Coronary Heart Disease

Distinct Heritable Patterns of Angiographic Coronary Artery Disease in Families With Myocardial Infarction

Marcus Fischer, MD; Ulrich Broeckel, MD; Stephan Holmer, MD; Andrea Baessler, MD; Christian Hengstenberg, MD; Bjoern Mayer, MD; Jeanette Erdmann, PhD; Gernot Klein, MD; Guenter Riegger, MD; Howard J. Jacob, PhD; Heribert Schunkert, MD

Background—Coronary artery disease (CAD) and myocardial infarction (MI) are significantly determined by genetic background. Whether distinct angiographic features of CAD are affected by inherited factors has never been investigated. Thus, we analyzed comprehensively the extent to which various aspects of CAD, including disease severity, distribution of lesions, presence of coronary calcification, morphology of stenoses, and anatomic characteristics, are under genetic control.

Methods and Results—We retrospectively studied the coronary angiograms of 882 siblings with CAD from 401 families. These families were ascertained through index patients defined by MI before the age of 60 years and at least 1 sibling with MI or coronary revascularization procedures. Heritability calculations were performed with variance-component analysis. Additionally, recurrence risks to siblings were analyzed. Traditional cardiovascular risk factors and age at the first coronary event displayed significant heritable components. After adjustment for age and sex, significant heritabilities were identified for proximal stenoses, in particular, left main CAD ($h^2=0.49 \pm 0.12; P=0.01$), coronary calcification ($h^2=0.51 \pm 0.17; P=0.001$), and ectatic coronary lesions ($h^2=0.52 \pm 0.07; P=0.001$). In contrast, no heritability was found for distal disease ($h^2=0.05 \pm 0.19; NS$), the pattern of coronary arterial blood supply, or the number of diseased vessels. Calculation of recurrence risks in siblings largely confirmed the heritability estimates.

Conclusions—Distinct morphological characteristics associated with CAD show different degrees of heritability. Notably, the most hazardous localizations, like left main or proximal disease, display a high heritability. In contrast, some features of coronary morphology, such as distal disease, do not appear to be markedly influenced by heritable factors.

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

The manifestation of coronary artery disease (CAD) is influenced by a complex interplay of numerous environmental and genetic factors. With regard to the genetic contribution, a positive family history for myocardial infarction (MI) is considered to be a strong cardiovascular risk factor. Despite extensive molecular genetic investigations, neither CAD nor MI has been reproducibly associated with specific genetic variants. This shortcoming has largely been explained by the complex pattern of the disease, suggesting different disease mechanisms. A more comprehensive clinical characterization could give additional discrimination of the disease phenotype and thus, narrow the heterogeneity. In general, invasive cardiologists judge the extent (number of vessels involved, location of lesions), the severity (percentage of diameter narrowing, length of lesions), and the morphology of coronary lesions of CAD to characterize each patient’s angiographic pattern of CAD. Accordingly, coronary angiography can provide usable heritable surrogates of CAD. Until now, only a few case reports on monozygotic or dizygotic twins have investigated the hereditary aspects of coronary morphology, but even these have produced inconsistent results. Therefore, a large angiographic database for patients with familial MI was established to investigate the hypothesis that specific coronary morphologies have a genetic component. Detailed heritable disease patterns could enhance clinical risk characterization and offer new opportunities for clinical follow-up investigations in relatives of affected patients.

Methods

Ascertainment Strategy

CAD families were ascertained through index patients at 15 cardiac rehabilitation centers distributed throughout Germany. All index...
patients had suffered from an MI before 60 years of age. If at least 1 sibling presented with MI or severe CAD before 70 years of age, defined by percutaneous coronary intervention or coronary artery bypass grafting, the nuclear family (index patient, available parents, and all affected and unaffected siblings) was contacted and invited to participate in the study. In total, 401 families had coronary angiograms available for retrospective review in at least 2 siblings (882 individuals). Angiograms of index cases and at least 1 sibling were available for 309 families. In the remaining 92 families, 2 or more siblings with a coronary angiogram were identified apart from the index patient. The experimental design and technical operations have been defined in advance. The Ethics Committees of the University of Regensburg and the Medical College of Wisconsin approved the study protocol, and all participants gave written, informed consent.

Subjects and Phenotyping

The analyses included 369 pedigrees with 2 affected siblings and 32 pedigrees with >2 affected siblings (whites of northern European origin). From all study participants, answers to a standardized questionnaire were obtained by specially trained telephone interviewers; questions related to 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 from hospital stays and primary physicians. Additionally, all patients underwent a medical examination during a visit scheduled at their primary care physician’s office. If a relative had suffered from an MI or had undergone a coronary revascularization procedure, the respective information was verified in hospital discharge summaries, which were independently reviewed by 2 investigators. The diagnosis of MI was documented as described previously.14

Risk Factors

All cardiovascular risk factors were ascertained at the time of the first interview in a standardized fashion. We defined hypertension as a blood pressure >140/90 mm Hg. Hypercholesterolemia was defined as an LDL cholesterol value >130 mg/dl, or by the use of lipid-lowering agents. Current or former cigarette smoking (cessation at time of the index event) was used to define smoking status. Diabetes mellitus was defined by the use of antidiabetic medication or by elevated glycosylated hemoglobin (≥6.5%). All biochemical measurements were carried out in a single laboratory as previously reported.14

Angiographic Evaluation

Coronary angiograms were scored systematically and in random order by a single, experienced, interventional cardiologist. Much effort was expended to ensure the objectivity of evaluation of the angiograms. For this purpose, the reader was blinded with regard to family structure, and angiograms of family members were read on different days separated by the reading of other angiograms. For the evaluation of angiographic phenotypes, we categorized the coronary vasculature into the right and left coronary artery, as well as 18 coronary segments according to the classification of the Coronary Artery Surgery Study.15 On a standardized evaluation form, each of these coronary segments was characterized for several anatomic and morphological criteria: (1) The degree of stenosis was derived by relation of the stenotic segment to the diameter of the nearest reference segment, and the percent diameter stenosis for each lesion was graded on a scale of 0 to 4, where 0=no stenosis, 1=moderate stenosis [<50%], 2=severe stenosis [50% to 69%], 3=total occlusion. A lesion compromising the lumen by >50% was considered to represent a significant stenosis. (2) Left main CAD was defined as a lesion proximal to the bifurcation, including ostial stenosis. (3) “Diffuse CAD” was defined in cases where more than two thirds of the left or right coronary vessel tree was affected by wall irregularities or stenoses. (4) The morphology of stenoses was characterized in terms of length of the stenotic area (“long”=stenosis length >10 mm, “short”=stenosis length ≤10 mm) and in terms of ectatic (aneurysmal) coronary lesions (defined by a vessel diameter >125% of the healthy reference vessel). (5) A semiquantitative scoring system was used to grade the presence of calcifications of the coronary vessels (0=no calcification, 1=minimal calcifications [visible in 1 or 2 angulations], 2=moderate calcifications [visible in all angulations], 3=severe [≥1 cm] or circular calcifications). The calcification phenotype was analyzed as a dichotomous variable: yes (score 1 to 3) or no (score 0).

Coronary blood supply was divided into right-dominant, balanced, and left-dominant.16 Morphological CAD was classified as 1-, 2- or 3-vessel disease. Furthermore, because a number of “jeopardy scores” have been formerly used to quantify plaque burden and predict patient-based clinical outcomes, the data on grades of stenosis in individual segments for each patient were also used to compute a score for the extent of CAD. (Modified Gensini-index; segments were weighted by a value from 0.5 to 5.0. Percent diameter stenosis is weighted from 1 to 16. The product of these 2 weights is the total weight for each arterial segment. The severity score is the sum of all total weights.)13 With this modified Gensini index, a heavier weight was assigned to the more severe luminal narrowings.

Statistical Analysis

Because the sampling of multiple individuals from the same family does create within-family correlation, the comparison of clinical and angiographic characteristics between index cases and their siblings (1 or more) was analyzed by generalized estimating equations, which are an extension of the generalized linear models methodology applied to correlated data.17

Heritability estimates (h²) were obtained by variance-component methodology as implemented in the SOLAR (version 2.1.2) package.18 This approach has been expanded to allow for pedigrees of arbitrary size and complexity as well as for dichotomous traits by assuming that an individual belongs to a specific affected status if an underlying genetically determined risk (ie, liability) exceeds a certain threshold.19 The latent liability is assumed to have an underlying multivariate normal distribution. In addition to the variance components, covariate effects and environmental factors were included in the model: In all of the analyses, age and sex were included as covariates; additional covariates included the cardiovascular risk factors body mass index, mean arterial blood pressure, LDL-HDL ratio, diabetes, and cigarette smoking. Both variance components and covariate effects were estimated simultaneously by maximum-likelihood techniques. The null hypothesis of no genetic effect (h²=0) on phenotype was tested with a likelihood-ratio test by comparing the likelihood of a restricted model in which the parameter h² was constrained to a value of 0 with that for a general model in which the same parameter was estimated. Because our samples were ascertained via index patients, we conditioned the likelihood of a family on the phenotype of the initial proband to account partially for the nonrandom sampling.20

As an additional measure of familial aggregation, we performed logistic regression analyses of selected phenotypes to assess the ratio of sibling risk for affected individuals to sibling risk for unaffected individuals (conditional on the index case’s affected status), adjusted for age and sex.

Because a high degree of correlation between stenoses at different coronary sites was observed (all Spearman’s rho coefficients P<0.001), principal-component factor analysis was performed to determine subsets of clusters of correlated stenoses (“factors”). For the determination of the optimal number of factors, the Kaiser-Guttman rule was used.21 This analysis resulted in 5 noncorrelated factors, which were interpreted on the basis of their factor loadings (correlation between the generated factor and the original trait, Data Supplement Table and Figure 2). Factor loadings with coefficient absolute values >0.25 were considered significant. After excluding subjects with missing information, factor analysis was carried out for 693 individuals. This subset had features similar to those of the entire data set. To estimate the actual values of the factors for individual cases (observations), factor scores were derived and used as quantitative measurements to further estimate the heritability of the significant principal components. Bivariate genetic
### Results

#### Clinical and Angiographic Characteristics

Clinical and angiographic characteristics of index MI cases and their siblings are presented in Tables 1 and 2. As expected, index cases experienced their index event at significantly younger age and were more often male. With the exception of systolic blood pressure, risk factor distribution was very comparable between index patients and their siblings.

Siblings of MI cases presented with a slightly more prevalent of proximal disease was higher in siblings than in index MI cases. With regard to morphological characteristics, no differences between the 2 groups could be observed.

#### Heritability Analysis

Results of the heritability analyses are listed in Table 3. A significant degree of inherited influence on age- and sex-adjusted phenotypic variance could be detected for proximal localizations of stenoses, in particular, stenoses located at the left main coronary artery (h^2=0.49±0.12; p<0.001). In contrast, no heritability was found for distal disease (h^2=0.05±0.19; NS).

Moreover, a high proportion of the variation in coronary calcification was due to inherited effects (left coronary artery: h^2=0.42±0.12; p=0.002; right coronary artery: h^2=0.84±0.12; p=0.0000001). Furthermore, genetic effects markedly influenced the presence of ectatic coronary segments (h^2=0.52±0.07; p=0.001). Finally, age of onset and all cardiovascular risk factors were highly heritable.

With regard to the dichotomous parameter “focal versus diffuse disease,” no consistent genetic contribution could be observed; however, focusing the comparison on the left and the right coronary artery separately, we realized that these severity parameters showed higher heritabilities in the left coronary artery and reached significance. The number of diseased vessels and the length of lesions did not show significant heritable components.

Moreover, a multivariate analysis was carried out to test the contribution of risk factors in addition to age and sex.
TABLE 3. Age- and Sex-Adjusted and Multivariable-Adjusted Estimates of Heritability for Selected CAD Phenotypes and CAD Risk Factors

<table>
<thead>
<tr>
<th>Distribution of CAD</th>
<th>Age- and Sex-Adjusted $h^2 \pm SE$</th>
<th>Proportion of Variance due to Covariates/KL – $R^2$</th>
<th>Multivariable-Adjusted $h^2 \pm SE$</th>
<th>Proportion of Variance due to Covariates/KL – $R^2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-Vessel disease, yes/no</td>
<td>$&lt;0.10$ NS</td>
<td>...</td>
<td>$&lt;0.10$ NS</td>
<td>...</td>
</tr>
<tr>
<td>2-Vessel disease, yes/no</td>
<td>$&lt;0.10$ NS</td>
<td>...</td>
<td>$&lt;0.10$ NS</td>
<td>...</td>
</tr>
<tr>
<td>3-Vessel disease, yes/no</td>
<td>$0.11 \pm 0.10$ NS</td>
<td>0.04</td>
<td>$0.19 \pm 0.12$ 0.06</td>
<td>0.09</td>
</tr>
<tr>
<td>Severity score, modified Gensini</td>
<td>$&lt;0.10$ NS</td>
<td>...</td>
<td>$&lt;0.10$ NS</td>
<td>...</td>
</tr>
<tr>
<td>No. of stenoses, LCA</td>
<td>$0.22 \pm 0.12$ 0.03</td>
<td>0.04</td>
<td>$0.19 \pm 0.12$ 0.06</td>
<td>0.09</td>
</tr>
<tr>
<td>No. of stenoses, proximal</td>
<td>$0.28 \pm 0.10$ 0.003</td>
<td>0.03</td>
<td>$0.22 \pm 0.11$ 0.02</td>
<td>0.05</td>
</tr>
<tr>
<td>No. of stenoses, distal</td>
<td>$&lt;0.10$ NS</td>
<td>...</td>
<td>$&lt;0.10$ NS</td>
<td>...</td>
</tr>
<tr>
<td>LCA diffusely affected, yes/no</td>
<td>$0.25 \pm 0.12$ 0.04</td>
<td>0.05</td>
<td>$0.41 \pm 0.17$ 0.005</td>
<td>0.07</td>
</tr>
<tr>
<td>RCA diffusely affected, yes/no</td>
<td>$&lt;0.10$ NS</td>
<td>...</td>
<td>$&lt;0.10$ NS</td>
<td>...</td>
</tr>
<tr>
<td>Localization of stenoses</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left main disease,* yes/no</td>
<td>$0.49 \pm 0.12$ 0.01</td>
<td>0.03</td>
<td>$0.47 \pm 0.09$ 0.01</td>
<td>0.05</td>
</tr>
<tr>
<td>Proximal disease,† yes/no</td>
<td>$0.32 \pm 0.05$ 0.02</td>
<td>0.02</td>
<td>$0.32 \pm 0.06$ 0.02</td>
<td>0.02</td>
</tr>
<tr>
<td>Distal disease,‡ yes/no</td>
<td>$&lt;0.10$ NS</td>
<td>...</td>
<td>$&lt;0.10$ NS</td>
<td>...</td>
</tr>
<tr>
<td>Bifurcational, yes/no</td>
<td>$0.23 \pm 0.17$ 0.02</td>
<td>0.02</td>
<td>$0.25 \pm 0.21$ 0.02</td>
<td>0.02</td>
</tr>
<tr>
<td>Morphology of stenoses</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Length &gt;10 mm, yes/no</td>
<td>$&lt;0.10$ NS</td>
<td>...</td>
<td>$&lt;0.10$ NS</td>
<td>...</td>
</tr>
<tr>
<td>Ectatic lesions, yes/no</td>
<td>$0.52 \pm 0.07$ 0.001</td>
<td>0.01</td>
<td>$0.54 \pm 0.08$ 0.001</td>
<td>0.01</td>
</tr>
<tr>
<td>Calcification</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LCA or RCA, yes/no</td>
<td>$0.51 \pm 0.17$ 0.001</td>
<td>0.02</td>
<td>$0.51 \pm 0.07$ 0.001</td>
<td>0.02</td>
</tr>
<tr>
<td>LCA, yes/no</td>
<td>$0.42 \pm 0.12$ 0.002</td>
<td>0.02</td>
<td>$0.36 \pm 0.12$ 0.01</td>
<td>0.02</td>
</tr>
<tr>
<td>RCA, yes/no</td>
<td>$0.84 \pm 0.12$ 0.0000001</td>
<td>0.02</td>
<td>$0.81 \pm 0.18$ 0.000005</td>
<td>0.03</td>
</tr>
<tr>
<td>Circulation, right/balanced/left</td>
<td>$&lt;0.10$ NS</td>
<td>...</td>
<td>$&lt;0.10$ NS</td>
<td>...</td>
</tr>
<tr>
<td>Age of onset, y§</td>
<td>$0.55 \pm 0.08$ 0.0000001</td>
<td>0.02</td>
<td>$0.53 \pm 0.08$ 0.0000001</td>
<td>0.06</td>
</tr>
<tr>
<td>Risk factors</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes, yes/no</td>
<td>$0.69 \pm 0.13$ 0.0000001</td>
<td>0.02</td>
<td>$0.81 \pm 0.20$ 0.0000004</td>
<td>0.02</td>
</tr>
<tr>
<td>Systolic BP, mm Hg</td>
<td>$0.24 \pm 0.06$ 0.000001</td>
<td>0.04</td>
<td>$0.19 \pm 0.06$ 0.0008</td>
<td>0.10</td>
</tr>
<tr>
<td>Diastolic BP, mm Hg</td>
<td>$0.23 \pm 0.06$ 0.0001</td>
<td>0.02</td>
<td>$0.18 \pm 0.06$ 0.0009</td>
<td>0.10</td>
</tr>
<tr>
<td>LDL, mg/dL</td>
<td>$0.37 \pm 0.07$ 0.0000001</td>
<td>0.01</td>
<td>$0.47 \pm 0.07$ 0.0000001</td>
<td>0.05</td>
</tr>
<tr>
<td>HDL, mg/dL</td>
<td>$0.49 \pm 0.07$ 0.0000001</td>
<td>0.09</td>
<td>$0.48 \pm 0.07$ 0.0000001</td>
<td>0.14</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>$0.44 \pm 0.07$ 0.0000001</td>
<td>0.01</td>
<td>$0.46 \pm 0.07$ 0.0000001</td>
<td>0.10</td>
</tr>
</tbody>
</table>

See text and footnotes to Tables 1 and 2 for explanation of abbreviations.

*Mainstem stenoses and ostial lesions.
†Stenoses located at the ostia, left mainstem, proximal left anterior descending artery, proximal circumflex artery, and proximal RCA.
‡Distal disease without evidence of proximal disease.
§Age was not considered as a covariate.
| For continuous traits, the proportion of variance due to all covariates and for discrete traits the Kullback-Leibler $R^2$ ($=KL – R^2$, which measures the proportionate reduction in uncertainty due to the inclusion of covariates), are given. This analysis was performed for significant traits only.

Incorporating additional cardiovascular risk factors into the variance-component analysis did not significantly influence the heritability estimates of coronary morphological features (Table 3).

Additionally, age- and sex-adjusted odds ratios and 95% confidence intervals of second siblings’ affected status conditional on the index patients’ affected status for the specific phenotype are shown (Figure 1). These risks largely confirmed our heritability estimates.

Principal-Component Factor Analysis

Using the detailed angiographic information, we established whether certain localizations of coronary lesions are preferentially influenced genetically. Because a high degree of correlation between stenoses at different coronary sites was observed (all Spearman’s rho coefficients $P<0.001$; data not shown), principal-component factor analysis was performed to reduce the number of variables and to determine subsets of clusters of correlated coronary lesions. Subsequently, we
determined whether such clustered manifestations of CAD are heritable. Five distinct factors (ie, regions) could be extracted as described in Figure 2 and in the Data Supplement Table. In summary, on the basis of this factor analysis, a reduction of the initial 18 coronary segments to these 5 independent coronary regions appeared appropriate for further analyses. Heritabilities were estimated for all 5 factors (Figure 2). Whereas heritability estimates for factor 1 (ostia and left mainstem; $h^2=0.32\pm0.13$; $P=0.008$) and factor 2 (proximal left anterior descending, proximal circumflex, and proximal right coronary artery; $h^2=0.30\pm0.13$; $P=0.01$) were significant, no genetic contribution could be detected for factors 3 through 5 that summarized the peripheral localizations of coronary arteries. Using bivariate analysis, we estimated the genetic correlation between each of these factors. The genetic correlation between each of these traits was weak and did not reach statistical significance (data not shown). Thus, different genetic mechanisms rather than a pleiotropic action of one gene or a group of genes can be assumed for the development of CAD.

**Discussion**

We investigated the hypothesis that various morphological characteristics of CAD have a genetic component. To dissect the complex diagnosis of CAD into heritable components, variance-component analysis on specific anatomic and morphological features was performed on coronary angiograms of 882 individuals from 401 families with CAD. The data demonstrate that several angiographically distinct aspects of CAD are heritable; however, the degree of the genetic contribution varies in different areas of the coronary arteries. Particularly, a highly heritable component was observed for hazardous manifestations of coronary atherosclerosis, namely, ostial lesions and left main CAD. To our knowledge, this is the first analysis to dissect the complex phenotype of coronary atherosclerosis and to explore the genetic contribution to the anatomic localization of coronary lesions.

So far, only a few case reports have described angiographic findings in twin pairs with CAD. Our review of the available literature shows that 9 of 12 monozygotic twin pairs displayed concordance for proximal lesions, whereas only 3 of 12 were concordant for distal lesions.\(^5\)–\(^13\) This finding is congruent with our observation that stenoses are particularly heritable at proximal localizations. The reason for different heritability estimates of proximal and distal lesions remains speculative. One possibility might relate to the distinct ontogenetic determination of both sites. Particularly, the proximal parts of the coronary arteries develop from origins distinct from the peripheral parts.\(^22\) Whereas the proximal portion of the coronary arteries develops as buds on the walls of the truncus arteriosus, the distal portion is the forerunner of the subepicardial branches of the coronary arteries and develops as a subepicardial vascular network.\(^22\) Alternatively, constellation of risk factors or local hemodynamic factors, especially alterations of arterial shear stress, may account for different angiographic appearances, as suggested by similar findings of angiographic CAD.\(^23\),\(^24\) However, the distinction between proximal and distal disease with respect to the degree of heritability was consistent in multiple models that adjusted for measurable risk factors or anatomic features.

Consistent with other reports based on fast-gated helical and electron-beam computed tomography,\(^25\),\(^26\) a major genetic contribution in the variation of angiographically derived vascular calcification was found. Furthermore, heritability estimates for calcification at other anatomic sites, such as abdominal aortic and carotid calcific deposits, were found to be of the same magnitude.\(^27\),\(^28\) In conjunction, these studies provide strong and consistent evidence that vascular calcification is influenced by so far unknown genetic factors.

It has been shown previously that positive remodeling and aneurysmal coronary lesions of human coronary arteries occur in response to the development of intimal plaques\(^29\),\(^30\) and are modulated by diabetes mellitus, smoking, and hypercholesterolemia.\(^31\)–\(^33\) Our findings suggest that coronary remodeling is also influenced by genetic factors. Interestingly, Nishioko et al\(^34\) found that proximal
coronary segments show more prominent compensatory enlargement than do distal segments of the same patients, albeit a similar degree of luminal narrowing. These results support our findings, because proximal stenoses and arterial enlargements are influenced to a higher degree by genetic factors.

Further observations of the present study include the similarity between sibling pairs with respect to the initial age at clinical manifestation of CAD and the coronary risk profile. Indeed, the data suggest that the impact of genetic factors in the development of CAD may be complex and is modulated by age and coronary risk factors. By contrast, the absence of concordance for the dominant coronary vessel implies involvement of nonhereditary factors in the modulation of coronary anatomy. This finding is in agreement with other observational studies, which found considerable variability in the coronary blood supply in monozygotic twins.5,7–10

With regard to future research, our findings may open a new window of opportunity for screening strategies in relatives of CAD patients. Focusing on the most heritable manifestations of CAD might be an effective strategy to increase the power to detect susceptibility loci for such complex diseases. In fact, the high heritability of left main CAD may have important clinical implications, including a refined risk prediction in relatives of patients affected with such particularly severe manifestations. In this context, noninvasive imaging techniques might become established methods for routine cardiac diagnostics.15 The high negative predictive value of magnetic resonance imaging or multislice computed tomography scans suggests that these methods may have a role in ruling out clinically significant coronary disease in subgroups of patients with medium- to high-risk scores, ie, in relatives of patients with left main CAD. The clinical value and cost-effectiveness of this approach remain to be determined.

The high variability of the morphological aspects and related degrees of heritability suggest a diversity of genetic mechanisms that may require consideration when genetic variants are being associated with CAD. Currently, most genetic investigations of CAD use a dichotomous affected/unaffected phenotypic specification, irrespective of morphological characteristics of the coronary arteries. Our results indicate, however, that a narrowly defined phenotype can offer advantages over broad definitions.

Some limitations of the present study should be mentioned. Our heritability estimates may overestimate the true genetic contribution because we did not account for shared environmental exposures among family members in our model. Although most siblings (>90%) reported living in separate households from one another and their parents, it might be possible that a shared environment early in life contributes to specific phenotypes seen in adulthood. Furthermore, in a traditional sib-pair design, the heritability is estimated by sibling correlations. With this approach, already deceased siblings could not be included in the analyses. Our study sample was ascertained via index cases for MI before 60 years of age, and a selection bias might therefore exist in that the heritability of coronary morphology may decrease with advancing age. Nevertheless, sibling recurrence risks conditioned on the index patients’ affected status revealed congruent results to our heritability estimates. Another form of selection bias might exist in that siblings of MI patients seek medical help more quickly when a family member experiences an MI. As a result, siblings with advanced or peripheral CAD might be underrepresented in our study sample. However, two thirds of second siblings underwent angiography before the index cases did. In fact, a secondary analysis in which the index population consisted of those who underwent angiography after their siblings resulted in similar heritability estimates (data not shown).
Some of the heritability estimates, particularly low-frequency traits, should be interpreted cautiously because of the fact that a considerable number of siblings were concordant for not expressing the phenotype of interest. In this regard, the low-frequency traits ostial stenoses and left mainstem stenoses have been summarized as “left main CAD” to increase the frequency for estimating heritability. Notably, recurrence risks to siblings were highly significant for both ostial and left mainstem stenoses. Moreover, by means of principal-component factor analysis, we determined factor scores that quantified individual cases on a latent continuum. Thereby, factor analysis provides a basis for quantitative phenotypes for each individual for further analysis. We demonstrated that the heritability estimates obtained for these quantitative traits were also congruent with our initial heritability estimates. In our retrospective study, cardiovascular risk factors were ascertained after index cardiac catheterization. We preferred to ascertain valid risk factors systematically from all individuals homogeneously at the same time, although misclassifications due to initiated therapy might occur. However, prospective ascertainment of risk factors before MI was not feasible, and retrospective survey of risk factors before the index coronary event would be flawed, too. The issue of multiple testing should be mentioned. In this regard, we report alternative measures of familial aggregation by use of different analytical approaches: Heritability estimates, sibling recurrence risks, and results from factor analysis essentially conveyed the same trend. Thus, it is unlikely that our findings are solely explained by chance. Finally, our cohort was restricted to whites, such that our findings may not be generalizable to other ethnicities. Altogether, a limited generalizability of our heritability estimates might be considered, and independent confirmation is warranted.

With the ultimate goal of understanding the genetic basis of CAD, we have demonstrated that multiple distinct features of coronary atherosclerosis display a heritable component. The high variability of morphological aspects and related degrees of heritability suggest a diversity of genetic mechanisms that may require consideration when genetic variants are being associated with CAD. Moreover, the high heritability of particularly severe manifestations of CAD, including ostial lesions and left main disease, may have important clinical implications for screening strategies in asymptomatic relatives.

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References


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Marcus Fischer, Ulrich Broeckel, Stephan Holmer, Andrea Baessler, Christian Hengstenberg, Bjoern Mayer, Jeanette Erdmann, Gernot Klein, Guenter Riegger, Howard J. Jacob and Heribert Schunkert

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