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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

Print ISSN: 0009-7322. Online ISSN: 1524-4539

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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.[1–6] However, independent validations and mechanistic explanations of the underlying functional basis for many of these findings are still under investigation.

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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.[7–9] Recently, Wang and coworkers[10] 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.[10] Functional studies revealed that this deletion blocks the nuclear localization of the MEF2A protein and suppresses MEF2A-mediated transcription activation.[10] These studies lead to the conclusion that this genetic variant is causative for MI/CAD in this particular family.[10] 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 also may play a role in the pathogenesis of MI/CAD in nonfamilial (sporadic) cases.[11] The role of MEF2A was subsequently studied in a few small

Received July 17, 2007; accepted October 26, 2007.

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Circulation **is available at http://circ.ahajournals.org** **DOI: 10.1161/CIRCULATIONAHA.107.728485**

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 15 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.[10] 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 (autocaller 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′-ATC AGC ATC AAG TCC GAA CC-3′) and MEF-2A-R (5′-AGA GCT GCT CAG ACT GTC CAC-3′) by PCR as previously described.[22] In brief, the forward primer was labeled with [γ-^{32}P]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

Table 1. Baseline Characteristics of the MI Patients With a Positive Family History for MI/CAD and Controls (Married-In Spouses), Sporadic MI Patients (No Family History for MI), and Population-Based Controls of the MONICA/KORA Echocardiographic Substudy and 23 MI Patients From Extended MI Families

	German MI Family Study				
	Familial MI Patients (n=1181)	Controls (Married-In Spouses) (n=1021)	MI Patients From Extended MI Families* (n=23)	KORA Heart Study, Sporadic MI Patients (n=579†)	MONICA/KORA Echocardiographic Substudy, Population-Based Controls (n=1465†)
Men, %	77.1	36.1	87.0	87.4	49.4
Age, y	58.3±8.7	56.9±9.8	61.5±9.2	56.3±7.3	50.5±13.8
BMI, kg/m^2	27.5±3.6	26.7±4.2	27.6±3.7	28.4±3.7	26.7±4.2
SBP, mm Hg	137.5±19.1	134.6±17.9	151.0±19.7	132.2±17.1	133.7±20.0
DBP, mm Hg	82.3±10.1	82.3±9.9	87.0±11.0	84.2±10.4	80.4±11.6
Total cholesterol, mg/dL	226.3±46.6	236.9±44.2	236.6±43.0	238.6±47.2	233.3±43.9
HDL cholesterol, mg/dL	49.2±12.8	60.0±15.5	47.6±10.5	50.2±15.4	54.3±16.7
LDL cholesterol, mg/dL	150.7±43.7	146.6±36.0	160.0±36.2	141.3±40.5	143.3±42.9
Smoking status, %	71.5	50.2	73.9	77.8	57.1
Diabetes, %	15.8	6.1	8.6	15.4	4.7

BMI indicates body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HDL, high-density lipoprotein; and LDL, low-density lipoprotein. Data are mean±SD when appropriate.

*Each patient represents a family with ≥5 affected members (on average, 8.0 affected members per family) and an apparently autosomal-dominant mode of inheritance.

†Individuals genotyped for the P279L polymorphism in exon 7, the (CAG)n repeat in exon 11, or both.

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.[22] Ten 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 (RS2290446, RS325410) that initially did not fulfill the quality criteria have been regenotyped using 5′-exonuclease activity (TaqMan) assays.

All studies (German MI Family Study, KORA Heart Study, MONICA/KORA study) 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 χ^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 Šidak-Holm procedure. Associations with adjusted values of $P\leq0.05$ 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.[23] 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 Pro279Leu 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; $P=1.00$).

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)

rs No.	Region	Contig Position	Sequence Around SNP	Protein Position
New	Intron 1	1610853	GTGGCTAAACTAATTTACATTCTCA[G/C] CAACAATGTGTAAATATTCCCCTTG	
New	Intron 1	1610900	CTTGCTCTGTAACCTCACAAACATC[T/A] TTTTTTTTTTTTTTTTGGGACATT	
rs34131461	Intron 8	1693339	AGACAGCTGCTAGTGTCCAAATATG[-/T] TTTTTCTAAAGAAATATTTTGTTTG	
rs3730281	Intron 9	1693523	TCTTACGTGTTGTTATCTAACCAAT[G/A] TTCCCTTTGTTACACAAATTTTTTT	
rs325409	Intron 9	1696685	ATCATCAGTGCTTCAGAAAATGACA[T/G] TCATATGAAACTGTGAAAAATGTCA	
rs325408	Exon 10	1696787	TTTTCTCTTTTTTGATCTCACAGAA[T/C] ACCCAGAGGATCAGTAGTTCTCAAG	p.N297N
rs325403	Intron 11	1700866	CATCTTTACTCCTGGCCTACACACT[C/G] TCTTTTCCTATCAGTGACAGCCTTT	
rs3138597	Exon 11	1702561	GGATCGTATGACCCCATCGGGCTTC[(CAG)n] CCGCCGCCACCACCGCAGCCCCAGC	p.420-430 (11) p.420-429 (10) p.420-428 (9)
rs10628004	3′UTR	1702978	TATATGTATGTGGGTGTGAGTGTGT[-/GTGT] ATGTGTGGGTGTGTGTTACATACAC	
rs897074	3′UTR	1704576	GCGGGGAGAAACACTCTTAGGGTGC[C/T] GGTCCTTGGCATGACTCTTGCCATT	

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 χ^2 test at $\alpha=0.05$[14]). 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 ≥5 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,[10] who described a 21-bp deletion as the first disease-causing gene mutation for familial MI/CAD,

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

	German MI Family Study, n (%)					
Genotype	Patients With Familial MI	Controls (Married-In Spouses)	*P**	KORA Heart Study, Patients With Sporadic MI, n (%)	MONICA/KORA Echocardiographic Substudy, Population-Based Controls, n (%)	*P**
279PP	1178 (99.7)	1018 (99.7)	1.00	532 (99.8)	1052 (99.7)	1.00
279PL	3 (0.3)	3 (0.3)		1 (0.2)	3 (0.3)	
279LL	0	0		0	0	

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

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

	Allele					
	<9	9	10	11	>11	*P**
MI patients, n (%)	15 (1.4)	393 (36.2)	164 (15.1)	510 (47.0)	4 (0.3)	0.80
Controls, n (%)	26 (1.1)	865 (36.3)	350 (14.7)	1132 (47.6)	7 (0.3)	

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

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 *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.[10] Subsequently, 3 genetic variants in the *MEF2A* gene (N263S, P279L, and G283D) were found in 4 of 207 independent patients (1.9%) with MI/CAD (in part without a positive family history for CAD), suggesting that the *MEF2A* gene could even play a significant role in the pathogenesis of MI/CAD in nonfamilial (sporadic) cases.[11] In accordance with these results, the P279L variant also was associated with the prevalence of MI in a Spanish case-control study (483 cases, 1189 controls[14]). In the present study, by contrast, no association of this genetic variant with MI was detected in 2 large samples of patients with sporadic and familial MI, respectively. A (CAG)n repeat in exon 11 displayed some evidence for association with CAD in a small Chinese case-control study, the (CAG)(9)-allele being overrepresented in the cases.[15] However, this variant was not associated with MI in our much lager sample of patients with nonfamilial MI and displayed no association with MI in the above-mentioned Spanish MI population.[14]

Our findings are in line with the results obtained by Weng et al[12] and Horan et al.[24] 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[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 *MEF2A* mutations are responsible for only a relatively small proportion of familial MI cases. By sequencing the *MEF2A* gene in 1 MI patient from each of our 23 extended MI families, we identified several genetic variants within the *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.

Comparable results were obtained by Kajimoto and colleagues,[13] who found several genetic variants but no clearly pathogenic mutation within the *MEF2A* gene in Japanese MI patients by sequencing the gene in 379 MI patients.

Study Strengths and Limitations

Some limitations of this comprehensive search for an association between the *MEF2A* gene and MI should be mentioned. By sequencing the *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.[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

Table 5. SNPs Covering the *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

RS ID	Affymetrix ID	BP Pos	Region	Missing, %	MAF, %	*P*, HWE	*P* for Trend*
RS2570934	SNP_A-2069795	97961522	Intron 1	1.04	24.95	0.8303	0.9634
RS9888651	SNP_A-2209851	98002944	Intron 3	2.90	4.20	0.7967	0.4419
RS3743180	SNP_A-2083837	98016953	Intron 4	0.04	40.53	0.4993	0.9147
RS3784450	SNP_A-2184937	98026949	Intron 4	1.59	7.41	0.5572	0.1940
RS8037206	SNP_A-2128598	98062116	Intron 9	0.20	45.01	0.3328	0.9151
RS2290446	SNP_A-4205077	98064141	Intron 9	0.89	6.5	0.97869	0.3403
RS325410	SNP_A-4233948	98064241	Intron 9	0.10	20.25	0.63767	0.2863
RS325406	SNP_A-2225520	98065263	Intron 10	0	27.16	0.1067	0.1975
RS325403	SNP_A-2004447	98068538	Intron 11	0	35.98	0.3536	0.9634
RS325380	SNP_A-2310343	98074141	3′UTR	0.36	42.66	0.07211	0.9634
RS1808723	SNP_A-1830197	98080351	3′UTR	0.16	36.93	0.2138	0.9634

BP Pos indicates base pair position; MAF, minor allele frequency; *P*, 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.

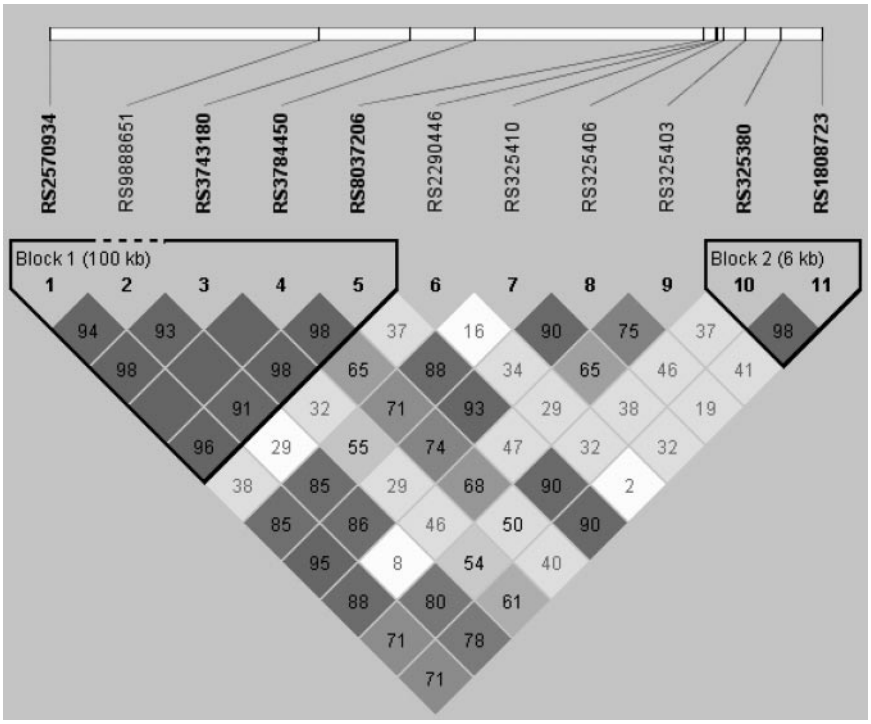

Figure. Linkage disequilibrium structure of 11 SNPs covering the *MEF2A* gene (data from a genome-wide association scan using the GeneChip Mapping 500K Array), including 1644 controls of the KORA 500K Study and 753 cases of the German MI Family Study with pairwise D′ between SNPs.

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 01GB9403), 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-Grimmke-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.

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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.