The chymase \( A_{-1903}G \) gene polymorphism is not associated with the risk and extent of coronary heart disease

Dear Sir

The renin–angiotensin system (RAS) has been shown to be involved in the pathogenesis of coronary artery disease (CAD) and myocardial infarction (AMI). The angiotensin I-converting enzyme (ACE) has a key position within this pathway by catalysing the conversion of angiotensin I to angiotensin II and by inactivating bradykinin. Besides ACE, other proteinases have been shown to be capable of angiotensin II formation. In human hearts, cardiac ventricular tissue contains the serine proteinase chymase (CMA), which contributes to most of the angiotensin II formation in this tissue. In an earlier investigation, we analysed the relation of the ACE I/D gene polymorphism to CAD and AMI in a population of more than 2000 patients who underwent coronary angiography for diagnostic purpose, and found that the D allele of the ACE I/D gene polymorphism was associated with the risk and extent of CAD in younger subjects and with the risk of AMI in older patients [1]. Recently, a \(-1903\) G/A transition in the 5’ untranscribed region of the CMA gene could be identified [2]. An association of the ACE I/D gene polymorphism, but not of the CMA gene variation with hypertrophic cardiomyopathy [2] or the risk of AMI [3,4] was found. The relation between the CMA gene polymorphism and the risk and extent of CAD has not been investigated so far. Since we identified a link between the ACE D allele and coronary heart disease [1], we analysed in the same study sample whether the CMA gene variation might be related to CAD and AMI and whether this variant might interact with other RAS gene polymorphisms (ACE I/D, angiotensinogen T174M and M235T, angiotensin II type 1 receptor A1166C gene variations) on the risk and extent of coronary heart disease.

Detection of CAD and AMI, characterisation of the study sample, measurements of substrates, statistical analysis, definition of variables and of low- and high-risk groups have been described in [1]. The chymase \( A_{-1903}G \) gene polymorphism was detected according [2].

A deviation of the chymase \( A_{-1903}G \) genotypes from Hardy–Weinberg equilibrium were not observed in the total sample or in any subpopulation. Coronary risk factors did not differ between chymase \( A_{-1903}G \) genotypes.

### Table 1

<table>
<thead>
<tr>
<th>Controls/cases</th>
<th>Degree of CAD</th>
<th>No vessel disease</th>
<th>Single vessel disease</th>
<th>Double vessel disease</th>
<th>Triple vessel disease</th>
<th>No AMI</th>
<th>At least 1 AMI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>n (AA)</td>
<td>n (AG)</td>
<td>n (GG)</td>
<td>A (95% CI)</td>
<td>G (95% CI)</td>
<td>A (95% CI)</td>
</tr>
<tr>
<td>No vessel disease</td>
<td>584</td>
<td>162</td>
<td>298</td>
<td>124</td>
<td>0.53 (0.50–0.53)</td>
<td>0.47 (0.44–0.50)</td>
<td></td>
</tr>
<tr>
<td>Single vessel disease</td>
<td>500</td>
<td>137</td>
<td>260</td>
<td>103</td>
<td>0.53 (0.50–0.64)</td>
<td>0.47 (0.44–0.47)</td>
<td></td>
</tr>
<tr>
<td>Double vessel disease</td>
<td>560</td>
<td>164</td>
<td>279</td>
<td>117</td>
<td>0.54 (0.51–0.57)</td>
<td>0.46 (0.43–0.49)</td>
<td></td>
</tr>
<tr>
<td>Triple vessel disease</td>
<td>870</td>
<td>260</td>
<td>416</td>
<td>194</td>
<td>0.54 (0.51–0.57)</td>
<td>0.46 (0.44–0.49)</td>
<td></td>
</tr>
<tr>
<td>No AMI</td>
<td>1332</td>
<td>375</td>
<td>669</td>
<td>288</td>
<td>0.53 (0.51–0.55)</td>
<td>0.47 (0.45–0.49)</td>
<td></td>
</tr>
<tr>
<td>At least 1 AMI</td>
<td>1182</td>
<td>348</td>
<td>584</td>
<td>250</td>
<td>0.54 (0.52–0.56)</td>
<td>0.46 (0.44–0.48)</td>
<td></td>
</tr>
</tbody>
</table>

\* Vessels were defined as diseased if at least 50% stenosis were demonstrated. Acute myocardial infarction was diagnosed according to criteria by the World Health Organisation. No vessel disease: persons without any angiographic signs of CAD or patients with <50% stenosis of coronary arteries.

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1. Coronary artery disease

In the total sample, no association was detected between the chymase gene polymorphism and the risk and extent of CAD (Table 1). The distribution of genotypes was only different between cases and controls when the analyses were restricted to non-smokers. In this subgroup, the chymase G allele was associated with the presence of CAD \((P = 0.004; \text{ odds ratio } 1.89 (95\% \text{ Cl } 1.22–2.91))\) and also with the extent of this disease defined either by the degree of diseased vessels \((P = 0.004)\) or by the Gensini score \((P = 0.03)\). In other low-risk and also high-risk subgroups, an association with CAD was not detected.

2. Myocardial infarction

In the total sample, an association of the chymase gene polymorphism with AMI was not detected (Table 1). Similar findings were made in low- and high-risk subpopulations (data not shown) and when a control group of AMI negative patients without vessel disease \((n = 492)\) was compared with AMI patients \((n = 1182)\).

3. Interactions with other RAS gene polymorphisms on CAD and AMI

These analyses clearly demonstrated that the CMA gene variation did not interact with other RAS gene polymorphisms on the risk and extent of coronary heart disease.

4. Conclusions

The present results are in line with earlier observations [4] in that also in the present investigation an association of the CMA \(A_{1903}G\) gene variation with the risk of AMI could not be detected. The present study extends earlier observations [4] by the findings that, only in a low risk group of non-smokers, an association of the CMA G allele with the risk and extent of CAD was detected and that interactions between the chymase \(A_{1903}G\) gene variation and other RAS gene polymorphisms on the risk and extent of CAD and on the risk of AMI were not observed.

The present data indicate that the chymase \(A_{1903}G\) gene variation — in contrast to the ACE I/D gene polymorphism — has no significant impact on the risk and extent of coronary heart disease.

References


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