Genetic Etiology of Isolated Low HDL Syndrome
Incidence and Heterogeneity of Efflux Defects

Robert S. Kiss, Nihan Kavaslar, Kei-ichiro Okuhira, Mason W. Freeman, Stephanie Walter, Ross W. Milne, Ruth McPherson, Yves L. Marcel

Objective—We have used a multitiered approach to identify genetic and cellular contributors to high-density lipoprotein (HDL) deficiency in 124 human subjects.

Methods and Results—We resequenced 4 candidate genes for HDL regulation and identified several functional nonsynonymous mutations including 2 in apolipoprotein A-I (APOA1), 4 in lecithin:cholesterol acyltransferase (LCAT), 1 in phospholipid transfer protein (PLTP), and 7 in the ATP-binding cassette transporter ABCA1, leaving 88% (110/124) of HDL deficient subjects without a genetic diagnosis. Cholesterol efflux assays performed using cholesterol-loaded monocyte-derived macrophages from the 124 low HDL subjects and 48 control subjects revealed that 33% (41/124) of low HDL subjects had low efflux, despite the fact that the majority of these subjects (34/41) were not carriers of dysfunctional ABCA1 alleles. In contrast, only 2% of control subjects presented with low efflux (1/48). In 3 families without ABCA1 mutations, efflux defects were found to cosegregate with low HDL.

Conclusions—Efflux defects are frequent in low HDL syndromes, but the majority of HDL deficient subjects with cellular cholesterol efflux defects do not harbor ABCA1 mutations, suggesting that novel pathways contribute to this phenotype.

Key Words: lipoproteins ■ cholesterol ■ genes ■ HDL ■ monocyte ■ macrophage

Partial HDL deficiency or hypoalphalipoproteinemia, defined as an age- and sex-adjusted plasma high-density lipoprotein cholesterol (HDL-C) concentration below the 10th percentile, is a major risk factor for coronary heart disease and stroke. Metabolic and genetic etiologies are varied. Overproduction and/or impaired clearance of triglyceride-rich lipoproteins results in triglyceride enrichment of HDL and accelerated apolipoprotein A-I (apoA-I) catabolism and may account for low HDL-C levels in patients with hypertriglyceridemia.1–3 Low HDL can also result from and may account for low HDL-C levels in patients with Tangier disease, an autosomal recessive disorder characterized by almost complete HDL deficiency, is characterized by defective cellular lipid efflux to apoA-I, resulting from homozygosity or compound heterozygosity for mutations in the ATP-binding cassette transporter ABCA1.13–19 Defective lipid efflux is also a significant factor in familial HDL deficiency, and, in several of these kindreds, affected subjects are heterozygous carriers of ABCA1 mutations.17,20,22 These genetic studies demonstrate the key role of ABCA1 in cholesterol efflux to apoA-I and, as we have reported previously,22 sequence variants in ABCA1 account for a significant proportion of low HDL. Here we demonstrate that cholesterol efflux defects are a common feature in subjects with low HDL, even in the absence of coding sequence mutations in ABCA1. Furthermore, we provide preliminary evidence that, even in the absence of ABCA1 coding mutations, defective cholesterol efflux is a heritable cellular phenotype that cosegregates with low HDL.

Methods

Selection of Hypoalphalipoproteinemia Subjects and Controls

Patients referred to the Lipid Clinic of the University of Ottawa Heart Institute were selected based on the following criteria: white
race; HDL-C of <10th percentile (most <5th percentile) for age and sex; triglycerides of <95th percentile (most <75th percentile); and low-density lipoprotein cholesterol (LDL-C) of <75th percentile, measured on 2 occasions before treatment with lipid modifying medications. Exclusion criteria included diabetes and clinical conditions or medications causative of low HDL, including short bowel syndrome, nephrotic syndrome, malignancies including multiple myeloma, or treatment with stanozolol or danazol.

There was no other selection bias, as most subjects were recruited in chronological order of referral. The control group was selected among healthy and normolipidemic volunteers of the same ethnic background recruited from the Ottawa region. The study was approved by the University of Ottawa Heart Institute Human Research Ethics Committee, and written informed consent was obtained from all participants.

For all methods, please see the online data supplement, available at http://atvb.ahajournals.org.

Results

A total of 124 subjects meeting the criteria for low HDL and 48 age- and sex-matched controls were recruited for the study, as described in Methods. The recruitment was chronological and was exclusively based on referral by primary physicians. In the low HDL population, 112 of 124 had HDL cholesterol levels below the <5th percentile and 12 of 124 between the 5th and 10th percentile, whereas 73 of 124 had triglyceride levels below the <75th percentile and 50 of 124 between the 75th and 95th percentile. The ethnic origin of subjects in the low HDL and control groups was similar (see Table I in the online data supplement).

Sequence Variants in Candidate Genes

All low HDL subjects and controls were then screened for mutations in 4 candidate genes, APOAI, LCAT, PLTP, and ABCA1. Cholesterol ester transfer protein and hepatic lipase, which would require a gain-of-function mutation to decrease HDL, were not resequenced in this population.

DNA isolated from blood lymphocytes was used for sequencing of APOAI, LCAT, PLTP, and ABCA1. In APOAI, 3 novel heterozygous nonsynonymous sequence variants were detected: S36A, ΔK182, 33X (sequence numbers refer to mature apoA-I). The S36A variant is predicted to have very little effect on apoA-I structure and function, whereas the ΔK182 deletion (in the middle of helix 7 of apoA-I) is predicted to disrupt the structure of helix 7 and alter its functional properties. These predictions are based on in silico modeling of apoA-I amphipathic helices and the previously described effect of the ΔK107 mutation, which predicted that a single amino acid in the middle of the α helix disrupts the periodicity of the helix and the amphipathic nature that is necessary for helix bundle stability and protein–lipid interactions. Finally, the premature stop codon at position 33 produces a nonfunctioning apoA-I and, as expected, caused a marked reduction in plasma HDL-C.

In LCAT, 5 nonsynonymous sequence variants were detected. These included W61X, G104S, N131D, S208T, and D277N (referring to the mature protein). The novel in frame premature stop codon at position 61 would cause defective LCAT function. The novel mutation G104S, although not a drastic change, could cause LCAT functional deficiency, as other G to S mutations have been reported in familial LCAT deficiency. The mutation N131D has been reported by others to cause fish-eye disease in subjects homozygous for this mutation. The previously reported sequence variant S208T was detected in 1 subject in the control population (a thin physically active woman with a HDL-C at the 25th percentile) and in 2 subjects in the low HDL population, suggesting that this mutation may contribute to low HDL. The sequence variant D277N, resulting in conversion from an acidic to a neutral residue, is also novel.

In the coding region of PLTP, 2 heterozygous nonsynonymous sequence variants were detected in the low HDL population: S107Y and R459Q. By reference to a model of PLTP structure, serine 107 is in a hydrophobic binding pocket and substitution by tyrosine would greatly change the accessibility of the substrate to the binding pocket. Previous studies demonstrated the importance of the C-terminal region for the functional activity of PLTP and the arginine at position 459 is within the C-terminus. PLTP expression in COS7 cells showed that PLTP mutants S107Y and R459Q had normal and 33% decrease in specific activity relative to wild-type protein, respectively (115.3±11.2, 66.7;2±6.0 of wild-type activity). These results suggest that S107Y mutant has normal function, but the R459Q mutant had a significant reduction in activity, which could contribute to impaired HDL metabolism.

In ABCA1, a total of 19 nonsynonymous coding sequence variants; some of these we reported previously. Of these, 9 sequence variants were common polymorphisms (ie, reported in the literature as common or of similar prevalence in control subjects): P85L, R85A, R219K, V399A, V771M, V825I, I883M, E1172D, R1587K. Another 5 sequence variants, identified here, were previously reported to be disease causing: W590L (reported as W590S); C1477F (reported as C1477R); S1731C (only found in French–Canadian populations); N1800H; and 1851X. Seven sequence variants were novel: K199F, H551D, R965C, E1386Q, and D1706N. Each subject was heterozygous for their respective coding sequence change, with the exception of 1 subject homozygous for the E1386Q variant. Eight subjects with sequence variants in ABCA1 had defective cholesterol efflux (measured in repeated assays cholesterol-loaded monocyte-derived macrophage [MDMs]), and these ABCA1 sequence variants were tested in an in vitro expression system for cholesterol efflux activity. ABCA1 proteins containing the sequence variants W590L, C1477F, D1706N, S1731C, or N1800H were all found to have significantly impaired cholesterol efflux, whereas the H551D and E1386Q variants had very minor, if any, effects on cholesterol transport (Figure 1A). The H551D variant had close to normal efflux capacity but reduced cell surface presentation (Figure 1B), thereby affecting activity. As it was previously shown that deletion of the C-terminal 60 aa of ABCA1 inactivates its cholesterol transport function, the 1851X variant would also be predicted to lose cholesterol efflux activity. Therefore, 7 of the ABCA1 sequence variants are clearly loss-of-function mutants.

In summary, the nonsynonymous sequence variants detected in the population included 3 novel heterozygous mutations in APOAI (2 predicted to affect activity), 5 heterozygous mutations in LCAT (4 predicted to affect activity), 2 heterozygous mutations in PLTP (1 shown to affect
activity), and a total of 19 nonsynonymous coding sequence variants in ABCA1 (7 were classified as loss-of-function mutants) (Table 1).

**Efflux Activity in MDMs of Low HDL and Control Subjects**

MDMs were prepared from each of the low HDL and control subjects, cholesterol-loaded, and labeled by incubation with acetylated-LDL prelabeled with 3H-cholesterol. Efflux assays were performed in the absence and presence of apoA-I or HDL to evaluate ABCA1- or ABCG1/scavenger receptor class B type I–mediated efflux, respectively.

Normal efflux was defined based on values obtained for the control population. Measured apoA-I–specific efflux was close to 0.5% of the total cellular cholesterol radioactivity per 2 hours. The efflux values for the control population formed a Gaussian distribution with a mean of 0.52% and a SD of 0.07% (Figure 2). In contrast, apoA-I–mediated efflux values for the low HDL population varied over a wide range, with a mean of 0.47% and a SD of 0.20% (Figure 2). Although a large number of low HDL subjects had normal apoA-I–specific efflux rates similar to the controls, a significant proportion demonstrated low cholesterol efflux. Values were compared using the Wilcoxon nonparametric test. The median value (25th, 75th percentile) for the control and low HDL populations were 0.536 (0.4, 0.6) and 0.4 (0.26, 0.6), respectively ($P=0.0156$). The Ansari–Bradley 2-sample test was performed to compare the dispersion of the 2 sample populations. A probability value of 0.0045 demonstrated that the 2 populations were distributed significantly differently.

Subjects were defined as efflux defective on the basis of efflux values 2 SD below the mean for the control subjects (efflux <0.38%). Twenty-three low HDL subjects were recalled, and the efflux assays were repeated. In every case, the defective or normal efflux values were confirmed, with an average variance of 26%. This is in accordance with a previous study that efflux in MDMs from the same individual measured multiple times over 10 months varied by 25%.

Forty-one low HDL subjects (33%) met the criterion for defective efflux as compared with only 1 control subject (2%). Thus, defective apoA-I/ABCA1-mediated cholesterol efflux was uniquely prevalent in subjects with low HDL. In contrast, we observed no defect in HDL-mediated efflux in any of the low HDL subjects.

**Figure 1.** Efflux assay and cell surface expression of ABCA1 mutants describes mutations leading to impaired ABCA1 activity. The ABCA1 sequence variants, with the exception of the 1851Stop mutant, were tested in an in vitro expression system.38 The mutations were encoded into ABCA1 and then compared with wild-type ABCA1 in a standardized ABCA1 cell expression system (HEK 293 cells). A, The efflux of radioactive cholesterol to apolipoprotein A-I (10 µg) for 20 hours was measured. All mutants were found to have significantly impaired cholesterol efflux, with the exception of E1386Q and H551D. Q2215X is a truncation mutant and was used to demonstrate that the C terminus of ABCA1 is necessary for function, and therefore the 1851X mutant would also be nonfunctional. The percentage of cholesterol efflux (cpm media/cpm media + cell-associated cpm)×100 (where cpm indicates counts per minute) was determined by scintillation counting. B, Cell surface expression was measured at 4°C by binding of an M2 anti-FLAG antibody to the cells. Cell surface ABCA1 was calculated as counts per minute of 125I-labeled secondary antibody bound per milligram of total cell protein. The H551D mutant had significantly decreased cell surface presentation.

**Figure 2.** A significant proportion of low HDL subjects have low efflux. MDMs from 124 low HDL subjects and 48 control subjects were cultured and loaded with acetylated LDL before a cholesterol efflux assay was performed for 2 hours (see Methods). The average efflux for the control subjects was 0.52±0.07% per 2 hours, demonstrating that 41/124 low HDL subjects fall below 2 SDs (33%). Each square represents a low HDL subject, and each triangle represents a control subject.

**Table 1.** Summary of the Screening of a Low HDL Population for Functional Mutations in ApoA-I, ABCA1, LCAT, and PLTP

<table>
<thead>
<tr>
<th>Mutations</th>
<th>No. of Subjects</th>
<th>Percentage of Total Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>ApoA-I 23X, ΔK182</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>ABCA1 7F, W590L, C1477F, D1706N, S1731C, N1800H, 1851X</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>LCAT W61X, G104S, N131D, S208T</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>PLTP R459Q</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Unknown</td>
<td>88</td>
<td></td>
</tr>
</tbody>
</table>

Total no. of subjects was 124.
Native Gel Electrophoresis of Plasma From Low HDL Subjects

HDL particle size of control and low HDL subjects were evaluated by native gel electrophoresis followed by Western blot against apoA-I. Compared with a control subject with normal HDL-C levels (1.31 mmol/L) and a high HDL subject (3.25 mmol/L), the low HDL subjects (0.42 and 0.62 mmol/L) had significantly smaller apoA-I–containing particles and little apoA-I found in the regions corresponding to buoyant HDL2 size particles (supplemental Figure I). This pattern was true of the 18 low HDL subjects tested (data not shown).

There was an observable but not quantifiable correlation between plasma HDL-C levels and the amount of immunodetectable apoA-I. Interestingly, there was no difference among subjects with LCAT, APOAI, or ABCA1 heterozygous mutations or unknown conditions in terms of particle size (data not shown). Thus, the low HDL state in study subjects was characterized by small, lipid-poor HDL particles.

Segregation of Low HDL Subpopulations

After exclusion of all subjects with sequence variants in APOAI, LCAT, or PLTP, subjects were divided into 4 age- and sex-matched groups: group A (low HDL-C, low efflux, no ABCA1 mutation); group B (low HDL-C, low efflux, ABCA1 mutation); group C (low HDL-C, normal efflux); group D (controls with normal HDL-C and normal efflux). The age, body mass index, total cholesterol, triglyceride, and LDL- and HDL-cholesterol of the subjects in each group are summarized in Table 2. The control group (group D) demonstrated plasma levels of triglycerides and LDL-C that were similar to other groups and, by definition, higher HDL-C and hence higher total cholesterol concentrations. The 3 low HDL-C groups demonstrated similar plasma lipoprotein values, and all groups were well matched for age, sex, and body mass index. None of the control subjects had clinical evidence of cardiovascular disease, whereas 8% of subjects in the low HDL-C groups had a documented history of coronary artery disease (data not shown).

Heritability of Efflux Defects

Relatives of low HDL subjects (those with low efflux: group A) were also recruited. MDMs were isolated and cultured, and an efflux assay was performed. As a positive control, we recruited first-degree relatives of a group B subject possessing a novel ABCA1 mutation, H551D. In this family, there was a clear cosegregation of ABCA1 carrier status, low HDL, and low efflux (Figure 3). The families were of different European white backgrounds: family 1, French Canadian; family 2, English German; family 3, Great Britain. In these 3 families with normal ABCA1 coding sequence, we also noted cosegregation of low HDL with low cholesterol efflux (Figure 3). Although the size of these kindreds was small, these results provide preliminary evidence of a heritable low efflux/low HDL phenotype not linked to an ABCA1 mutation.

Discussion

We have made a number of significant findings regarding the prevalence of mutations in a low HDL population. Approximately one-third of subjects recruited with low HDL exhibited cellular cholesterol defects, and the majority of these subjects did not have functional mutations in ABCA1 (Table 1). Overall, nonsynonymous sequence variants in major candidate genes were found in a minority (25%) of low HDL subjects. Loss-of-function mutations in ABCA1 were documented in 6% of the present low HDL cohort, but the total number of rare nonsynonymous variants19 represented a prevalence of 15%. In subjects in the Dallas Heart Study, we reported nonsynonymous sequence variants in ABCA1 in 10.9% of subjects with HDL-C concentrations below the 5th percentile, as compared with 1.6% of subjects with HDL-C of >95th percentile. Similarly, Marcil et al40 reported coding sequence variants in ABCA1 mutations in 16% of 64 subjects with HDL-C concentrations below the 5th percentile. Population differences as well as criteria for subject selection and in the definition of cutoff values for an efflux defect may account for these small reported differences in the prevalence of lipid efflux defects and ABCA1 mutations in HDL deficiency. A recent study of a large Turk population with generally low HDL identified common polymorphisms, in-

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**TABLE 2. Demographics, Lipid Levels, and Efflux Activity in Low HDL-C and Control Groups**

<table>
<thead>
<tr>
<th>Low HDL Groups</th>
<th>Group D (Control)</th>
<th>Total Low HDL Group</th>
<th>Group A (Low HDL, Low Efflux, Normal ABCA1)</th>
<th>Group B (Low HDL, Low Efflux, ABCA1 Mutation)</th>
<th>Group C (Low HDL, Normal Efflux, Normal ABCA1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No.</td>
<td>48</td>
<td>124</td>
<td>33</td>
<td>7</td>
<td>74</td>
</tr>
<tr>
<td>Age, y</td>
<td>48.9±14.8</td>
<td>55.0±10.5</td>
<td>53.7±12.5</td>
<td>62.9±9.1</td>
<td>54.9±11.5</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>27.3±3.8</td>
<td>26.9±3.9</td>
<td>28.9±5.6</td>
<td>31.1±5.4</td>
<td>26.9±3.9</td>
</tr>
<tr>
<td>TC, mmol/L</td>
<td>5.37±1.09</td>
<td>4.45±1.39*</td>
<td>4.44±1.02*</td>
<td>3.77±1.18*</td>
<td>4.53±1.57*</td>
</tr>
<tr>
<td>HDL-C, mmol/L</td>
<td>1.35±0.22</td>
<td>0.62±0.13*</td>
<td>0.64±0.14*</td>
<td>0.59±0.19*</td>
<td>0.63±0.13*</td>
</tr>
<tr>
<td>LDL-C, mmol/L</td>
<td>3.23±0.93</td>
<td>2.93±1.39</td>
<td>2.75±0.88</td>
<td>2.21±0.87</td>
<td>3.11±1.59</td>
</tr>
<tr>
<td>TG, mmol/L</td>
<td>1.72±0.84</td>
<td>2.13±1.15</td>
<td>2.39±1.08</td>
<td>2.11±1.05</td>
<td>2.00±1.07</td>
</tr>
<tr>
<td>Efflux, %</td>
<td>0.52±0.07</td>
<td>0.47±0.20</td>
<td>0.27±0.07*</td>
<td>0.30±0.05*</td>
<td>0.57±0.15</td>
</tr>
</tbody>
</table>

Values are the mean±SD; fasting plasma lipid levels were determined before any lipid modifying treatment. BMI indicates body mass index; TC, total lipoprotein cholesterol; LDL-C, calculated LDL-C; TG, triglyceride; efflux, measured cholesterol efflux value calculated as percentage of radioactive cholesterol effluxed per total cellular radioactive cholesterol per 2 h. *P<0.05 vs controls (group D).
including a functional promoter polymorphism in \textit{ABCA1}, C-14T, associated with HDL.\textsuperscript{41} In this study, we sequenced exons, and intron/exon boundaries in all subjects. We also sequenced 2 kb of the \textit{ABCA1} proximal promoter in 50 low HDL subjects. The polymorphism in the Turkish population would be within this region, but we did not detect the C-14T variant in any of the subjects analyzed. We cannot rule out the possibility that additional regulatory sequences further upstream or in the 3’ flanking sequence may affect \textit{ABCA1} gene expression. As part of the present study, we have also documented the overall prevalence of nonsynonymous sequence variants in \textit{APOAI, PLTP}, and \textit{LCAT} in a large population of low HDL subjects. We identified 3 coding sequence variants in \textit{APOAI}, representing less than 3% of our low HDL cohort. A similar prevalence (6%) was noted in 65 children with HDL-C below the 5th percentile selected from a group of 1264 Japanese school children, representing a general population frequency of less than 1%.\textsuperscript{42} Mutations of \textit{LCAT} may lead to either familial LCAT deficiency or fish-eye disease, characterized by marked hyperalphalipoproteinemia.\textsuperscript{7–9} Here in the cohort of 124 low HDL subjects, we have identified 5 heterozygous nonsynonymous sequence variants in \textit{LCAT}. Assuming that all of these are disease causing, mutations in \textit{LCAT} would account for approximately 4% of low HDL, consistent with findings in a previous study of 66 subjects with hyperalphalipoproteinemia.\textsuperscript{20} Finally, we have identified 2 novel sequence variants in \textit{PLTP}, and functional analysis of these mutants revealed that 1 of these had reduced in vitro activity. This is the second study to examine the incidence and functional consequences of naturally occurring sequence variants in \textit{PLTP} in a low HDL population. Our findings indicate that mutations in \textit{PLTP} are an uncommon cause of partial HDL deficiency. Aouizerat et al recently reported 4 missense mutations in \textit{PLTP} in 276 low HDL subjects, only 1 of which was associated with decreased transfer activity.\textsuperscript{12}

Importantly, we demonstrate that one-third of HDL-deficient subjects (41/124 subjects) exhibit cellular cholesterol efflux defects and that the majority of these individuals do not harbor functional mutations in \textit{ABCA1} (34/41 subjects). Overall, functional nonsynonymous sequence variants in major candidate genes contribute to the low HDL-C phenotype in a minority (12%) of subjects (Table 1). Thus the majority of low HDL syndromes (88%) with or without documented cholesterol efflux defects are not attributable to coding-sequence variants in the 4 major candidate genes. Further studies in this population may identify novel genes causally linked to HDL deficiency and the regulation of cholesterol efflux. For example, we have recently demonstrated in a parallel study that cathepsin D, a lysosomal aspartic protease, affects cholesterol efflux by regulating \textit{ABCA1} function.\textsuperscript{43}

The most relevant tissues for HDL production are the liver, intestine, and macrophages. However, MDMs are the most pertinent human cell type in which to study HDL metabolism and cholesterol efflux mechanisms relevant to reverse cholesterol transport. This is the first large-scale study using human macrophages. In addition to demonstrating that 33% of the low HDL subjects had low cholesterol efflux, we were able to show, in 3 families, cosegregation of low efflux with an HDL-deficient state. Although these studies need to be expanded to include larger kindreds, the results suggest that the low-efflux phenotype in the absence of \textit{ABCA1} mutations is inheritable. In a follow-up study, we have measured \textit{ABCA1} mRNA levels by real-time polymerase chain reaction and showed that \textit{ABCA1} mRNA levels are reduced in low HDL-C subjects as compared with controls. However, we noted no significant difference in MDM \textit{ABCA1} mRNA levels between subjects with and without efflux defects, suggesting that the defective efflux phenotype was not caused by reduced \textit{ABCA1} gene expression (L. Sarov-Blat et al, manuscript submitted). Future studies will focus on the
identification of novel genes and gene products regulating cholesterol efflux to lipid poor apoA-I.

In conclusion, the prevalence of efflux defects is high in subjects with partial HDL deficiency, but a majority of the efflux defective low HDL subjects do not harbor mutations in major candidate genes, suggesting that novel targets can be identified from this population and that novel pathways may exist for examination of low HDL syndromes.

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Disclosures
None.

References


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