11 of the MEF2A gene is associated with MI. Furthermore, no mutations in the MEF2A gene were found in any of the 23 representative patients from extended MI families with affected family members. Finally, analyzing SNPs covering the MEF2A gene from the GeneChip Mapping 500K Array genotyped in 753 MI patients and 1644 controls revealed no evidence for association.

The research on the role of genetic variants within the MEF2A gene for the pathogenesis of MI/CAD has been stimulated by Wang et al., who described a 21-bp deletion as the first disease-causing gene mutation for familial MI/CAD, and by the work of others in the field.

### Table 2. Genetic Variants in the MEF2A Gene Found by Sequencing of 23 MI Patients (1 per Family) From Families With an Autosomal-Dominant Pattern of Inheritance (Extended MI Families Within the German MI Family Study)

<table>
<thead>
<tr>
<th>rs No.</th>
<th>Region</th>
<th>Contig Position</th>
<th>Sequence Around SNP</th>
<th>Protein Position</th>
</tr>
</thead>
<tbody>
<tr>
<td>New Intron 1 1610853</td>
<td>GGTGCTAAACTAATTTACATTCACA(G/C)</td>
<td>CAACATGCTGAAATATTTCCCTTTG</td>
<td></td>
<td></td>
</tr>
<tr>
<td>New Intron 1 1610900</td>
<td>CTTGCTCTGACCTCCAAACACT(C/A)</td>
<td>TTTTTTTTTTTTTGGGACATT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>rs34131461 Intron 8 1693339</td>
<td>AGACAGCTGATGTCACAAATAGT(</td>
<td>T/C)</td>
<td>TTTTCTAAAGAAATTTTTGTTG</td>
<td></td>
</tr>
<tr>
<td>rs3730281 Intron 9 1693523</td>
<td>TTCTAACGTTGTGTTATCTACCAAT(G/A)</td>
<td>TTTTCTTTTTTACAAATAATTTTT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>rs325409 Intron 9 1696685</td>
<td>ATCATCACTGGCTTCAGAATATACAT(T/G)</td>
<td>TCTATGAAACATGGAATATGCTCA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>rs325408 Exon 10 1696787</td>
<td>TTTCCTTTTTTTGATCTACAGAA(T/C)</td>
<td>ACCGACAGGATCATATTTCTCAAG</td>
<td></td>
<td></td>
</tr>
<tr>
<td>rs325403 Intron 11 1700866</td>
<td>CTTGCTCTGTCGACCACTACACT(CT/G)</td>
<td>CATATTACTACCTGCGATGGCCAGCTTT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>rs3138597 Exon 11 1702561</td>
<td>GGATCGTATGACCCCATCGGCTC(G/C)</td>
<td>GCCGCCGCCACCCCGACAGCCCAGC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>rs10626004 3’UTR 1702978</td>
<td>TATATGATGTGGAAGGTGT</td>
<td>GTGTGTTACATACAA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>rs897074 3’UTR 1704576</td>
<td>GCCGGGAGAGAACATCTTTAGGTTGTC(T/C)</td>
<td>GCTTCTCTGGAGACTCTCCGATT</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Table 3. Genotype Frequencies of the P279L Polymorphism in Patients With Familial and Sporadic MI and Controls

<table>
<thead>
<tr>
<th>Genotype</th>
<th>German MI Family Study, n (%)</th>
<th>KORA Heart Study, Patients With Sporadic MI, n (%)</th>
<th>MONICA/KORA Echocardiographic Substudy, Population-Based Controls, n (%)</th>
<th>$P^*$</th>
</tr>
</thead>
<tbody>
<tr>
<td>279PP</td>
<td>1178 (99.7)</td>
<td>532 (99.8)</td>
<td>1052 (99.7)</td>
<td>1.00</td>
</tr>
<tr>
<td>279PL</td>
<td>3 (0.3)</td>
<td>1 (0.2)</td>
<td>3 (0.3)</td>
<td>1.00</td>
</tr>
<tr>
<td>279LL</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

*Two-sided probability value from Fisher’s exact test.

188 Circulation January 15, 2008
regardless of classic risk factors. In a large kindred with 13 affected family members, genome-wide linkage analysis revealed a positive linkage signal with a logarithm of the odds score of 4.19 at chromosome 15q26. In the \textit{MEF2A} gene, located within this critical region, a 21-bp deletion was identified in all living affected family members. This variant was absent in 119 controls with normal coronary angiograms.\textsuperscript{10} Subsequently, 3 genetic variants in the \textit{MEF2A} gene (N263S, P279L, and G283D) were found in 4 of 207 cases, 1189 controls\textsuperscript{14}. In the present study, by contrast, no gene could even play a significant role in the pathogenesis of MI/CAD in nonfamilial (sporadic) cases.\textsuperscript{11} In accordance with these results, the P279L variant also was associated with MI/CAD in nonfamilial (sporadic) cases.\textsuperscript{11} Weng and colleagues found no causative MI mutation in 300 CAD cases, and Horan and associates failed to detect the 21-bp deletion described by Wang et al\textsuperscript{10} in 1481 individuals with a positive family history for ischemic heart disease. Similarly, we found no disease-causing mutation in our 23 extended MI families, suggesting that \textit{MEF2A} mutations are responsible for only a relatively small proportion of familial MI cases. By sequencing the \textit{MEF2A} gene in 1 MI patient from each of our 23 extended MI families, we identified several genetic variants within the \textit{MEF2A} gene, in part so far unpublished (Table 2). However, these variants do not seem to be pathogenic because of their intronic localization or because they are not leading to a change in the amino acid sequence.

Comparative results were obtained by Kajimoto and colleagues,\textsuperscript{13} who found several genetic variants but no clearly pathogenic mutation within the \textit{MEF2A} gene in Japanese MI patients by sequencing the gene in 379 MI patients.

\textbf{Study Strengths and Limitations}

Some limitations of this comprehensive search for an association between the \textit{MEF2A} gene and MI should be mentioned. By sequencing the \textit{MEF2A} gene, we identified several genetic variants in introns and 1 synonymous polymorphism. It has recently been reported that synonymous polymorphisms and intronic genetic variants might have functional effects and could be disease causing.\textsuperscript{25,26} Therefore, we cannot entirely rule out that these variants might have a disease-causing effect. Furthermore, although using large study populations, we cannot entirely exclude associations of smaller degree, especially for infrequent variants. However, we had a power of 73.7\% in the sporadic and familial MI populations.

\textbf{Table 4. Alleles of the (CAG)\textit{n} Repeat in Exon 11 (rs3138597) in Patients With Sporadic MI (KORA Heart Study) and Population-Based Controls of the MONICA/KORA Echocardiographic Substudy}

<table>
<thead>
<tr>
<th>Allele</th>
<th>MI patients, n (%)</th>
<th>Controls, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;9</td>
<td>15 (1.4)</td>
<td>26 (1.1)</td>
</tr>
<tr>
<td>9</td>
<td>393 (36.2)</td>
<td>865 (36.3)</td>
</tr>
<tr>
<td>10</td>
<td>164 (15.1)</td>
<td>350 (14.7)</td>
</tr>
<tr>
<td>11</td>
<td>510 (47.0)</td>
<td>1132 (47.6)</td>
</tr>
<tr>
<td>&gt;11</td>
<td>4 (0.3)</td>
<td>7 (0.3)</td>
</tr>
<tr>
<td>(P^*)</td>
<td>&gt;0.80</td>
<td>&gt;0.80</td>
</tr>
</tbody>
</table>

\*Two-sided probability value from Cochran-Armitage trend test.

\textbf{Table 5. SNPs Covering the \textit{MEF2A} Gene From a Genome-Wide Association Scan (GeneChip Mapping 500K Array) of 1644 Controls of the KORA 500K Study and 753 MI Patients of the German MI Family Study}

<table>
<thead>
<tr>
<th>RS ID</th>
<th>Affymetrix ID</th>
<th>BP Pos</th>
<th>Region</th>
<th>Missing, %</th>
<th>MAF, %</th>
<th>(P, \text{HWE})</th>
<th>(P) for Trend*</th>
</tr>
</thead>
<tbody>
<tr>
<td>RS2570934</td>
<td>SNP_A-2069795</td>
<td>97961522</td>
<td>Intron 1</td>
<td>1.04</td>
<td>24.95</td>
<td>0.8303</td>
<td>0.9634</td>
</tr>
<tr>
<td>RS9888651</td>
<td>SNP_A-2209851</td>
<td>98002944</td>
<td>Intron 3</td>
<td>2.90</td>
<td>4.20</td>
<td>0.7967</td>
<td>0.4419</td>
</tr>
<tr>
<td>RS3743180</td>
<td>SNP_A-2083387</td>
<td>98016953</td>
<td>Intron 4</td>
<td>0.04</td>
<td>40.53</td>
<td>0.4993</td>
<td>0.9147</td>
</tr>
<tr>
<td>RS3784450</td>
<td>SNP_A-2184937</td>
<td>98026949</td>
<td>Intron 4</td>
<td>1.59</td>
<td>7.41</td>
<td>0.5572</td>
<td>0.1940</td>
</tr>
<tr>
<td>RS8037206</td>
<td>SNP_A-2128598</td>
<td>98062116</td>
<td>Intron 9</td>
<td>0.20</td>
<td>45.01</td>
<td>0.3328</td>
<td>0.9151</td>
</tr>
<tr>
<td>RS2290446</td>
<td>SNP_A-4205077</td>
<td>98064141</td>
<td>Intron 9</td>
<td>0.89</td>
<td>6.5</td>
<td>0.97869</td>
<td>0.3403</td>
</tr>
<tr>
<td>RS325410</td>
<td>SNP_A-4233948</td>
<td>98064241</td>
<td>Intron 9</td>
<td>0.10</td>
<td>20.25</td>
<td>0.63767</td>
<td>0.2863</td>
</tr>
<tr>
<td>RS325406</td>
<td>SNP_A-2225520</td>
<td>98065263</td>
<td>Intron 10</td>
<td>0</td>
<td>27.16</td>
<td>0.1067</td>
<td>0.1975</td>
</tr>
<tr>
<td>RS325403</td>
<td>SNP_A-2004447</td>
<td>98068538</td>
<td>Intron 11</td>
<td>0</td>
<td>35.98</td>
<td>0.3536</td>
<td>0.9634</td>
</tr>
<tr>
<td>RS253580</td>
<td>SNP_A-2310343</td>
<td>98074141</td>
<td>3’UTR</td>
<td>0.36</td>
<td>42.66</td>
<td>0.07211</td>
<td>0.9634</td>
</tr>
<tr>
<td>RS1808723</td>
<td>SNP_A-1830197</td>
<td>98080351</td>
<td>3’UTR</td>
<td>0.16</td>
<td>36.93</td>
<td>0.2138</td>
<td>0.9634</td>
</tr>
</tbody>
</table>

\(BP\) Pos indicates base pair position; MAF, minor allele frequency; \(P, \text{HWE}\), 2-sided probability value from test for deviation from Hardy-Weinberg equilibrium; and UTR, untranslated region.

\*Two-sided probability value from Cochran-Armitage trend test adjusted for the multiple testing of 11 SNPs.
a power of 88.2% in the familial MI patients to detect similar effects as previously described.14

Conclusion
The present study, the largest to date, revealed no evidence for a significant role of MEF2A mutations in MI/CAD.

Acknowledgment
We gratefully acknowledge the excellent technical assistance of Petra Bruse.

Sources of Funding
This study was supported by the Deutsche Forschungsgemeinschaft (Schu672/9–1, Schu672/10–1, Schu672/12–1, Schu672/14–1), the Federal Ministry of Research (Dr Schunkert, KBF-FKZ 01GB0403), the National Genome Network (01GS0418 to Drs Schunkert, Erdmann, and Hengstenberg; 01GS0416 to Dr Kreutz; 01GR0466 to Drs Ziegler and König), the Ernst- and Berta-Grimmek-Stiftung (Drs Hengstenberg and Schunkert), the Wilhelm-Vaillant-Stiftung (Drs Hengstenberg and Schunkert), the Deutsche Stiftung für Herzforschung (Drs Hengstenberg and Schunkert), and the European Union–sponsored project Cardiogenics (LSH-2005–037593). The KORA research platform was initiated and financed by the GSF–National Research Centre for Environment and Health, which is funded by the German Federal Ministry of Education and Research and of the State of Bavaria. This genetic association study was funded by the German Federal Ministry of Education and Research in the context of the German National Genome Research Network by grants to Drs Wichmann (01GR0464 and 01GS0499) and Meitinger (01GR0103).

Disclosures
None.

References
CLINICAL PERSPECTIVE

After the initial report of a 21-bp deletion in the MEF2A gene as the disease-causing genetic variant in a large family with autosomal-dominant inheritance of coronary artery disease, case-control studies on single genetic variants within the MEF2A gene revealed controversial results. In the present, and thus far the largest, analysis, no evidence was found for a significant association of the MEF2A gene with myocardial infarction. We studied defined genetic variants in 2 large study populations of patients with familial and sporadic myocardial infarction and 2 control populations and also analyzed single-nucleotide polymorphisms from a genome-wide association study comprehensively covering the MEF2A gene. Thus, MEF2A is added to a growing list of candidate genes for complex diseases in which no consistent association with a defined phenotype across various populations could be observed. Therefore, results from molecular genetic association studies have to be interpreted with caution and should not yet be transferred or should be transferred in only a very limited fashion to clinical practice (eg, estimating the individual genetic risk for a complex disease). However, genome-wide association studies analyzing hundreds of thousands of single-nucleotide polymorphisms might offer new opportunities in this regard. Recently, 4 genome-wide association studies for myocardial infarction and coronary artery disease revealed very promising results in that chromosomal regions could be identified that displayed robust association with myocardial infarction and coronary artery disease in various independent populations.


Lack of Association Between the MEF2A Gene and Myocardial Infarction

_Circulation_. 2008;117:185-191; originally published online December 17, 2007;
doi: 10.1161/CIRCULATIONAHA.107.728485

_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2007 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the
World Wide Web at:
http://circ.ahajournals.org/content/117/2/185

Data Supplement (unedited) at:
http://circ.ahajournals.org/content/suppl/2008/01/14/CIRCULATIONAHA.107.728485.DC1

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in _Circulation_ can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to _Circulation_ is online at:
http://circ.ahajournals.org//subscriptions/