The Low HDL Cholesterol/High Triglyceride Trait

Dennis L. Sprecher, Heather S. Feigelson, and Peter M. Laskarzewski

In 748 probands and 3,283 first-degree relatives from the Collaborative Lipid Research Clinics (LRC) Family Study, our specific aim was to examine the degree to which low (bottom decile) high density lipoprotein cholesterol (HDL-C, hypoalpha) and high (top decile) triglyceride (TG, hyperTG) levels occur conjointly (CT) and to what extent these characteristics were shared within families. To control for family size and permit a comparison with the proband percentages, mean familial percentages of HDL-C/TG abnormalities were calculated. Concurrent low HDL-C and high TG levels were present in 2.7% of the probands, a value that was enriched to 12.7% (p=0.003) of their associated first-degree relatives. If the proband had a low HDL-C value, 7.7% (p=0.013) of relatives had CT. Familial (proband and at least one first-degree family member share the same lipoprotein/lipid phenotype) hypoalpha was observed in 2.4% of families while familial hyperTG was observed in 4.1%. Familial CT was seen in approximately 0.7%. If the proband had CT, 80% of their families had at least one other first-degree member with an HDL-C/TG abnormality, whereas the corresponding percentage for families associated with probands with only hypoalpha was 64% and for those with hyperTG alone, 54%. A broadly shared environmental factor cannot easily explain the familial association of hypoalpha, hyperTG, and CT. In probands with low HDL-C values alone or the conjoint low-HDL-C/high-TG trait, family screening is extremely valuable because low HDL-C/high TG is enriched in the respective family members, a conjoint trait closely associated with increased coronary heart disease risk. (Arteriosclerosis and Thrombosis 1993;13:495-504)

KEY WORDS • hypoalphalipoproteinemia • familial hypertriglyceridemia

The results of the Helsinki Heart Trial1 and less directly, the Familial Atherosclerosis Treatment Study2 and the Cholesterol Lowering Atherosclerosis Study3 have focused interest on the hypothesis that raising high density lipoprotein cholesterol (HDL-C) and lowering triglyceride (TG) and low density lipoprotein cholesterol (LDL-C) levels may reduce the risk of coronary heart disease (CHD). In the Helsinki Heart Trial, CHD events were reduced in hypertriglyceridemic (hyperTG) individuals regardless of their LDL-C levels (lipoprotein phenotypes IIB or IV).4 In the Seattle myocardial infarction survivor study of Goldstein et al5 as well as in the Stockholm Ischemic Heart Disease Trial,6 nearly half of the subjects studied were hyperTG. In the Stockholm study,5 reduction in ischemic heart disease mortality was directly related to TG lowering. It is likely that many of the Stockholm patients also had depressed HDL-C levels.6 Regrettably, HDL-C was not measured in either the Seattle or Stockholm investigations.5,6

The close association of a primary depression of HDL-C levels with CHD has been well documented.7-10 As previously defined, primary and “familial” hypoalphalipoproteinemia (hypoalpha; hypoalphalipoproteinemic proband and at least one similarly affected first-degree family member) excluded kindreds in which the proband had a TG level greater than the age-, sex-, and race-specific 90th percentile.11 This may be appropriate in that metabolic differences between patients with low HDL-C levels alone and those with low HDL-C and concurrent high TG levels have been reported.12 However, the Collaborative Lipoprotein Phenotype Study has indicated an association between CHD and HDL-C levels, independent of TG, whereas the association between TG and CHD appears to be HDL-C dependent.13 Patients with depressed HDL-C in association with elevated TG levels are commonly observed clinically.14,15 A conjoint dyslipidemia that, according to the Framingham data, is related to an enhanced risk for the development of cardiac disease.16 To date, neither family transmission, prognostic, nor treatment implications of the conjoint low HDL-C (bottom decile; hypoalpha)/high TG (top decile; hyperTG) phenotype (conjoint trait [CT]) have been closely evaluated, perhaps in part because it has been assumed that a low HDL-C level alone was the independent predictor of CHD outcome. The potential genetic transmission of this CT has been previously evaluated through quantitative genetic methods using the Lipid Research Clinics (LRC) Family Study data.17,18 It has been demonstrated that factors beyond the family environment are critical to the familial expression of the dual lipoprotein phenotype.17,18

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Our specific aim was to determine whether and to what degree low HDL-C and high TG levels occur conjointly and to characterize the families that are associated with a proband having this low HDL-C/high TG trait, as compared with those families associated with a proband having a low HDL-C or high TG level alone.

Methods

The LRC Family Study, which has been previously described, was used in this analysis. The Family Study random sample contains 942 probands of all ages. By selecting all white probands regardless of age, we included 748 probands and their 3,283 first-degree relatives in the analysis. Spouses were excluded, as were probands who had no first-degree relatives.

After a 12-hour fast, blood was obtained for quantification of plasma total cholesterol, TG, HDL-C, and LDL-C, following previously described LRC methodology. The Quetelet index (QI) was calculated as (weight/height²) × 1,000.

All subjects were classified into LRC age- and sex-specific percentile distributions for each of their HDL-C, TG, LDL-C, and QI values. These distributions were then used to identify all hypoalpha (bottom-decile HDL-C) probands. Their first-degree relatives were then classified as either “familial” or “nonfamilial” hypoalpha. Consistent with previous publications that examined familial hypoalpha, suspected familial hypoalpha was arbitrarily identified in family units in which the proband and at least one first-degree relative demonstrated hypoalpha without concurrent high TG.

Hence, nonfamilial was defined for those family units in which the proband was hypoalpha but there were no hypoalpha first-degree relatives. Familial hyperTG was defined as the presence of upper-decile TG for the proband (regardless of the HDL-C level) and upper-decile TG for at least one additional family member. Finally, familial CT was defined as a proband with CT (bottom-decile HDL-C and top-decile TG) and at least one first-degree family member with CT.

Kindred distributions of HDL-C and TG were then compiled as follows. First, the number of probands was counted, as was the number of their first-degree relatives. Second, the age- and sex-specific percentile of each variable for each family member was determined (using the LRC percentile distributions). Then the overall distribution of family members was obtained by averaging the percentage of a family in a given percentile range over the total number of families. For example, if family No. 1 had 20% of its members below the 10th percentile of the HDL-C distribution, family No. 2 had 50% of its members below the 10th percentile, and family No. 3 had 0% of its members below the 10th percentile, the average percentage below the 10th percentile of the HDL-C distribution for the three families would be 23.33%. This method of averaging allows each family to be weighted equally, regardless of family size.

To assess the degree to which hypoalpha and hyperTG occur conjointly, probands were categorized into one of three groups: 1) hypoalpha, hyperTG (conjoint trait, CT); 2) hypoalpha, normal (<90th percentile) TG; or 3) normal (>10th percentile) HDL-C, hyperTG. First-degree relatives of these probands were then classified as hypoalpha, hyperTG, or both, and the average percentages computed as above. The percentage of probands and the percentage of affected families with more than one first-degree relative with LDL-C >90th percentile were also determined, in part to assess the likelihood of familial combined hyperlipidemia.

Significance associated with the average percentage of a family demonstrating a disorder was evaluated empirically. Distributions were generated by drawing 1,000 samples each of 44, 20, and 46 individuals from the 748 families. Average percentages of family members with a specific disorder were computed. For example, 44 probands were randomly selected from the 748 families in the random cohort. This procedure was repeated 1,000 times. The average percentage of family members among each sample of 44 individuals with the traits 1) hypoalpha alone, 2) hyperTG alone, 3) CT, 4) hypoalpha (normal TG and hyperTG), 5) hyperTG (hypoalpha and normal HDL-C), and 6) hypoalpha and/or hyperTG was then computed, yielding a frequency distribution of average percentages. The average percentage of family members demonstrating a specific trait was considered to be significantly high or low if it was either greater than the 97.5th percentile or less than the 2.5th percentile. This can be thought of as being equivalent to a two-tailed test of statistical significance with α = 0.05. The distributions of the empirical analyses are presented in the “Appendix.”

The aforementioned analysis was repeated, excluding all individuals with ages less than 20 years. In addition, all probands and family members with a QI and LDL-C >90th percentile were identified.

Results

Sixty-four probands (8.6%) had a bottom-decile HDL-C and a total of 303 family members, resulting in an average family size of 5.7 (including the proband). Of these 64 probands, 44 had hypoalpha with TG ≤90th percentile and 20 had hypoalpha with a top-decile TG. Spouses have been excluded from all computations. The TG distribution of the 64 probands with bottom-decile HDL-C exhibits a pronounced skew, with 84% of the probands found in the upper half of the distribution and 31% in the upper decile. Seventy-eight percent of the probands with bottom-decile HDL-C have a QI in the upper half of their respective age- and sex-specific distribution.

An average of 22% of all first-degree relatives of probands with bottom-decile HDL-C is contained in the bottom decile of their respective age- and sex-specific HDL-C distribution. Moreover, 23% of the first-degree relatives of probands with bottom-decile HDL-C are found in the upper decile of their TG distributions. Thirty-two percent of the first-degree relatives of hypoalpha probands were in the upper quartile of their QI distributions, with 12% in the upper decile.

Thirty-three of the 64 families were classified as familial hypoalpha as previously described. The familial probands had 193 first-degree relatives with an average family size of 6.8 (including the proband), which is about twice the size of nonfamilial hypoalpha families. The percentage of familial hypoalpha first-degree relatives estimated to fall within percentiles of their age- and sex-specific HDL-C, TG, and QI distributions is shown in Figure 1. An average of 42% of first-degree relatives of probands with bottom-decile HDL-C and TG, as well as a QI, were familial hypoalpha.
relatives are hypoalpha. Thirty-one percent of first-degree relatives were found to be hyperTG, and 17% are in the upper decile for QI.

Figure 2 represents all 110 families in which the proband has one of the three HDL-C/TG abnormalities. Each column of three boxes represents one family. For example, in the last column in Figure 2a, "Families of Probands With Low HDL-C Alone," the family has 14 first-degree family members exclusive of the proband. Two of these members have bottom-decile HDL-C alone, two of these members have high TG alone, and one member has CT. The proband, as described by the subtitle, has low HDL-C alone. The proband, however, is not in the upper decile for LDL-C or QI, since no "L" or "Q" is printed above the column of boxes. Furthermore, there are no family members who are in the upper decile for either LDL-C or QI, since no "L" or "Q" is printed below the column of boxes. All other columns can be read similarly. Twenty-eight of the 44 hypoalpha families (bottom-decile HDL-C, TG <90th percentile; 64%) identified by a proband with low HDL-C alone had an HDL-C/TG abnormality. Sixteen of the 20 families (80%) identified by probands with CT had first-degree relatives with an HDL-C/TG abnormality. HDL-C/TG abnormalities were present in 21 of 46 families (46%) identified by a proband with high TG alone. Figure 2 demonstrates that the number of affected family members increases as the size of the family increases.

One can estimate the prevalence of familial hypoalpha to be 2.4% (18/748) by using the first column of row 3 of Table 1. If TG levels are not part of the definition, the prevalence is 4.4% [(23 + 10)/748]. Similarly, one can estimate the prevalence of hyperTG to be 4.1% [(11 + 20)/748], regardless of HDL-C level, by using the last two columns of the seventh row of Table 1. These percentages reflect the arbitrary definition of familial that requires at least one family member in addition to the proband with a given trait. Altering the definition to require at least two family members in addition to the proband with a given trait yields three additional estimates: the prevalence of familial hypoalpha is estimated to be 1.1% (8/748); if TG levels are not part of the definition, the prevalence is 2.8% [(14 + 7)/748]; and the estimate of the prevalence of hyperTG, regardless of HDL-C level, is 2.1% [(8 + 8)/748]. One can also note that the percentage of families related to a CT proband having two or more first-degree relatives with an HDL-C/TG abnormality is enhanced when compared with similar families of probands with either low HDL-C alone or high TG alone (60% versus 43% or 22%, respectively).

To distinguish familial combined hyperlipidemia from HDL-C/TG abnormalities, especially CT, the LDL-C distributions for probands and family members are also presented in Figure 2. The percentages of probands with upper-decile LDL-C in the CT and high-TG groups (i.e., coincident high LDL-C and high TG) are 15% and 9%, respectively. In the low-HDL-C proband group, high LDL-C is observed in 14%. The percentage of families (exclusive of probands) in which one or more members express upper-decile LDL-C and TG (in combination or separately) is 23%, 25%, and 24% for low HDL-C, CT, and high-TG-proband–defined family groups, respectively. This percentage is 14% (101/748) when all 748 families are analyzed. LDL-C and TG levels do not distinguish those families specifically related to a CT proband. Furthermore, the apparent enrichment for LDL-C/TG elevations among HDL-C/TG–abnormal subjects is at least partially due to an already enhanced frequency of hyperTG. Therefore, this small discrepancy in percentage is inconsistent with
### a) Families of Probands with Low HDL-c Alone (n=44)

<table>
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<th>Number of Family members</th>
<th>Proband descriptor</th>
<th>Family member descriptor</th>
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<tr>
<td></td>
<td>L</td>
<td>1. LDL-c&lt;90%ile in proband</td>
</tr>
<tr>
<td></td>
<td>Q</td>
<td>2. LDL-c and Q&lt;90%ile in proband</td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>Both LDL-c and Q&lt;90%ile in proband</td>
</tr>
</tbody>
</table>

#### Number of Affected Family Members
- with low HDL-c alone
- with CT
- with high TG alone

#### Number of Family members
 1. 2. 3. 4. 5. 6. 7. 8. 9. 10. 11. 12.

### b) Families of Probands with CT (n=20)

<table>
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<td>L</td>
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</table>

#### Number of Affected Family Members
- with low HDL-c alone
- with CT
- with high TG alone

#### Number of Family members
 1. 2. 3. 4. 5. 6. 7. 8. 9. 10. 11. 12.

### c) Families of Probands with High TG Alone (n=46)

<table>
<thead>
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<tbody>
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</table>

#### Number of Affected Family Members
- with low HDL-c alone
- with CT
- with high TG alone

#### Number of Family members
 1. 2. 3. 4. 5. 6. 7. 8. 9. 10. 11. 12.

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**Figure 2.** Graphs showing prevalence of cholesterol and triglyceride abnormalities in 110 families. Each column in Figures 2a, 2b, and 2c represents the family of a proband with low high density lipoprotein cholesterol (HDL-C; panel a) alone, conjoint trait (CT; panel b), or high triglyceride (TG; panel c) alone. The first row designates family members with low HDL-C alone. The second row designates family members with CT. The third row designates family members with high TG alone. The bracketed numbers under column clusters represent the number of family members represented in each column. A boldface symbol above a column indicates that the proband has upper-decile low density lipoprotein cholesterol ("L"), upper-decile Quetelet index ("Q"), or both ("B"). Absence of a symbol above the column indicates a lack of these characteristics in the proband. A symbol beneath the column indicates that at least one family member (exclusive of the proband) has upper-decile low density lipoprotein cholesterol ("L"), upper-decile Quetelet index ("Q"), or both ("B"). The latter "B" denotes a family with at least one member with both characteristics or at least two members, each of whom has at least one of the two characteristics. Absence of a symbol indicates the lack of these characteristics in any of the family members. LDL-C, low density lipoprotein cholesterol.
an equivalence between the HDL-C/TG–abnormal cohort and familial combined hyperlipidemia. Finally, there is not enough evidence to suggest a relation between high TG, low HDL-C, or CT phenotypes in family members and their specific expression of high LDL-C levels (Figure 2).

Upper-decile QI is found in 14%, 15%, and 17% of probands and in at least one member of 41%, 25%, and 24% of families for low-HDL-C-alone-, CT-, and high-TG-alone-proband–defined groups, respectively. High QI appears to be enriched particularly in the low-HDL-C families. High QI in at least one family member is found in 29% (215/748) of the full random cohort.

Figure 3 summarizes the data given in Figure 2 for the individual families. Hypoalpha, hyperTG, and CT are displayed as they occur in probands and their first-degree relatives. The uppermost two intersecting circles represent data for the probands. The left circle represents all hypoalpha probands (n=64, 5.9%+2.7%=8.6% of 748 total probands), whereas the right circle represents all hyperTG probands (n=66, 2.7%+6.1%=8.8% of 748 total probands). The overlap of these two proband groups represents CT, hypoalpha/hyperTG (2.7%). The other three sets of intersecting circles represent the average percentage of first-degree relatives of the probands in each phenotypic group. They represent 214, 89, and 193 first-degree relatives, respectively (left to right).

In the left pair of intersecting circles in Figure 3 (families associated with low-HDL-C-alone probands), CT is observed in 7.7% of first-degree relatives, an enhanced frequency (p=0.016). The left circle represents the percentage of the average family with hypoalpha (12.4%+7.7%=20.1%, p=0.001), whereas the right circle represents the percentage of an average family with hyperTG (7.7%+12.9%=20.6%, p=0.005). Hypoalpha/normal TG is observed in 12.4% of first-degree relatives (p=0.003). Normal HDL-C/hyperTG is observed in 12.9% of first-degree relatives (p=0.065).

The bottom pair of intersecting circles represents families of probands with conjoint hypoalpha/hyperTG (Figure 3). This proband phenotype was associated with the most striking enrichment in first-degree relatives affected with HDL-C/TG abnormalities, with a significant increase in the average percentage of family members with each trait. Specifically, hypoalpha occurs in 28.5% of family members (p<0.0001), hypoalpha alone in 15.8% (p=0.004), hyperTG in 29.3% (p<0.001), and hyperTG alone in 16.6% (p=0.022), and finally CT is observed in 12.7% of family members (p=0.003).

The right pair of intersecting circles demonstrates the prevalence of hypoalpha, hyperTG, or CT in first-degree relatives of probands having normal HDL-C/ hyperTG. Only the percentage of family members with hypoalpha alone approaches significance, that being significantly smaller than one would expect in a random distribution (p=0.055). Distribution of HDL-C/TG abnormalities and related statistical analyses are generally unaffected when subjects less than 20 years of age are removed.

Comparison of CT- and high-TG-alone-proband–associated families indicates that each subgroup (hypoalpha alone, CT, and hyperTG alone) is relatively enriched in the CT proband–associated first-degree relatives (p=0.001, p=0.009, and p=0.047, respectively). Hypoalpha overall (p<0.001) and hyperTG overall (p<0.001) are observed more frequently in CT proband–associated family members. A comparison of all HDL-C/TG abnormalities between these two groups also demonstrates a significant difference (45.1% versus 16.4%, p<0.001).

Comparison of CT- and low-HDL-C-alone-proband–associated families indicates that only hypoalpha overall, hyperTG overall, and hypoalpha and/or hyperTG are marginally enriched in the CT proband–associated first-degree relatives (p=0.057, p=0.050, and p=0.032, respectively). While the average percentages of a family with hypoalpha alone, hyperTG alone, and CT are higher in the CT proband–associated families, they are not significantly higher.

**Discussion**

The estimated prevalence of familial hypoalpha (2.4%), familial hyperTG (4.1%), and familial CT (0.7%), the latter being newly described in this report, has been determined in the random sample of the LRC Family Study. In addition, there appears to be a unique enrichment pattern of HDL-C/TG phenotypes among three groups of first-degree family members, where each

### Table 1. Number of Proband-Defined Families With Specific Family Member Phenotypes

<table>
<thead>
<tr>
<th>No. of affected family members*</th>
<th>Affected family member phenotype</th>
<th>Low HDL-C alone (n=44)</th>
<th>CT (n=20)</th>
<th>High TG alone (n=46)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥1</td>
<td>Low HDL-C</td>
<td>23</td>
<td>10</td>
<td>13</td>
</tr>
<tr>
<td>≥2</td>
<td>Low HDL-C</td>
<td>14</td>
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<td>7</td>
</tr>
<tr>
<td>≥1</td>
<td>Low HDL-C alone</td>
<td>18</td>
<td>8</td>
<td>6</td>
</tr>
<tr>
<td>≥2</td>
<td>Low HDL-C alone</td>
<td>8</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>≥1</td>
<td>CT</td>
<td>12</td>
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<td>5</td>
<td>5</td>
</tr>
</tbody>
</table>

HDL-C, high density lipoprotein cholesterol; CT, conjoint trait; TG, triglyceride.

*"≥" Indicates at least one or two affected family members.
LEFT CIRCLE: low HDL-c
RIGHT CIRCLE: high TG

The average percentage of family members among 44 families of low HDL-c--normal TG probands (214 total first-degree family members). 33.0% (p=0.001)

The average percentage of family members among 46 families of normal HDL-c--high TG probands (193 total first-degree family members). 16.4% (p=0.001)

The average percentage of family members among 20 families of low HDL-c--high TG probands (89 total first-degree family members). 45.1% (p=0.001)

FIGURE 3. Graphical distribution of high density lipoprotein cholesterol (HDL-C)--triglyceride (TG) phenotypes is presented for the probands (top pair of circles) and first-degree relatives of a specific proband phenotype (three lower pairs of circles). The percentage of individuals with hypoalphalipoproteinemia (hypolipidemia, or low HDL-C; left circle) is denoted by the number in boldface type to the left of this circle. The percentage of hypertriglyceridemia (hyperTG, or high TG; right circle) is denoted by the number in boldface type to the right of this circle. The percentage with hypolipidemia and/or hyperTG is presented underlined beneath each of the four intersecting circles. The three percentages within the circles sum to the aforementioned percentage. For the probands, the percentages reflect the fraction of all probands. In all other cases, the average percentage of first-degree relatives affected is presented.
group is defined as having a related proband who expresses only one of the following: hyperTG, hypoalpaha, or CT. These data persuade the clinician to expect different familial HDL-C/TG patterns when the proband has TG elevation alone in contrast to when the proband has HDL-C reduction alone or conjoint low HDL-C/high TG.

We initially defined and enumerated those families in which the proband and at least one other first-degree family member demonstrated a specific familial HDL-C/TG abnormality. This approach permits a general estimate of familial HDL-C/TG abnormalities when large multigenerational families are not available. However, it is dependent on the number of family members required to meet the arbitrary definition of familial (Table 1). The frequency of familial hypoalpaha drops from 2.4% to 1.1% when the familial definition requirement increases from one to two affected family members, exclusive of the proband. However, the total number of subjects in a particular family is relevant to the probability of finding an expressed HDL-C/TG abnormality. Families are progressively more familial as family size increases, as noted in Figure 2. Alternatively, calculating the percentage of members within a family who express a particular phenotype adjusts for the total number of family members. Enrichment of a clinically expressed phenotype can be determined by comparing phenotype expression of a proband-identified cohort and a random distribution, the latter constructed from the overall data set. Enrichment indicates familial clustering but does not explain whether it is of environmental or genetic origin.

Within the context of a single blood measurement, results from the analysis of our data suggest (Figure 3) that low HDL-C levels measured in an adult with or without a concurrent high TG level convey a familial enrichment in both low-HDL-C and high-TG phenotypes. It appears in addition that the frequency of all HDL-C/TG abnormalities is higher in families related to CT probands versus families related to low-HDL-C-alone probands (p = 0.032). In contrast, again within the context of a single blood measurement, a high TG level measured in an adult with but not without a concurrent low HDL-C level conveys a familial enrichment in both low HDL-C and high TG. In fact, in the 46 families of normal-HDL-C/high-TG probands, only 2.8% of their first-degree relatives had bottom-decile HDL-C alone, less than expected in a random population (p = 0.055). Thus, each proband phenotype is associated with a different frequency or makeup of HDL-C/TG phenotypes in first-degree family members, thereby suggesting that the HDL-C/TG interaction may itself be transmitted among generations.

Even though there is a known inverse relation between plasma HDL-C and TG levels, there are no established guidelines (or derived genetic or environmental parameters) that provide a specific and generalizable algorithm that inversely correlates HDL-C and TG, especially among hypoalpaha subjects. Segregation and path analyses on subsets of the LRC Family Study data17,18 have focused on genetic and environmental contributions to familial lipoprotein associations. Multivariate analyses of the HDL-C-very low density lipoprotein (VLDL) relation in the Cincinnati LRC Family Study indicated moderate genetic influence and a significant residual environmental correlation for HDL-C-VLDL covariation.17 Bivariate path analysis performed in the same population suggested that the phenotypic relation between HDL-C and VLDL could not be explained exclusively in terms of common family environmental defects.18 Path analysis performed on twin families determined the HDL-C level to be influenced by both genetic and environmental factors.30 Our current study data are consistent with a genetic component related to CT but do not exclude environmental issues, findings that are congruent with previous quantitative genetic analyses performed on this same data set.18

The observation from our data that a low HDL-C level alone in the proband conveys an enrichment in high-TG states, both alone and conjoined with low HDL-C, among first-degree family members may also indicate low HDL-C to be a more stable and reliable marker for compromised TG metabolism. The mechanisms underlying low HDL-C are at least partially interdependent and are all tightly related to parameters of TG metabolism, some of which may be heritable.32 These include an increased fractional catabolic rate for apoproteinA-I (regardless of TG level) and a decreased apoproteinA-I synthetic rate4 (in low-HDL-C-normal-TG subjects), as well as alterations in intravascular HDL processing.35 In the setting of compromised TG metabolism, intravascular HDL processing due to lipid interchange with apoproteinB particles results in TG-enriched HDL particles that are smaller and depleted of their cholesterol ester moiety. These particles are potentially filtered out by the kidney.36,37 Furthermore, such an HDL particle may be less amenable to modification by lecithin:cholesterol acyltransferase and cholesterol ester transfer protein and thus less effective in the process of reverse cholesterol transport.38 Cohen and Grundy39 have reported elevated levels of postprandial lipemia, a marker for compromised TG particle processing, in high-TG/low-HDL-C but not in low-HDL-C-alone subjects.39 This is consistent with a physiological difference for the TG–HDL interaction between these two phenotypes. In addition, high-TG/normal-HDL-C may be observed when an enhanced lipoprotein lipase to hepatic lipase ratio is present,52 or when there is a reduction in lipid transfer activity.33,40 All of these HDL-C/TG phenotypes may thus represent different physiological origins, which are individually relevant to the probability of a subject suffering cardiovascular consequences.41

It is unlikely that the HDL-C/TG abnormalities are explained or differentiated on the basis of coincident familial combined hyperlipoproteinemia, since the frequency of families in which at least one member expressed upper-decile TG and one member upper-decile LDL-C levels in the current study was equivalent between groups (approximately 24%), a value that remained unchanged when subjects less than 20 years old were excluded, and was only mildly enriched compared with the 14% found in the random population of 748 families. Other described entities that are associated with abnormal TG and HDL-C levels include primary familial hypoalpaha,11,38 familial hyperTG,5 and the “atherogenic lipoprotein phenotype” locus (phenotype B), as well as hyperapobetalipoproteinemia44 and/or familial dyslipidemic hypertension.45 The underlying mechanism(s) for these above-described phenotypes, all of which predict enhanced cardiovascular risk, may share one or more pathophysiological features.11,46
Enhanced body mass may be partially responsible for familial CT, but it does not appear to fully explain the familial patterns observed. Only two of 20 CT probands had an upper-decile QI (the expected 10%). However, other measures (e.g., fat distribution) may be more relevant to these familial lipoprotein phenotypes. Furthermore and apparently independent of body mass, insulin levels are associated with HDL-C and TG, and insulin levels in turn correlated with hypertension and obesity. In addition, the expression of elevated TG levels may be age dependent. However, the equivalent distribution of HDL-C/TG abnormalities when proband and family members with ages less than 20 years are removed from the analysis does not support penetrance as a major factor in CT expression. Finally, the clear transmission of HDL-C/TG abnormalities may be complicated by the single measurement of the proband’s TG. Compared with cholesterol levels, TG plasma levels are not as highly reproducible and are more variable. In addition to the phenomenon of regression toward the mean, these factors may in aggregate be partially responsible for the lack of enrichment observed in first-degree relatives related to hyperTG probands.

In summary, the association between probands and first-degree relatives for the three defined HDL-C/TG phenotypes suggests that the HDL-C/TG inverse relation is not uniform throughout a population. Low HDL-C cannot be understood simply as a result of hyperTG levels. In the current study, when the proband had a low HDL-C with or without a high TG level, the distribution of low HDL-C, high TG, or both in their respective first-degree family members was similar, even though the enrichment of each phenotype, especially CT, was more striking among the family members related to the CT proband. However, when the proband had an increased TG with a normal HDL-C level, then the HDL-C/TG phenotype distribution in their respective first-degree family members was generally similar to that of the probands. This is important because it suggests that low HDL-C is a more critical determinant of familial hypoalpha and/or CT than hyperTG alone. Data from the Framingham Study indicate that TG values are predictors of cardiovascular risk when the population has low HDL-C levels (<40 mg/dL, approximate bottom quartile for men). Thus, the unique expression of the combined phenotype of low HDL-C and high TG values is clinically important. Therefore, when patients are found to have low HDL-C and particularly CT in the clinical setting, these data provide the basis for proceeding on to the evaluation of their generally higher-risk first-degree relatives.

Appendix

Table 2. Distributional Characteristics of First-Degree Relatives With Specified Traits for Sample Sizes Representing Three Different Proband Groups

<table>
<thead>
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<th>Trait</th>
<th>n</th>
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<th>5th</th>
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<td>8.3</td>
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<td>0.8</td>
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<td>0.6</td>
<td>0.9</td>
<td>1.3</td>
<td>3.5</td>
<td>6.3</td>
<td>7.1</td>
<td>8.2</td>
</tr>
<tr>
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<td>0.8</td>
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<td>11.7</td>
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<td>14.7</td>
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<td>9.6</td>
<td>10.2</td>
<td>11.6</td>
</tr>
<tr>
<td></td>
<td>46</td>
<td>1.6</td>
<td>2.2</td>
<td>2.7</td>
<td>5.6</td>
<td>9.1</td>
<td>10.0</td>
<td>11.0</td>
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<td>Normal HDL-C,hyperTG</td>
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<td>15.3</td>
<td>16.4</td>
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<td>11.8</td>
<td>12.5</td>
<td>18.0</td>
<td>24.3</td>
<td>25.6</td>
<td>27.1</td>
</tr>
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</table>

CT, conjoint trait; hypoalpha, hypopalphalipoproteinemia; TG, triglyceride; HDL-C, high density lipoprotein cholesterol; hyperTG, hypertriglyceridemia.
The low HDL cholesterol/high triglyceride trait.
D L Sprecher, H S Feigelson and P M Laskarzewski

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