Absence of ABCA1 Mutations in Individuals with Low Serum HDL-Cholesterol

To the Editor:

Over the last quarter century, a decreased concentration of serum HDL-cholesterol (HDL-C) has emerged as one of the major risk factors for coronary artery disease (1, 2). The antiatherogenic role of HDL-C has been proposed to be a result of its role in reverse cholesterol transport—removal of excess cholesterol from peripheral tissues to the liver for reuse or excretion as bile acids (3). An important discovery was made recently with regard to the first step in reverse cholesterol transport: the efflux of the intracellular cholesterol and its subsequent uptake by nascent HDL particles is now thought to be catalyzed by an enzyme that is a member of the ATP-binding cassette transporter (ABC) family, known as the ABCA1 enzyme. Deleterious mutations, when present in both alleles in the ABCA1 gene, have been found to be the cause of Tangier disease (TD), which is characterized by an almost complete absence of serum HDL-C (<70 mg/L) (4–6). The carrier state of deleterious mutations in the ABCA1 gene has also been found to be the cause of familial hyperalphalipoproteinemia (FHA), which is characterized by low serum HDL-C (150–350 mg/L) (7).

Many different mutations have been identified in the ABCA1 gene in both TD and FHA patients (4–9). However, the prevalence of these mutations in a general population with low HDL-C remains unknown. We chose seven mutations, two associated with TD (T4369C and A1730G) and five associated with FHA (del2017–2019, C6370T, C2665T, T3212C, and del5618–5623), and screened 257 individuals with serum HDL-C ≤300 mg/L [mean (SD), 258 (39) mg/L] and serum triglycerides ≤2500 mg/L [1570 (470) mg/L] for these mutations. Of the 257 individuals, 209 were patients with premature coronary artery disease (documented by angiographically confirmed atherosclerosis and/or one or more episodes of myocardial infarction or coronary artery bypass surgery before age of 55 years), including 193 males ranging in age from 19 to 69 years [mean (SD) age, 49.7 (5.7) years], and 16 females ranging in age from 25 to 59 years [47.5 (8.2) years]. The remaining 48 individuals were patients undergoing diagnostic evaluation for cardiovascular disease; of these, 40 were males ranging in age from 19 to 69 years [48.7 (12.2) years], and 8 were females ranging in age from 17 to 59 years [40.5 (14.3) years]. The patients represented individuals seen over a period of 4 years at the Minneapolis Heart Institute and were of mixed ancestry common to the upper Midwestern region of the US, belonging to no particular ethnic group. This study was approved by the Institutional Review Board: Human Subjects Committee of the University of Minnesota, and all participants gave informed consent. Mutations were detected as described previously (4, 7).

None of the seven mutant alleles were found in our population of 257 individuals with low HDL-C (Table 1). To our knowledge, no previous study has reported the prevalence of ABCA1 gene mutations in a population with low HDL-C. Our results may be interpreted to mean that mutations in the ABCA1 gene, which have been found in patients with TD and FHA, are not present to a high degree in the general population with low HDL-C. This has also been suggested previously by Clee and coworkers (10, 11). A weakness of the current study is in limiting the screening to only 7 of the initially described mutations, whereas >30 mutations have now been reported in the ABCA1 gene (4–9). However, the interpretation of our results is indirectly supported by other studies. For example, many segregation studies have been done and failed to detect major gene loci influencing variation of HDL-C in either Caucasian or non-Caucasian populations (12–14). Furthermore, published reports of genome-wide anonymous marker scans have not shown significant linkage of HDL-C to the chromosome region (9q22–31) where the ABCA1 gene has been mapped (15–17). Because TD is quite rare, we speculate that there are relatively few heterozygous carriers in the general population (1:400 to 1:600) and that they therefore account for only a few of the large number of individuals with low HDL-C. We speculate that genetic influence on HDL-C may result from the combined influence of polymorphisms and rare mutations present in the ABCA1 gene as well as a large number of other genes coding for enzymes and cofactors that are involved in HDL metabolism. Genes coding for cholesteryl ester transfer protein, hepatic lipase, lipoprotein lipase, and apolipoprotein CII and CIII are only some of the examples. Further investigations involving the more deleterious mutations of the ABCA1 gene are needed to confirm our finding. In addition,

Table 1. ABCA1 mutations in individuals with serum HDL-C ≤300 mg/L and serum triglycerides ≤2500 mg/L.

<table>
<thead>
<tr>
<th>Genotype, n</th>
<th>Mutation</th>
<th>Amino acid change</th>
<th>Wild type</th>
<th>Heterozygous</th>
<th>Mutant</th>
</tr>
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<tbody>
<tr>
<td>ABCA1 A1730G</td>
<td>Q537R</td>
<td>257</td>
<td>0</td>
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<tr>
<td>ABCA1 del2017–2019</td>
<td>∆Δ633</td>
<td>257</td>
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<td>0</td>
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<tr>
<td>ABCA1 C2665T</td>
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<td>0</td>
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</tr>
<tr>
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<td>M1031T</td>
<td>257</td>
<td>0</td>
<td>0</td>
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<tr>
<td>ABCA1 T4369C</td>
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<td>243a</td>
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<td>0</td>
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</tr>
<tr>
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</tbody>
</table>

aNotal 257 individuals were screened because some individuals' DNA did not amplify after second repeat.

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given that the ABCA1 enzyme has a rapid turnover (18), it may be important to study the regulation of this turnover. These studies, along with more comprehensive studies of the common polymorphisms of the ABCA1 gene, will ultimately determine the extent to which the ABCA1 gene participates as a genetic determinant of serum HDL-C concentrations in the general population.

References

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γ-Glutamyltransferase and Vascular Disease

To the Editor:
In their recent report, Whitfield et al. suggest that serum γ-glutamyltransferase (GGT) may originate from atheromatosous plaques. This interesting proposal can be further supported. There is evidence showing that human platelets may be a source of GGT (2, 3), but this contribution may be small (3). Therefore, increased platelet consumption at the site of these plaques may contribute to an increase in serum GGT activity.

In Table 1 of their report, the authors (1) do not consider serum bilirubin among the variables correlating with serum GGT activity. It may be interesting to assess that link because bilirubin concentrations may be lower in patients with vascular disease (4). Stronger evidence indicates that women and smokers have lower serum bilirubin even if they have vascular disease (4). The rationale is that bilirubin acts as an antioxidant and that its consumption is increased in smokers and patients with vascular disease (4, 5). A similar argument applies to serum albumin (4).

Finally, there is evidence that fibrates lower serum alkaline phosphatase activity as well as improving the lipid profile (6, 7). [Alkaline phosphatase is not considered in Table 1 of the Whitfield et al. report (1).] There is also evidence that serum GGT activity decreases in hypertriglyceridemic patients after treatment with a fibrate (6, 7). These changes thus may help toward a better understanding of the relationship between lipid variables and serum GGT activity or other liver function tests.

The elegant work of Whitfield et al. (1) may help develop new and easily accessible predictors/markers of vascular disease.

References