Dear Editor,

The ATP-binding cassette transporter A1 (ABCA1) influences the initial steps in high-density lipoprotein (HDL) formation and the cholesterol efflux across cell membranes to acceptor molecules in the plasma. Both functions are likely to play an important role in the development of atherosclerosis and coronary heart disease (CHD) [1]. Mutations in the ABCA1 gene have been found to be responsible for the rare Tangier disease and familial hypo-alpha-lipoproteinemia, two forms of HDL deficiency that predispose carriers to coronary atherosclerosis [2]. The ABCA1 gene is highly polymorphic and to-date a large number of sequence variations have been identified (http://www.abca1mutants.all.at), many of them affecting HDL cholesterol (HDL-C) concentrations [3–5]. As low plasma HDL-C is strongly correlated with an increased cardiovascular risk, the ABCA1 gene has been suggested to be a potential mediator for atherosclerotic conditions [3,4,6]. Consequently, several association studies have investigated the influence of ABCA1 variation on lipid metabolism or CHD phenotype—often with controversial results. For many of the analyzed polymorphisms, inconsistent findings have been reported in different populations [3,4,6–11].

In the present study, we have examined the potential association between the five known coding polymorphisms R219K, V771M, I883M, E1172D and R1587K in the ABCA1 gene and early-onset CHD in a large ethnically homogeneous sample from the northernmost province in Germany. Both cases (n = 1090) and healthy control individuals (n = 728) are part of the PopGen biobank and representative of the general population in the catchment area [12]. A detailed description of the samples and the recruitment procedure is given elsewhere [13]. Patients were required to have coronary catheterization demonstrating significant CHD (at least a 70% stenosis in one major epicardial coronary vessel) before the age of 55 years. The majority of subjects (90.3%) had a history of severe CHD and had undergone a coronary revascularization procedure (percutaneous coronary intervention or coronary artery bypass grafting). All subjects gave informed, written consent prior to participation. The study was approved by the Ethics Committee of the University Hospital Schleswig-Holstein.

Single-point case control analysis revealed a marginally significant association only for marker I883M (Table 1). None of the other four SNPs showed any statistically significant frequency differences between CHD and control subjects, either using the entire collection (Table 1) or subsamples stratified for gender (data not shown). Multivariate logistic regression was performed, using the R-package [14], to model the relationship between a binary outcome variable (CHD versus healthy) and carriership of the five SNPs. Gender was also included as a predictive variable. The results are given in Table 2. Gender was clearly not associated with disease status in our already well-matched data-set and removing this variable from the model did not alter the fit of the model (P = 0.699). In concordance with the single-point analysis, only marker I883M exhibited significant association with CHD (P = 0.034). Marker R219K showed marginal association (P = 0.066). Haplotype reconstruction for the five non-synonymous SNPs yielded 25 haplotypes, of which the 10 common ones accounted for 98.5% of all haplotypes. The estimated haplotype frequencies differed significantly between CHD cases and controls (global P value after 10,000 permutations = 0.0049; estimated using the program HAPRAND [15]). When individual haplotypes were similarly examined, the commonest one, which carried the wildtype alleles at all five loci, was significantly over-represented in controls (0.558 in controls versus 0.489 in CHD patients; P = 0.0003).

We examined the five known ABCA1 polymorphisms R219K, V771M, I883M, E1172D and R1587K in early-onset
CHD and matched control samples from northern Germany. Only I883M was found to modulate susceptibility to CHD in the German population, albeit with a relatively modest effect (OR of ~1.3 for carriers of the rare variant). Our association between I883M and CHD is consistent with several previous reports that have demonstrated an increased CHD risk for carriers in other populations [4,6,7]. However, additional studies have indicated no relevant effects for the I883M genotype on CHD or HDL-C levels [8,10,11]. The other four SNPs R219K, V771M, E1172D and R1587K exhibited no clear effects in the German CHD samples investigated here. Our findings are both in accordance and in contradiction with those obtained from different populations [4,6,8–11].

Allelic variants in the ABCA1 gene have been shown to be associated with CHD in various population samples, including the present one from Germany. This indicates that the gene is an important player in the pathogenesis of the disease. However, many of the reported findings remain unreplicated, and reported results are sometimes contradictory. How can these divergent observations be explained? The ABCA1 gene is large (spanning ~150 kb of chromosome 9q) and polymorphism-rich. The linkage disequilibrium (LD) structure of the gene is not clearly understood. The five markers analyzed in our samples were in moderate LD with each other and a relatively large number of haplotypes were inferred. Many of the previous studies did not take pair-wise LD between the SNPs into account and therefore it is difficult to assess whether the noted effects were truly independent or due to LD with other polymorphisms. The investigation of population-specific LD patterns among the SNPs and more detailed haplotype and interaction analyses will be valuable in unravelling the differences among the reported associations. Further, the contradictory association reports may reflect real differences in the genetic and/or environmental backgrounds of the studied populations. Thus, detailed functional assessment of these SNPs is essential if we are to understand their impact on CHD in the various populations.

Acknowledgement

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References


Table 1
Summary association statistics for common ABCA1 coding SNPs in German CHD patients and controls

<table>
<thead>
<tr>
<th>ABCA1 variant</th>
<th>MAFa CHD</th>
<th>MAFa control</th>
<th>Pallele</th>
<th>Pgenotype</th>
<th>PCarrierb</th>
<th>ORcarrierc</th>
<th>95% CIcarrierd</th>
</tr>
</thead>
<tbody>
<tr>
<td>R219K (rs2230806)e</td>
<td>0.265</td>
<td>0.258</td>
<td>0.656</td>
<td>0.582</td>
<td>0.438</td>
<td>1.08</td>
<td>0.89–1.30</td>
</tr>
<tr>
<td>V771M (rs2066718)f</td>
<td>0.026</td>
<td>0.034</td>
<td>0.188</td>
<td>0.255</td>
<td>0.222</td>
<td>0.78</td>
<td>0.53–1.16</td>
</tr>
<tr>
<td>I883M (rs1499313)e</td>
<td>0.138</td>
<td>0.112</td>
<td>0.023</td>
<td>0.068</td>
<td>0.021</td>
<td>1.31</td>
<td>1.04–1.64</td>
</tr>
<tr>
<td>E1172D (hCV25924149)e</td>
<td>0.025</td>
<td>0.025</td>
<td>0.064</td>
<td>0.071</td>
<td>0.098</td>
<td>1.00</td>
<td>0.65–1.55</td>
</tr>
<tr>
<td>R1587K (rs2230808)e</td>
<td>0.261</td>
<td>0.234</td>
<td>0.067</td>
<td>0.197</td>
<td>0.097</td>
<td>1.18</td>
<td>0.97–1.42</td>
</tr>
</tbody>
</table>

a MAF, minor allele frequency.
b OR, odds ratio.
c CI, confidence interval.
d R219K, V771M, I883M, E1172D and R1587K were typed using TaqMan® SNP Assays (Applied Biosystems, Foster City, USA). Each SNP had a call rate of at least 98% and was in Hardy–Weinberg equilibrium in both the CHD and the control samples (P>0.05).

table 2
Logistic regression analysis for five coding SNPs in the ABCA1 gene in German CHD patients and controls

<table>
<thead>
<tr>
<th>Predictora</th>
<th>ORb</th>
<th>95% CId</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>1.05</td>
<td>0.81–1.36</td>
<td>0.721</td>
</tr>
<tr>
<td>R219K</td>
<td>1.20</td>
<td>0.99–1.47</td>
<td>0.066</td>
</tr>
<tr>
<td>V771M</td>
<td>0.90</td>
<td>0.57–1.41</td>
<td>0.645</td>
</tr>
<tr>
<td>I883M</td>
<td>1.28</td>
<td>1.02–1.61</td>
<td>0.034</td>
</tr>
<tr>
<td>E1172D</td>
<td>0.78</td>
<td>0.52–1.19</td>
<td>0.253</td>
</tr>
<tr>
<td>R1587K</td>
<td>1.10</td>
<td>0.90–1.34</td>
<td>0.361</td>
</tr>
</tbody>
</table>

a Each marker binary classified for carriership of rare allele.
b OR, odds ratio.
c CI, confidence interval.


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