Familial Aggregation of Blood Lipid Response to Exercise Training in the Health, Risk Factors, Exercise Training, and Genetics (HERITAGE) Family Study

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Background—Fasting levels of plasma lipids and lipoproteins are reported to improve with regular exercise training. However, little is known on whether the training responses are influenced by heritable factors.

Methods and Results—The lipid profile was assessed in 115 black (224 individuals) and 99 white families (469 individuals), who participated in the HERITAGE Family Study, while in a sedentary state (baseline visit) and after exercise training for 20 weeks (post visit). Variables included total cholesterol, triglyceride, low-density lipoprotein cholesterol (LDL-C), apolipoprotein B (ApoB), high-density lipoprotein cholesterol (HDL-C), apolipoprotein A-I, and HDL-C subfractions 2 (HDL2-C) and 3 (HDL3-C). Familial correlations for the training responses (Δ=post−baseline) were significant for most variables, and the percent variance accounted for by familial factors (ie, maximal heritabilities) ranged from 25% to 38%. Exceptions were for higher heritabilities near 60% for ΔApoB in blacks and ΔHDL2-C in whites and a lower estimate of zero for ΔLDL-C in blacks.

Conclusions—Heritable factors in part determine lipid profile responses to regular exercise. Maximal heritabilities were similar across ethnic groups and variables, except for ΔLDL-C, ΔApoB, and ΔHDL2-C. Molecular studies to identify the markers and genes associated with these influences are currently underway. (Circulation. 2002;105:1904-1908.)

Key Words: genetics ■ heritability ■ lipids ■ exercise

Plasma levels of lipids and lipoproteins are risk factors for coronary heart disease (CHD).1 Apolipoprotein B (ApoB), the primary surface component of low-density lipoprotein (LDL), functions by binding to specific receptors in the liver and peripheral tissue surface membrane for cholesterol delivery2 and is strongly associated with an increased risk for CHD.1 The anti-atherogenic effects of high-density lipoprotein (HDL)3 are thought to be associated with cholesterol removal from peripheral tissues (including arteries) directly to the liver by the reverse cholesterol transport processes.4 HDL subfraction 3 (HDL3) assimilates lipids and is converted to HDL subfraction 2 (HDL2),5 and CHD risk increases with reduced levels of either subfraction.6 Increases in the levels of the principal surface protein of HDL (apolipoprotein A-I [ApoA-I]) may reflect higher HDL synthesis and conversion of HDL1 to HDL2. Exercise training can improve the lipid profile and may reduce CHD risk.7-11 Moreover, these responses can be affected by several interacting factors12,13 such as age, sex, ethnicity, and steroid hormones, although the strongest predictors are exercise-induced plasma volume changes, dietary habits, and initial fitness levels.

Although it is well documented that baseline lipids and lipoproteins are influenced by heritable factors,14 less is known of familial components for lipid responses to exercise. That is, are some individuals, because of their genetic make-up, more likely to have an improved lipid profile with exercise training? The HERITAGE Family Study is unique with regard to investigating this question because sedentary families were assessed at baseline and then again after 20 weeks of endurance exercise training. Although there were mean changes only for high-density lipoprotein cholesterol (HDL-C), ApoA-I, and triglyceride (TG),15 there was a great deal of variability for all lipids. This variability, when contrasted between and within families, constitutes the basis for estimates of heritability. In the current investigation of...
these HERITAGE families, we address whether the responses to exercise training cluster in families.

**Methods**

**Sample and Study Design**

The HERITAGE Family Study of 99 white families (229 males, 240 females) and 115 black families (83 males, 141 females) included data at baseline and again after 20 weeks of exercise training. Family structures consisted of 2 parents and at least 2 to 3 offspring, although the black family units were often smaller. The criteria for participation have been described elsewhere. Briefly, parents were <66 years of age and offspring were >16 years of age. All were sedentary at baseline, which was defined as no regular strenuous physical activity over the previous 6 months (ie, lasts 30 minutes or more and involves an expenditure of ≥7 METs [1 MET = 3.5 mL O₂ uptake/kg/min] for subjects 50 years or older and ≥8 METs for subjects younger than 50 years). With a few exceptions approved by a physician, body mass index was ≤40 kg/m². Systolic blood pressure was ≤150 mm Hg, and diastolic blood pressure was ≤99 mm Hg. Analysis of dietary questionnaires ensured that the subjects maintained the same diet composition throughout the protocol.

Each individual was trained on a cycle ergometer 3 times per week for 20 weeks. The training intensity and/or duration was adjusted every 2 weeks to ensure that the participant was working at a heart rate associated with 75% of baseline VO₂ max for 50 minutes during the last 6 weeks. The power output was adjusted automatically to the heart rate response by a computer program that controlled the cycle ergometer during all training sessions. Sessions were supervised on site, and adherence to the protocol was strictly monitored.

**Measures**

Blood samples were obtained from an antecubital vein into Vacutainer tubes that contained EDTA and were taken in the morning after a 12-hour fast with participants in a semirecumbent position, twice at baseline, and again at 24- and 72-hours after the last training session. For eumenorrheic women, all samples were obtained in the early follicular phase of the menstrual cycle when blood plasma cholesterol alterations are minimal. Plasma samples for lipid assays were packed with ice for shipping to the Core Laboratory at the Lipid Research Center of Laval University.

Total cholesterol (TC) and TG levels were determined in plasma and in lipoproteins by enzymatic methods using a Technicon RA-500 Analyzer (Bayer Corporation Inc, Tarrytown, NY), Plasma VLDLs were isolated by ultracentrifugation. The HDL-C fraction was obtained after precipitation of LDL in the infranatant by the heparin manganese chloride method. Selective precipitation was used to isolate the HDL₂-C and HDL₃-C subfractions using dextran sulfate. ApoA-I was measured in the infranatant and ApoB was measured in the plasma and infranatant fraction by the rocket immunoelectrophoretic method.

The Apo measurements were calibrated with reference standards from the Centers for Disease Control and Prevention (Atlanta, Ga). Extensive quality control procedures were implemented to ensure that the participant was working at a heart rate associated with 75% of baseline VO₂ max for 50 minutes during the last 6 weeks. The power output was adjusted automatically to the heart rate response by a computer program that controlled the cycle ergometer during all training sessions. Sessions were supervised on site, and adherence to the protocol was strictly monitored.

**Familial Aggregation**

A sex-specific family correlation model was used to assess heritability. Four types of individuals (fathers = F, mothers = M, sons = S, and daughters = D), lead to 8 correlations within 3 groups: 1 spouse (FM), 4 parent-offspring (FS, FD, MS, and MD), and 3 sibling (SS, DD, and SD). Correlations were estimated using maximum likelihood methods, as outlined in more detail elsewhere (see Data Supplement). Maximal heritability (h²), defined as the percent of variance due to additive familial effects, was adjusted for degree of the sex by generation by race group. Only terms that were significant at the 5% level were retained.

**Results**

Table 1 gives means and standard deviations for baseline measures. For covariate adjustments (see Data Supplement), baseline level was the most consistent predictor and accounted for 10% to 40% of the variance. Other significant covariates (eg, physical activity and fitness, dietary habits, and hormonal and medication usage) accounted for <10% of the variance.

A summary of the most parsimonious familial correlations is in Table 2. A detailed description of all of the tests that lead to these models is found elsewhere (see Data Supplement). There was significant familial resemblance for most variables, with ~30% of the phenotypic variance accounted for by familial factors (maximal heritabilities). The exceptions were for no heritability for ΔLDL-C in blacks (0%) and higher estimates of ~60% for ΔApoB in blacks and ΔHDL₃-C in whites. These traditional heritabilities are expressed as a percentage of the residual variance (ie, after removing effects caused by covariates). Heritability may be expressed alternatively as a percent of total variance (Data Supplement), ie, h² = h²*(1−R²), in which h² is the heritability expressed in Table 2 and R² is the variance due to covariates.

**Discussion**

Previous studies that investigate lipid and lipoprotein responses to exercise training distinguish between acute and
No previous studies were found reporting heritability estimates for these training responses. In the current study, familial factors accounted for approximately 30% of the variation of the adjusted training responses with little evidence for ethnic differences. The exceptions were for no familial influence on \( \Delta \)LDLC (\( h^2 = 0.0 \)) in blacks and higher estimates approaching 60% for \( \Delta \)ApoB in blacks and \( \Delta \)HDL2-C in whites. These estimates also can be expressed as a percent of the total variation. For example, the total percentage of variance accounted for in \( \Delta \)LDLC in blacks is 37%, stratified into that due to the covariates (37%) and heritability (0%). Similarly, in whites, the total variance accounted for is 39%. However, it is stratified differently due to covariates (7%) and familial factors (32%). Thus, for \( \Delta \)LDLC, the total accounted for is approximately the same across ethnic groups, although the source is partitioned differently. This discrepancy between blacks and whites may indicate genetic heterogeneity in possible underlying pleiotropic genes (i.e., a gene or genes that affect multiple traits) for the LDL-training responses and the covariates. For example, baseline values of LDL-C and VO2max account for a significant percentage of the variance in blacks but not in whites. If the “genes” for initial LDL-C or fitness levels also affect the LDL response (i.e., pleiotropic effect), then the adjustment would remove their effects and the heritability would decrease. These results are consistent with Crouse et al who reported that changes in LDL-C vary depending on training level. Our results suggest this depen-
A related discrepancy specific to the black sample involves LDL-C and ApoB. The heritability for \( \Delta LDL\text{-}C \) is lower (\( h^2 = 0\% \)) than that for \( \Delta ApoB \) (\( h^2 = 59\% \pm 26\% \)). Although ApoB is the primary surface component of LDL, it is not the only carrier of ApoB; thus, we should not expect the circulating plasma levels and, therefore, the heritabilities for the 2 responses to be the same. The genetic pleiotropic hypothesis outlined above with respect to \( \Delta LDL\text{-}C \) and baseline LDL-C and \( \text{VO}_2\text{max} \) is still applicable with respect to the low \( \Delta LDL\text{-}C \) finding. However, we note that the within-individual correlation between the covariance-adjusted \( \Delta LDL\text{-}C \) and \( \Delta ApoB \) responses is significant in the blacks (\( r = 0.55 \)), which suggests that some common factors, either genetic or nongenetic, underlie their covariation. If genetic, then presumably they are pleiotropic with respect to baseline LDL-C and fitness measures. These various hypotheses for LDL-C and ApoB responses and baseline LDL-C and \( \text{VO}_2\text{max} \) warrant further investigation with multivariate methods to disentangle the possible common genetic causes.

A few studies investigated whether genetic markers are associated with lipid responses to exercise training. For example, a greater training-induced improvement was found in individuals with the E2 or E3 alleles of the apolipoprotein E genotypes. Similarly, the \( \text{PvuII} \) polymorphism of the lipoprotein lipase and the ID polymorphism of the angiotensin-converting enzyme gene were both associated with training-induced improvements. Other genes that directly or indirectly affect lipid metabolism should also be considered in this context. For example, genes that affect baseline levels of LDL include the LDL receptor, the LDL-receptor binding region of ApoB, cholesterol 7alpha-hydroxylase, and others mapped to chromosomes 1p (autosomal dominant hypercholesterolemia), 13q (LDL-C-lowering gene), and 15q (precocious hypercholesterolemia). Whether these genes also affect the lipid and lipoprotein responses to exercise training warrant investigation.

In summary, these HERITAGE data represent the first report that indicates chronic responses to exercise training are in part determined by heritable factors. The possible exception is for changes in LDL-C. However, pleiotropic hypotheses among LDL-C, ApoB, and initial fitness measures are needed to thoroughly investigate this issue. It is important to note that the training responses in the current study were adjusted for baseline levels, so that these estimates are specific to the response and are independent of initial levels. In fact, the responses were adjusted for other known confounding factors, including adiposity, physical fitness and activity levels, and hormonal and behavioral characteristics. Although these factors accounted for a significant proportion of the variance in the blood lipid training responses, even more variance was accounted for by familial factors. Thus, some individuals, because of their genetic makeup, will be more likely to have an improved lipid profile with training. Given these results, molecular studies are needed to identify the markers that are linked with these responses.

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### Table: Familial Correlations and Maximal Heritabilities for Responses Under the Most Parsimonious Models

<table>
<thead>
<tr>
<th>Parameters</th>
<th>( \Delta TC )</th>
<th>( \Delta TG )</th>
<th>( \Delta LDL\text{-}C )</th>
<th>( \Delta ApoB )</th>
</tr>
</thead>
<tbody>
<tr>
<td>FS = FD</td>
<td>0.17 ± 0.09</td>
<td>0.15 ± 0.04</td>
<td>0.17 ± 0.09</td>
<td>0</td>
</tr>
<tr>
<td>MS = MD</td>
<td>0.17 ± 0.15</td>
<td>0</td>
<td>0.17 ± 0.21</td>
<td>0.018 ± 0.07</td>
</tr>
<tr>
<td>SS = DD = SD</td>
<td>0.17 ± 0.15</td>
<td>0</td>
<td>0.17 ± 0.13</td>
<td>0.018 ± 0.06</td>
</tr>
<tr>
<td>h², %</td>
<td>32 ± 18</td>
<td>29 ± 8</td>
<td>32 ± 18</td>
<td>29 ± 13</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>( \Delta HDL\text{-}C )</th>
<th>( \Delta ApoA\text{-}I )</th>
<th>( \Delta HDL\text{-}C )</th>
<th>( \Delta HDL\text{-}C )</th>
</tr>
</thead>
<tbody>
<tr>
<td>FS = FD</td>
<td>-0.48 ± 0.18</td>
<td>0</td>
<td>0.55 ± 0.16</td>
</tr>
<tr>
<td>MS = MD</td>
<td>-0.64 ± 0.17</td>
<td>0</td>
<td>0.36 ± 0.07</td>
</tr>
<tr>
<td>SS = DD = SD</td>
<td>-0.25 ± 0.13</td>
<td>0</td>
<td>0.36 ± 0.13</td>
</tr>
<tr>
<td>h², %</td>
<td>26 ± 22</td>
<td>29 ± 10</td>
<td>38 ± 30</td>
</tr>
</tbody>
</table>

B indicates black; W, white.
References

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