Familial aggregation of left main coronary artery disease and future risk of coronary events in asymptomatic siblings of affected patients

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Introduction

A positive parental history for myocardial infarction (MI) is a strong cardiovascular risk factor. The predictive value of a positive family history may be even higher for siblings of MI patients. Nowadays, coronary angiography is being performed in most patients with premature coronary artery disease (CAD) and the resulting knowledge of the coronary anatomy and morphology has numerous implications for the affected patient, but it may also refine the risk prediction in children and siblings of these patients.

We previously performed a comprehensive phenotypic analysis of coronary angiograms in more than 400 MI families. Specifically, multiple affected siblings in these families allowed to determine the heritability (i.e. the proportion of total phenotypic variation that is due to genetic effects) of morphologically and anatomically distinct CAD manifestations. Indeed, evidence emerged that the genetic contribution varies between specific angiographic patterns of CAD. Importantly, left main disease (LMD) and proximal stenoses in the major epicardial coronary arteries are not only the most hazardous localizations, but also display a high heritability.

Our initial investigation was limited, however, by its exploratory nature lacking a specific hypothesis on the heritability of a distinct coronary disease pattern. In the present study, we thus aimed to test specifically whether LMD carries a high heritable component. Furthermore, we wanted to determine whether validated occurrence of LMD in a sibling is a more powerful prospective predictor of unexpected coronary events in seemingly healthy individuals than simply the information of family history for premature

KEYWORDS

Left main coronary disease; Familial risk; Heritability; Angiography; Prevention

Aims Recently, we observed in a hypothesis-generating exploratory search on the heritability of coronary morphology that left main coronary disease (LMD) was frequently shared by siblings with coronary artery disease (CAD). Thus, our aims were, first, to test specifically the familial aggregation of LMD and, second, to investigate whether LMD is a stronger predictor for future incident events than other manifestations of CAD in seemingly healthy siblings of CAD patients.

Methods and results Coronary angiograms of 1801 patients (n = 882 from the initial exploratory study and 919 additional angiograms) were analysed from families with ≥2 affected CAD siblings. We estimated the heritability using the variance-component methodology and sibling recurrent risks by logistic regression analysis. Moreover, we studied 1369 healthy siblings of CAD patients with known coronary morphology who had a subsequent coronary event by conducting a prospective, nested case-control study. LMD-frequency was comparable in our initial exploratory study (11%) and the new sample (12%). The heritability of LMD was significant in the exploratory 48%, P = 0.010, in the subsequent 45%, P = 0.045, and in the total study sample 49%, P = 0.002. The sibling recurrent risk ratio to present with LMD was 3.6 [CI 1.7–7.1] when another sibling was affected by LMD. In the prospective study on initially healthy family members of CAD patients, 79 siblings experienced an event during follow-up. LMD was more frequently found in families with an event than in families without (13.9 vs. 6.4%, P = 0.036). The relative risk for initially asymptomatic siblings of patients with LMD to suffer from a coronary event was 2.5 [CI 1.1–5.8] compared with siblings of patients with other manifestations of CAD.

Conclusion These data confirm our initial observation of familial aggregation of LMD. Moreover, in apparently healthy siblings of patients with LMD, this heritable component results in a risk increase for future events that is greater than that of a strong positive family history by itself.
MI. Ultimately, this line of research may allow to incorporate more detailed familial information, i.e. coronary anatomy, in future screening strategies for his or her asymptomatic relatives.

Methods

Ascertainment of study population

CAD families were ascertained through index patients at 15 cardiac rehabilitation centres throughout Germany. The ascertainment strategy has been described elsewhere. Briefly, index patients had suffered from MI before 60 years of age. If at least one additional living sibling presented with MI or severe CAD defined by percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG), the nuclear family (index patient, available parents and all siblings) was contacted and invited to participate in the study. In total, the German MI family study includes n = 1105 index patients, n = 1447 affected siblings, n = 1405 unaffected siblings, and n = 247 parents. The Ethics Committee of the University of Regensburg approved the study protocol, and all participants gave written informed consent.

Subjects and phenotyping

In total, coronary angiograms of 1801 patients from the German MI family study were available from families with ≥ 2 siblings affected by severe CAD. About 882 of those have been part of a previous exploratory study.11

Exploratory study

We previously performed an initial comprehensive phenotypic analysis of coronary angiograms in 401 CAD families (n = 882 individuals) with coronary angiograms in at least two siblings. All available angiograms of subjects participating on a previously performed genome wide linkage scan12 were collected and reviewed retrospectively from 2002 to 2004. Here, we determined the heritability of various morphological and anatomical phenotypes of CAD, including LMD.

Left main disease study

To confirm our initial findings, we subsequently decided to recruit a second sample of CAD families with available angiograms (n = 919). This second sample was recruited from subjects of the German MI family study who have not been part of the previously performed linkage scan. In this second sample, we specifically tested the hypothesis of the heritable component of LMD. The ascertainment and characterization of these additional angiograms was done in the years 2004-2006. Of these, 664 individuals (252 families) could be used for heritability and sibling recurrent risk calculations (two or more siblings affected from CAD with non-missing phenotype at the left main stem). About 26 families, which were analysed in the ‘exploratory study’, have been supplemented by additional individuals in whom a coronary angiogram was now available. The resulting 26 new sibling pairs that had not yet been analysed in the exploratory study were included in the ‘LMD study’. Results are reported for the initial exploratory study, the LMD study, and for the overall study sample.

The remaining phenotyped angiograms (n = 255) could not be used for heritability analysis or sibling recurrent risk calculations as they represent single angiographically phenotyped family members. However, they were used in the parallel investigation assessing prospective risk in seemingly healthy siblings from these families.

Angiographic evaluation

All CAD patients underwent invasive testing for clinical reasons that were not related to the conduct of this study. The cardiac catheterizations were carried out in different sites throughout Germany. All patients either suffered from MI and/or had coronary revascularization procedures and, thus, all patients without LMD had at least one clinically relevant stenosis distally of the left main stem and/or the right coronary artery distally to the ostium.

Coronary angiograms were scored systematically in a core lab by two experienced interventional cardiologists. Studies of satisfactory quality were analysed in random order. 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 present study, a lesion compromising the lumen by >50% was considered to represent a significant stenosis.

Prospective risk assessment of initially healthy siblings of coronary artery disease patients

As a further step, we conducted a prospective, nested case-control study in 1369 asymptomatic siblings of CAD patients with and without angiographically proven LMD derived from the German MI family study cohort. These initially asymptomatic siblings had a strong positive family history with at least one sibling suffering from premature MI (<60 years of age) and a second sibling with severe CAD (MI, CABG or PCIs <70 years of age). All subjects have been phenotyped by the same protocol: a standardized questionnaire was obtained by specially trained telephone interviewers regarding medical and social history, medication, angina, and clinical events. All patients underwent a thorough physical examination by their primary care physician, including a venipuncture to obtain a blood sample for cardiovascular risk factor analysis. Blood pressure was measured at standardized conditions. Additionally, all hospital records and all available records from the primary physician were obtained and critically revised. During a mean follow-up of 5.3 ± 0.6 years, 79 of the initially asymptomatic siblings either required CABG (n = 18) or experienced incident fatal (n = 26) or non-fatal MI (n = 35) or had both, CABG and MI (n = 9). All ‘cases’ came from different families. For each individual with a confirmed event, three control subjects were selected randomly from the 1290 siblings who remained free of reported cardiovascular events until the point of time when the case was diagnosed. In total, 235 controls were matched for age in decades and gender (for one case, only one control subject could be identified).

At follow-up investigations (at 2.5 years and after 5 years) clinical outcomes were recorded and a detailed history of current risk factors, medication, and discomforts was documented. For all possible events, clinical information was sought directly from hospital or general practitioners’ charts. All details of ECG, hospital admissions, enzymes, surgical operations, and treatment were collected. For all cases of MI, coronary death or CABG, hospital records were obtained and reviewed. MI was classified as confirmed if symptoms met the criteria of the World Health Organization and if the event was associated with abnormal levels of cardiac enzymes and diagnostic electrocardiographic changes. Diagnosis of death was confirmed with additional information from hospital records, autopsy reports, and family contact. Follow-up was achieved in >95% and >85% of the cohort at 2.5 years and after 5 years, respectively.

Risk factors

We defined hypertension as a blood pressure >140/90 mm Hg. Hypercholesterolaemia 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 (6.3%).

Statistical analysis

Clinical and angiographic characteristics within affected siblings were compared within the consecutively evaluated angiographic
study cohorts by use of generalized estimating equations (GEE) to account for significance of differences for within family relationships.\textsuperscript{13} The heritability ($h^2$, i.e. the proportion of total phenotypic variation that is due to genetic effects) was estimated by use of the variance component methodology as implemented in the SOLAR (version 2.1.4) package\textsuperscript{14} analogously to the previously described strategy.\textsuperscript{11} The patients in this study were ascertained through index patients. Thus, we conditioned the likelihood of a family on the phenotype of the initial index proband to account for the non-random sampling.\textsuperscript{15}

As an additional measure of familial aggregation, we performed logistic regression analyses to assess the ratio of sibling risk for individuals affected from LMD to sibling risk for unaffected individuals. Means and proportions for clinical characteristics and risk factors at baseline were calculated for cases (initially healthy siblings of CAD patients who subsequently suffered from fatal or non-fatal MI or had CABG, respectively) and randomly assigned controls (initially healthy siblings of CAD patients who remained free of any event). The student's $t$-test was used to evaluate differences in means and the $\chi^2$-statistic was used to compare proportions. In this nested case-control sample matched with respect to analysis time, age in decades and gender, relative risk estimates were obtained with use of conditional logistic regression models that in addition to crude models adjusted for several cardiovascular risk factors including systolic blood pressure, smoking, body mass index, history of diabetes, and measured plasma lipid levels. All $P$-values were two-tailed and values of less than 0.05 were considered to indicate statistical significance. All confidence intervals were calculated at the 95% level.

## Results

### Familial aggregation estimates

Clinical and angiographic characteristics of affected siblings in the exploratory\textsuperscript{18} and left main disease study are depicted in Tables 1 and 2, respectively. Clinical and angiographic characteristics were comparable between the initial and subsequent data.

### Figure 1

Age- and sex-adjusted estimates of heritability for left main disease in the original exploratory study\textsuperscript{18} ($n = 882$), the new independent left main disease study ($n = 664$) as well as in the total study population. $h^2$ = heritability in $\% \pm$ SE. $P$ values represent the significance of the heritability. However, the use of lipid lowering drugs was significantly higher in the LMD study than in the initial report.

The frequency of LMD and the extent of CAD manifestation were similar in the initially reported study and the present, subsequent study sample. In total, LMD was detected with a frequency of 12.0% (confidence interval 10.6–13.6%). Whereas the distribution of MI and PCI procedures were comparable, the frequency of CABG was lower in the subsequent LMD study sample.

Results of the heritability estimates of LMD in the exploratory and present, LMD specific study population are depicted in Figure 1. Analogously to our initial findings, a significant degree of inherited influence on age- and sex-adjusted phenotypic variance was detected for stenoses located at the left main coronary artery. In the total study sample, a heritability of 49% ($P = 0.002$) was estimated for this CAD manifestation.
Additionally, crude as well as adjusted odds ratios and 95% confidence intervals of second siblings’ affection status conditional on the first siblings’ affection status for this phenotype are shown in Figure 2. These risks confirm our significant heritability estimates in both study samples. Particularly, in a set of two siblings with known CAD we found a more than three-fold increased probability for second siblings to suffer from LMD when another sibling was affected by LMD.

**Prognostic implications of left main disease**

The baseline clinical characteristics of the healthy siblings of CAD patients who either subsequently developed a fatal or non-fatal MI or required CABG (‘cases’) and matched ‘controls’ who remained free of these cardiovascular events are shown in Table 3. These measurements were obtained on average 4 years before the subsequent event or census of data in siblings staying free of symptoms. As expected, subsequent cases displayed a more pronounced risk factor profile with a higher prevalence of arterial hypertension. Baseline levels of systolic blood pressure as well as LDL cholesterol levels were also significantly higher among individuals who subsequently developed a cardiovascular event as compared with controls. Family history for premature MI was positive in all participants (including the controls).

A positive sibling history of LMD was more frequently found in cases with incident events than in controls (13.9 vs. 6.4%, \( P = 0.036 \)). The corresponding crude and adjusted relative risks for incident MIs and/or CABG associated with a sibling history of LMD are displayed in Table 4. Using conditional logistic regression models, an increase of risk between a factor of 2.5 and 3 was observed for the initially healthy participants with the additional information of LMD in a sibling, as compared with matched controls with a positive family history of MI without LMD.

We also studied the hospital records of patients who received CABG as detailed information on the CAD distribution is available in these patients. Interestingly, from the total of 27 initially unaffected individuals who received CABG, 68% presented with LMD (stenosis or wall irregularities). Of these, 23% came from families in which other siblings had LMD as opposed to a 12% prevalence of LMD in our database in general.

**Table 3** Baseline characteristics in the prospective nested case-control study of initially healthy siblings with (cases) and without (controls) incident fatal or non-fatal MI or CABG.

<table>
<thead>
<tr>
<th></th>
<th>Controls ((n = 235))</th>
<th>Cases ((n = 79))</th>
<th>( P )-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>60.3 ± 0.6</td>
<td>60.5 ± 1.1</td>
<td>Matched(^a)</td>
</tr>
<tr>
<td>Sex, (n) (%) male</td>
<td>145 (61.7)</td>
<td>49 (62.0)</td>
<td>Matched(^a)</td>
</tr>
<tr>
<td>Body mass index, kg/m(^2)</td>
<td>27.0 ± 0.2</td>
<td>27.6 ± 0.4</td>
<td>0.262</td>
</tr>
<tr>
<td>Systolic BP, mmHg</td>
<td>140 ± 1</td>
<td>148 ± 2</td>
<td>0.0008</td>
</tr>
<tr>
<td>Diastolic BP, mmHg</td>
<td>85 ± 1</td>
<td>85 ± 1</td>
<td>0.890</td>
</tr>
<tr>
<td>Total cholesterol, mg/dL</td>
<td>253 ± 3</td>
<td>262 ± 5</td>
<td>0.181</td>
</tr>
<tr>
<td>LDL cholesterol, mg/dL</td>
<td>167 ± 3</td>
<td>180 ± 5</td>
<td>0.024</td>
</tr>
<tr>
<td>HDL cholesterol, mg/dL</td>
<td>56 ± 1</td>
<td>54 ± 2</td>
<td>0.366</td>
</tr>
<tr>
<td>Arterial hypertension, (n) (%)</td>
<td>122 (51.9)</td>
<td>52 (65.8)</td>
<td>0.036</td>
</tr>
<tr>
<td>Hypercholesterolaemia, (n) (%)</td>
<td>133 (57.1)</td>
<td>48 (62.3)</td>
<td>0.428</td>
</tr>
<tr>
<td>Diabetes, (n) (%)</td>
<td>32 (13.7)</td>
<td>18 (22.8)</td>
<td>0.075</td>
</tr>
<tr>
<td>Current or former smoking, (n) (%)</td>
<td>139 (59.2)</td>
<td>44 (55.7)</td>
<td>0.603</td>
</tr>
<tr>
<td>Antihypertensive drugs, (n) (%)</td>
<td>104 (44.4)</td>
<td>45 (57.0)</td>
<td>0.068</td>
</tr>
<tr>
<td>Lipid lowering drugs, (n) (%)</td>
<td>41 (17.5)</td>
<td>15 (19.0)</td>
<td>0.738</td>
</tr>
</tbody>
</table>

\(^a\)Minor gender differences result from the fact that using our matching criteria for one case only one instead of three control subjects could be identified.

**Discussion**

The present investigation demonstrates a high heritability of LMD which goes along with an increased risk for coronary events in presumably healthy siblings of patients with the phenotype. Specifically, we report consistently here as well as in a previous sample\(^1\) that the variability of left main morphology is under substantial heritable influence, with heritability estimates of almost 50%. In fact, the re-occurrence probability for symptomatic siblings of patients with LMD to present with the same condition is three-fold higher than that of asymptomatic siblings of CAD patients without this specific manifestation. In parallel, we demonstrate in a prospective investigation that asymptomatic siblings of patients with LMD are at high risk to suffer from MI or to require surgery for coronary revascularization. Remarkably, the risk in these siblings was even significantly higher than that in siblings with a strong positive family history including premature MI in addition to CAD manifestations other than LMD.

Although familial aggregation of MI has been demonstrated in several retrospective\(^6,8,16–18\) as well as prospective\(^3–7,19–23\) studies, few have examined the role of specific morphologic disease characteristics.\(^11\) Focusing on...
such coronary patterns underlying MI, the heritability of the trait LMD was found to be even higher than that of 'CAD' or 'MI' in general. Thereby, knowledge on coronary morphology may increase the ability of disease prediction. Moreover, the strategy might facilitate the search for susceptibility loci underlying the complex aetiology of coronary atherosclerosis. In fact, the data suggest the notion that not only familial clustering of coronary disease in general but also the outbreak of disease at the same location in the coronary tree relates to the genetic basis of this disease.

The high heritability of LMD may have important clinical implications. Despite a decline in CAD mortality over the last decade, only little proportionate change has been seen in the characteristics of unexpected cardiac deaths or survived MIs. The majority of these events is sudden and occurs out of hospital.24 Although the presence of clinically symptomatic CAD markedly increases the risk of MI, over half of sudden cardiac death victims were asymptomatic before the event.24 Although the actual event rate in asymptomatic persons may be low, the national burden of cardiovascular disease is substantial as is the individual lifetime risk. A major challenge for heart disease screening is to define populations in which the chance to detect relevant coronary atherosclerosis is high enough to justify the costs and risks of in-depth testing. Such sophisticated screening tests may include non-invasive coronary angiography, e.g. by multislice computed tomography, that allows to identify left main or other proximally located coronary lesions. In this context, asymptomatic siblings from families with the occurrence of LMD might offer the appropriate setting for intensified screening and prevention strategies.

Several limitations should be considered in discussing the present findings. First, we wish to reiterate the limitations of revealing heritability estimates in general.11 However, studying two sets of independent families that resulted in consistent heritability estimates reflects the robustness of the finding. Moreover, the effective sample size of the prospective study was low and the follow-up was short. Nevertheless, the association reached the level of significance in crude as well as adjusted statistical models. In addition, the present investigation includes to our knowledge one of the largest cohorts of unaffected family members with strong family history of CAD. Finally, we do not have detailed evidence from all incident cases as to whether they also suffered from LMD. At least in siblings who subsequently required coronary bypass grafting we found a high likelihood for re-occurrence of angiographically proven LMD in the prospective arm of our study as well.

Given these limitations as well as the clinical relevance of the findings independent confirmation is certainly warranted. Likewise, the mechanism by which a positive sibling history of LMD relates to coronary events and LMD in first-degree relatives deserves further studies. High-density whole genome genetic analyses evaluating different CAD phenotypes might give further insights to the pathophysiological mechanisms underlying the familial clustering of CAD.

In summary, LMD appears to be heritable to a substantial degree. This finding goes along with an increased risk for severe coronary events in healthy siblings of patients with LMD. Further studies might address the question whether LMD is also detectable with elevated frequencies in asymptomatic relatives of patients known to be affected by this condition in order to utilize this information for primary prevention in selected families.

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Conflict of interest: none declared.

References
Winslow’s pathway in 64-slice multi-detector computed tomography

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A 69-year-old man admitted to our hospital with unstable angina pectoris and claudication involving both lower extremities. His emergent coronary angiogram showed severe stenosis in ostium of the left main trunk and the unstable lesion was treated with a stent successfully. Fortunately, we could avoid an emergent coronary bypass surgery in this case. A month later, an abdominal aortogram showed subtotal occlusion of his right superficial femoral artery, but his left common iliac artery (CIA) was not visualized despite his ankle–brachial index was 0.7. To evaluate the collateral into his left CIA, enhanced 64-slice computed tomography (CT) (Siemens, Munich, Germany) was performed after injection of contrast covering the aortoiliac occlusive disease. Volume rendering images satisfactorily visualized his left CIA filled through Winslow’s pathway.

Winslow’s pathway is a collateral circulation from the subclavian artery via the internal mammary artery (IMA), the superior epigastric artery, and the inferior epigastric artery into the external iliac artery. This pathway is one of the collaterals supplying blood flow to the lower extremity in aortoiliac occlusive disease.

To detect Winslow’s pathway is important because the use of IMA as a coronary bypass graft would cause lower extremity ischaemia. As Winslow’s pathway is not the only collateral in the aortoiliac occlusive disease, multi-slice CT seems useful to detect other collaterals.

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