Low complement C4B gene copy number predicts short-term mortality after acute myocardial infarction

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Keywords: acute myocardial infarction, copy number polymorphism, C4, C4B, mortality

Abstract
Background and Objectives: Some recent data indicate that risk of death after acute coronary syndrome is under genetic control. Previously, we found that the C4B*Q0 genotype (low copy number of the C4B gene that encodes the fourth component of complement) is strongly associated with morbidity and mortality of cardiovascular diseases (CVD). The +252 G allele of the lymphotoxin-alpha (LTA) gene encoded close to the C4B gene was also reported to be related to CVD-related mortality in an Oriental population. Methods: The relationship between the copy number of the genes encoding the four component of complement (C4A and C4B) and LTA 252 single-nucleotide polymorphism (SNP) on the one hand and mortality after acute myocardial infarction (AMI) was studied in 142 Icelandic patients. The number of the C4A and C4B genes was determined in genomic DNA samples by a newly developed real-time PCR-based method; lymphotoxin-alpha (LTA) +252 A>G polymorphism was determined by PCR–restriction fragment length polymorphism analysis. Results: The C4B*Q0 genotype was found to be strongly associated with 1-year mortality, with a hazard ratio of 3.50 (1.38–8.87) (P = 0.008) (adjusted Cox regression analysis). This association was, however, restricted to ever-smoking patients. By contrast, neither C4A gene copy numbers nor LTA 252 SNP did confer increased risk of mortality after AMI. Conclusions: This observation indicates that low C4B copy number is a strong risk factor for short-term mortality after AMI in smoking Icelandic patients, whereas LTA 252 G allele is not a risk factor in Caucasian population.

Introduction
Several factors available from the patients’ history, physical examination, initial ECG and laboratory parameters are able to predict adverse cardiac events including short-term mortality after acute myocardial infarction (AMI) (1). According to large-scale clinical trials (2–5), heart failure, age, residual myocardial ischemia, type II diabetes mellitus, previous infarction or anterior infarct are strong predictors of adverse prognosis after AMI. Besides these factors that may contribute toward increased post-AMI mortality, according to recent studies obtained by candidate gene approach or genome-wide mapping the risk of death after acute coronary syndrome is influenced by genetic factors. Cardiovascular disease (CVD)-related mortality is thus reported to be associated with polymorphisms in the IL-6 (6), insulin-like growth factor-I (7) and lymphotoxin α (LTA) gene (8).

Previously (9), we found that the short-term mortality of AMI patients was markedly influenced by a copy number polymorphism in the genes encoding the fourth component of complement (C4A and C4B). The C4 genes (C4A and C4B) are located in short arm of chromosome 6 in the so-called RCCX module of central MHC region on the short arm of chromosome 6, at a 410 kb distance from the LTA gene (10, 11). Male carriers of a null allele of the C4B gene (called C4B*Q0) had a significantly (P = 0.024) higher risk...
for in-hospital mortality (25%) as compared with the non-carriers (12%). Elderly C4B*Q0 carriers were found to have significantly higher risk for myocardial infarction (9) and stroke (12) and were selected out from the healthy elderly population both in Hungary (13) and Iceland (14). Moreover, recently (15) we reported on a significant interaction between carrier state of C4B*Q0 and smoking in promoting CVD morbidity: smoking C4B*Q0 carriers were found to have a highly increased risk of coronary artery disease and myocardial infarction whereas no such risk was observed in patients who never smoked or stopped to smoke in time. These findings were confirmed recently by another group in Finland (16): they found that smokers who carry the C4B*Q0 genotype together with HLA-DRB1*01 are prone to the risk of CVD.

The aim of the present study was (i) to confirm and extend for a longer period of time (1-year post-infarction) our previous findings on the higher post-infarction mortality rate in a new cohort of Icelandic patients with AMI using a newly developed high-throughput genotyping method (17) and (ii) to check if the LTA 252 A>G single-nucleotide polymorphism (SNP) associated with AMI mortality in an oriental population (10) is predictor of mortality in a Caucasian population, too.

Methods

Subjects

The study involved 142 consecutive patients (66.9 ± 12.5 years old, 102 males, 40 females) admitted to the emergency room of Landspitali University Hospital in Iceland between 1995 and 1998 with AMI (Table 1). The patients were followed for a period of 53 weeks. The diagnosis of AMI was based on typical electrocardiographic changes and increased serum activities of relevant enzymes. All participants gave informed consent and the study was approved by the Ethics Committee of Landspitali University Hospital, the Icelandic Data Protection Authority and the National Bioethics Committee of Iceland.

Table 1. Demographic and clinical characteristic of the Icelandic patients with AMI who died in 1 year after the development of AMI or survived this period

<table>
<thead>
<tr>
<th>Variable</th>
<th>Lethal outcome (n = 24)</th>
<th>Survivors (n = 118)</th>
<th>P value</th>
<th>All patients (n = 142)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (IQ5 range)</td>
<td>80.5 (66.3–83.3)</td>
<td>66.0 (55.0–72.0)</td>
<td>&lt;0.001a</td>
<td>67.5 (57.0–74.8)</td>
</tr>
<tr>
<td>Males/females</td>
<td>18/6</td>
<td>84/34</td>
<td></td>
<td>102/40</td>
</tr>
<tr>
<td>Cholesterol, mmol l⁻¹, median (IQ range)</td>
<td>5.65 (4.70–7.12)</td>
<td>5.95 (5.18–6.83)</td>
<td>0.586a</td>
<td>5.90 (5.10–6.88)</td>
</tr>
<tr>
<td>Triglycerides, mmol l⁻¹, median (IQ range)</td>
<td>1.57 (1.27–2.04)</td>
<td>1.76 (1.27–2.52)</td>
<td>0.430a</td>
<td>1.73 (1.27–2.50)</td>
</tr>
<tr>
<td>HDL cholesterol, mmol l⁻¹, median (IQ range)</td>
<td>0.93 (0.76–1.15)</td>
<td>0.94 (0.76–1.14)</td>
<td>0.844a</td>
<td>0.94 (0.76–1.14)</td>
</tr>
<tr>
<td>LDL cholesterol, mmol l⁻¹, median (IQ range)</td>
<td>3.90 (3.25–4.60)</td>
<td>3.93 (3.31–4.75)</td>
<td>0.704a</td>
<td>3.93 (3.30–4.71)</td>
</tr>
<tr>
<td>Smoking history</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>4 (16.7)</td>
<td>32 (27.1)</td>
<td>0.136b</td>
<td>36 (25.3)</td>
</tr>
<tr>
<td>Quit</td>
<td>14 (58.3)</td>
<td>43 (36.4)</td>
<td>57 (40.1)</td>
<td></td>
</tr>
<tr>
<td>Current</td>
<td>6 (25.0)</td>
<td>43 (36.4)</td>
<td>49 (34.5)</td>
<td></td>
</tr>
<tr>
<td>Hypertension, yes (%)</td>
<td>15 (62.5)</td>
<td>67 (56.8)</td>
<td>0.656b</td>
<td>82 (57.7)</td>
</tr>
<tr>
<td>Type II diabetes mellitus, yes (%)</td>
<td>4 (16.7)</td>
<td>12 (10.1)</td>
<td>0.476b</td>
<td>16 (11.3)</td>
</tr>
<tr>
<td>Family history of CVD, yes (%)</td>
<td>13 (52.4)</td>
<td>76 (64.4)</td>
<td>0.124b</td>
<td>89 (62.7)</td>
</tr>
<tr>
<td>Previous AMI (%)</td>
<td>13 (54.2)</td>
<td>61 (51.7)</td>
<td>0.825b</td>
<td>74 (52.1)</td>
</tr>
<tr>
<td>PTCA, yes (%)</td>
<td>5 (20.8)</td>
<td>14 (11.9)</td>
<td>0.239b</td>
<td>19 (13.4)</td>
</tr>
<tr>
<td>Coronary bypass operation, (%)</td>
<td>3 (12.5)</td>
<td>15 (12.7)</td>
<td>0.977b</td>
<td>18 (12.7)</td>
</tr>
<tr>
<td>Maximal creatinine kinase (U ml⁻¹), median (IQ range)</td>
<td>260 (63–1435)</td>
<td>728 (306–1723)</td>
<td>0.045b</td>
<td>637 (245–1646)</td>
</tr>
</tbody>
</table>


Registration of smoking habits

Smoking behavior was registered by a physician at study entry and analyzed as described previously (18).

Measurements

The number of the C4A and C4B genes was determined in genomic DNA samples (19) by a newly developed real-time PCR-based method (17) as described previously with some modifications. C4A- and C4B-specific Taqman probes were labeled with FAM, and the reference RNaseP was labeled with VIC. The DNA amplification was carried out in an ABI 7300 Real-Time PCR System. Lymphotoxin-alpha (LTA) +252 A>G polymorphism was determined as described by Seidemann et al. (20).

Statistical analysis

The non-parametric Mann–Whitney test was used for group comparisons. Categorical data were compared using the Fisher’s exact test or χ² test for trend. Survival data were analyzed by multiple Cox regression. This tool and multiple logistic regression were used to evaluate potential confounders and to correct P values of univariate analyses. All tests were two-tailed. Statistical analysis was performed by the GraphPad Prism 3.0 (GraphPad Software Inc., San Diego, CA, USA, www.graphpad.com) and SPSS 13.0 (SPSS Inc., Chicago, IL, USA) softwares.

Results

One-year mortality of the carriers of different C4A/C4B gene copy numbers or LTA 252 A>G genotypes

In order to study the relationship between the C4A and C4B gene dosage as well as LTA 252 A>G SNP on the one hand and the short-term mortality of the AMI patients on the other hand, we compared the carriage distribution of these polymorphisms between the 24 patients who died in 1 year after infarction and the 108 patients who were alive at week 53.
Since few patients carried three or more C4B gene copies, only two groups [low (0 or 1) and high (2 or more)] were compared. Frequency of carriers of neither C4A gene copy number (Fig. 1, panel A) nor LTA 252 SNP genotypes (Fig. 1, panel C) differed between survivors and non-survivors. By contrast, we found a highly significant ($P = 0.003$) difference between carriers of low and high C4B copy numbers (Fig. 1, panel B): 12/24 (50.0%) of the patients who died but only 23/118 (19.5%) of the survivors carried low number of C4B gene copies. According to comparison to other direction, 12/35 (31%) and 12/107 (11%) of the carriers of low and high C4B copy numbers, respectively, died during the follow-up period. Both the early (week 1) and later (weeks 2–52) mortality was higher for the low C4B copy carriers (Fig. 2).

Copy number of the C4B genes was not linked to the LTA 252 A>G SNP ($P = 0.638$), whereas as it is expected (21) a significant ($P = 0.014$) disequilibrium was observed between low copy number of the C4A genes and the variant (252G) LTA allele.

**Multiple regression analysis**

Since patients who died in first year post-AMI and the survivors significantly differed in age (Table 1), we performed a multiple logistic regression analysis for the association between low C4B copy number and early mortality adjusted for age and other variables [gender, family history of CVD, smoking habits, smoking habits, hypertension, type II diabetes mellitus, atherosclerotic index [log(tryglicerides/HDL cholesterol)], application of PTCA and coronary bypass operation] which were previously (1) implicated in high risk for mortality after AMI (Table 2). The association with mortality remained significant even after adjustment; carriers of low (0–1) versus high (2–4) C4B copy number had a 4.65 (1.47–14.71) ($P = 0.009$) times higher risk of not surviving the first year post-AMI. Mortality was significantly and positively associated with the age of patients as well, and we found that current smokers and quitters had a higher odds of mortality than never smokers, the difference was, however, of marginal significance. By contrast, mortality was related to neither of the gender of patients.

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**Fig. 1.** Survival in 1 year after infarction of Icelandic patients with AMI stratified according to C4A gene copy number (A), C4B gene copy number (B) and LTA 252 genotypes (C). $P$-values for $\chi^2$ test for trend are indicated.

**Fig. 2.** Distribution of patients with low (0–1) or high (2–4) C4B copy numbers among patients who died in week 1 and weeks 2–52 and still alive on week 53 after infarction. $P$-value for $\chi^2$ test for trend is indicated.
patients, family history, hypertension, type II diabetes or atherogenic index. Short-term mortality was not associated with the use of PTCA, coronary bypass operation or with maximal creatinine kinase values either.

Similar results were observed when the data were evaluated by Cox proportional hazard regression analysis adjusted to same variables (Fig. 3), hazard ratio of 3.14 (1.32–7.46) \( (P = 0.010) \) were obtained for the mortality of the low versus high C4B copies.

Interaction between smoking habits and C4B gene copy number in prediction of short-term mortality

Previously, we reported an interaction between smoking and the C4B*Q0 carrier state for determining risk of CAD and myocardial infarction (15). In addition, in the present study we observed that smoking is weakly associated with mortality (Table 2). Therefore, we calculated the statistical interaction between smoking habits (ever/never trait) and low/high C4B copy number for predicting short-term post-AMI mortality. Highly significant \( (P = 0.003) \) interaction was found. Therefore, next by using multiple logistic regression analysis we calculated odds ratios of never- and ever-smoking low/high C4B copy carriers for death in 1 year after infarction adjusted to variables as above (except, of course, smoking). A significant odds ratio 4.25 (1.24–14.59) \( (0.022) \) was found for the ever-smoking patients whereas in the never-smoking patients no significant association 0.60 (0.00–105.19) \( (0.390) \) between the C4B gene copy number and short-term mortality was found (Table 3). An even higher odds 26.05 (1.09–621.17), \( P = 0.044 \) was obtained when only current smoking patients were considered, but due to low number of patients/groups, the confidence interval was very high. Interestingly enough, age of the patients was significantly related to mortality only in the smoker group (Table 3).

Discussion

Our results show a markedly higher short-term (1-year post-infarction) mortality of AMI among patients who had a low copy number (0–1) of the C4B gene compared with carriers of a high C4B copy number (2–4). This difference, however, could be detected only in patients who ever smoked and was the highest in the group of current smokers. Low copy number of the C4B gene can be considered nearly equal to the carrier state of C4B*Q0, determined by phenotyping\(^\text{16}\). Therefore, our present findings confirm our previous results obtained in Hungarian patients with AMI in which 3/6 (50%) of homozygote and 8/38 (21%) of heterozygote carriers compared with only 17/137 (12.4%) of non-carriers had a lethal outcome \( (P = 0.024) \). We performed the study in Icelandic patients who were admitted in the same hospital. Most important, according to recent studies the Icelandic gene pool is less heterogeneous than those of most other European populations (22); the allelic frequency distribution of Iceland is relatively even with a large number of haplotypes at polymorphic frequencies contrasting with other countries (23). In spite of this, we are aware that our present findings are hypothesis generating which should be repeated in a higher cohort of AMI patients.

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**Table 2.** Risk of patients carrying low (0 or 1) copy number of C4B to die in 1 year after AMI adjusted to gender, age and other variables (calculated by multiple logistic regression)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds ratio (unadjusted)</th>
<th>Odds ratio (adjusted to several factors(^a)) ( (P \text{ values}) )</th>
</tr>
</thead>
<tbody>
<tr>
<td>C4B 0-1 versus 2-4 gene copy number</td>
<td>4.13 (1.65–10.37) ( (0.003) )</td>
<td>4.65 (1.47–14.71) ( (0.009) )</td>
</tr>
<tr>
<td>Age, years</td>
<td>1.11 (1.05–1.18) ( (&lt;0.001) )</td>
<td>1.14 (1.07–1.22) ( (&lt;0.001) )</td>
</tr>
<tr>
<td>Gender, males/females</td>
<td>0.824 (0.301–2.252) ( (0.705) )</td>
<td>0.518 (0.143–1.879) ( (0.317) )</td>
</tr>
<tr>
<td>Smoking history (never/quit/current)</td>
<td>0.983 (0.556–1.741) ( (0.983) )</td>
<td>2.47 (1.00–6.08) ( (0.050) )</td>
</tr>
<tr>
<td>Family history of CVD, yes/no</td>
<td>0.718 (0.290–1.778) ( (0.475) )</td>
<td>1.55 (0.49–4.89) ( (0.452) )</td>
</tr>
<tr>
<td>Hypertension, yes/no</td>
<td>1.27 (0.51–3.13) ( (0.605) )</td>
<td>0.81 (0.24–2.68) ( (0.727) )</td>
</tr>
<tr>
<td>Type 2 diabetes mellitus, yes/no</td>
<td>1.37 (0.73–2.55) ( (0.323) )</td>
<td>1.09 (0.48–2.48) ( (0.841) )</td>
</tr>
<tr>
<td>Atherogenic index</td>
<td>0.61 (0.12–3.40) ( (0.40) )</td>
<td>2.16 (0.23–16.96) ( (0.496) )</td>
</tr>
<tr>
<td>PTCA, yes/no</td>
<td>1.96 (0.63–6.07) ( (0.246) )</td>
<td>1.81 (0.39–8.41) ( (0.447) )</td>
</tr>
<tr>
<td>Coronary bypass operation, yes/no</td>
<td>0.96 (0.09–10.10) ( (0.960) )</td>
<td>0.58 (0.12–2.95) ( (0.515) )</td>
</tr>
<tr>
<td>Maximal creatinine kinase values</td>
<td>1.00 (0.99–1.00) ( (0.446) )</td>
<td>1.00 (0.99–1.00) ( (0.195) )</td>
</tr>
</tbody>
</table>

\(^a\)Age, gender, smoking habits, family history of CVD, hypertension, type II diabetes mellitus, atherogenic index \([\log(\text{triglycerides/HDL cholesterol})]\), application of PTCA, coronary bypass operation and maximal creatinine kinase values.
The patients were divided into two groups according to their smoking habits (calculated by multiple logistic regression). Age, gender, family history of CVD, hypertension, type II diabetes mellitus, atherogenic index [log(triglycerides/HDL cholesterol)], application of PTCA and coronary bypass operation. Never smokers were younger than ever smokers (Table 3). In contrast to these observations, copy number of the C4A gene was not related to mortality of AMI. We did not found any correlation either between mortality of the patients and the LTA 252 A>G polymorphism. Previously in an Oriental population, Mizuno et al. (8) observed significantly higher mortality in patients carrying the LTA 252 G allele. The C4A/C4B genes and the LTA genes are at a relatively short distance (410 kb) and we found significant linkage disequilibrium between low copy number of C4A genes and the LTA 252 G allele. This finding is not unexpected since both genotypes are constituents of the so-called 8.1 ancestral haplotype (21, 24). By contrast, low C4B gene copy number was not linked to the LTA 252 SNP. Our present findings on the lack of association between short-term or long-term AMI mortality with the LTA 252 A>G SNP indicate that this association may be restricted to Oriental populations.

The hazard ratio of the C4B*Q0 carriers for an early death after myocardial infarction was found to be 3.14 (1.32–7.46) by Cox regression and 4.65 (1.47–14.71) by multiple logistic regression. Mortality after myocardial infarction, or more general after acute coronary syndrome, has previously been found to be associated with polymorphisms in the IL-6 gene (−174 G>C SNP; hazard ratio 3.89 (1.71–8.86)) (6), the insulin-like growth factor-I promoter [hazard ratio 1.49 (1.20–2.10)] (7) and, in Orientals, the LTA gene [252 A>G SNP; hazard ratio 2.46 (1.24–4.86)] (8). Therefore, carrier state of low C4B copies is associated with comparable or even higher risk of short-term post-AMI mortality than previously published polymorphisms. Thus, our present findings indicate that low copy number of the C4B gene can be strong risk factor for short-term mortality of AMI. This risk cannot be detected, however, in patients who never smoked and it was the highest in patients who were smokers even at the time of study. Due to the relatively low number of current smokers, no direct comparison between current smokers and quitters could be performed. Interestingly, short-term mortality was related to smoking at univariate analysis but clear-cut difference: higher mortality of the ever versus never smokers was found at multivariate analysis. This finding is most probable due to the so-called smoker’s paradox (25): compared with persistent smoker patients with AMI, non-smokers are younger and have fewer underlying medical problems, therefore at univariate analysis they have an apparently lower risk of death which, however, turns to the opposite after adjustment to the confounding variables. Higher mortality rate of the smoking AMI patients with low C4B copy number is in line with our previous findings (15) indicating that smoking carriers of this genotype exhibit an increased susceptibility for coronary artery disease and AMI and they are selected out for the healthy elderly population.

Table 3. Risk of patients carrying low (0 or 1) copy number of C4B to die in 1 year after AMI adjusted to gender, age and other variables

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds ratio (unadjusted)</th>
<th>Odds ratio (adjusted to several factors) (P values)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Never smokers</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C4B 0–1 versus 2–4 gene copy number</td>
<td>4.33 (0.50–37.26) (0.182)</td>
<td>0.60 (0.00–105.19) (0.390)</td>
</tr>
<tr>
<td>Age, years</td>
<td>—</td>
<td>1.91 (0.83–4.40) (0.127)</td>
</tr>
<tr>
<td>Ever smokers</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C4B 0–1 versus 2–4 gene copy number</td>
<td>4.06 (1.46–11.31) (0.007)</td>
<td>4.25 (1.24–14.59) (0.022)</td>
</tr>
<tr>
<td>Age, years</td>
<td>—</td>
<td>1.11 (1.04–1.19) (0.001)</td>
</tr>
</tbody>
</table>

The patients were divided into two groups according to their smoking habits (calculated by multiple logistic regression). Age, gender, family history of CVD, hypertension, type II diabetes mellitus, atherogenic index [log(triglycerides/HDL cholesterol)], application of PTCA and coronary bypass operation.
MHC haplotype and it seems that it is the low copy number of the C4B gene itself which is responsible for it. Two not mutually exclusive and testable hypotheses, may be, however, raised. According to the first hypothesis, low copy number of both the C4A and C4B genes is associated with enhanced immune complex formation which may represent one mechanism of premature atherosclerosis (33–35). This assumption is supported by several recent findings. In patients with different autoimmune diseases, a surrogate marker of in vivo immune complex handling and prevention of immune precipitation exhibited a very strong positive correlation with serum levels of C4B (36). Prevalence of the C4B*Q0 genotype was found to be increased in the IgA immune complex disease Henoch-Schoenlein purpura (37). In addition, an association was observed between smoking and the prototype immune complex disease, SLE (38). Unfortunately, only scarce comparative data are available on the levels of circulating immune complexes in smoking and non-smoking subjects (39, 40). These data obtained in patients with endarteritis obliterans indicates elevated immune complex concentration in smoking individuals. These observations—if they may be repeated in more subjects—may account for the additive effect of smoking and C4B*Q0 genotype for promoting post-AMI mortality. Although this assumption is in line with the observations summarized above, it cannot explain the selectivity of the observations: low copy number of the C4B but not of the C4A gene was found to be associated with increased post-AMI mortality. According to the alternative hypothesis, low C4B copy number which means the lack of C4B gene in one or both chromosomes may result in impaired function of genes of the neighboring CYP21B gene, with serious consequences, e.g. inadequate mobilization of steroid hormones during stress in critical situations (41, 42) and high IL-6 production (43) known to be a severe risk factor for AMI and cardiac mortality (44). Since according to the studies of Hautanen and Adlercreutz (45) that smoking inhibits the adrenal 21-mortality (44). Since according to the studies of Hautanen (43) known to be a severe risk factor for AMI and cardiac ces, e.g. inadequate mobilization of steroid hormones during CYP21B

Acknowledgements
We are greatly indebted to the study participants.

Abbreviations
AMI  acute myocardial infarction
CVD  cardiovascular disease
C4A and C4B  genes encoding for fourth component of complement
LTA  lymphotixin-α
SLE  systemic lupus erythematosus
SNP  single-nucleotide polymorphism

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