Evidence of Major Genes for Plasma HDL, LDL Cholesterol and Triglyceride Levels at Baseline and in Response to 20 Weeks of Endurance Training: The HERITAGE Family Study

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Abstract

This study assessed major gene effects for baseline HDL-C, LDL-C, TG, and their training responses (post-training minus baseline) in 527 individuals from 99 White families and 326 individuals from 113 Black families in the HERITAGE Family Study. The baseline phenotypes were adjusted for the effects of age and BMI, and the training response phenotypes were adjusted for the effects of age, BMI, and their respective baseline values, within each of the sex-by-generation-by-race groups, prior to genetic analyses. In Whites, we found that LDL-C at baseline and HDL-C training response were under influence of major recessive genes (accounting for 20–30% of the variance) and multifactorial (polygenic and familial environmental) effects. Interactions of these major genes with sex, age, and BMI were tested, and found to be non-significant. In Blacks, we found that baseline HDL-C was influenced by a major dominant gene without a multifactorial component. This major gene effect accounted for 45% of the variance, and exhibited no significant genotype-specific interactions with age, sex, and BMI. Evidence of major genes for the remaining phenotypes at baseline and in response to endurance training were not found in both races, though some were influenced by major effects that did not follow Mendelian expectations or were with ambiguous transmission from parents to offspring. In summary, major gene effects that influence baseline plasma HDL-C and LDL-C levels as well as changes in HDL-C levels in response to regular exercise were detected in the current study.

Key words
Major gene effect · multifactorial effect · lipids · baseline · training response

Introduction

Atherogenic lipid profile, i.e., low levels of plasma high-density lipoprotein (HDL) cholesterol (HDL-C) and elevated levels of plasma low-density lipoprotein (LDL) cholesterol (LDL-C) and triglyceride (TG), is an important risk factor for cardiovascular disease. This profile promotes coronary artery atherosclerosis, the most frequent cause of cardiac ischemia and infarction [22]. Regular endurance exercise is known to increase HDL-C and decrease TG levels, although it seldom changes LDL-C levels [9]. Similar observations have been made in the HERITAGE Family Study (HERITAGE) in response to 20 weeks of endurance exercise [18]. Furthermore, these changes were associated with changes in body fatness rather than in aerobic fitness *per se* [15], and the

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Accepted after revision: May 10, 2004

Bibliography
Int J Sports Med 2005; 26: 414–419 © Georg Thieme Verlag KG · Stuttgart · New York · DOI 10.1055/s-2004-821160 · Published online September 10, 2004 · ISSN 0172-4622

training program was found to be particularly beneficial in men with abdominal obesity and with low HDL-C and elevated TG levels [6]. Although the mechanisms whereby exercise training influences plasma lipids are not well-understood, they are characterized by familial resemblance, and could be in part under genetic control. Evidence of major genes (statistically referred single genes with large effects) on baseline HDL-C, LDL-C, and TG has been reported in recent family studies [7,16,19]. However, it is still unclear whether a major gene effect is also contributing to the inter-individual variability in each of these complex lipid phenotypes in response to endurance exercise training. The main purpose of the current study is to test the hypothesis of a major gene effect on plasma HDL-C, LDL-C and TG not only at baseline but also in response to endurance exercise training, as well as to test for genotype-specific covariate effects.

Methods

The HERITAGE Family Study participants were recruited through extensive media publicity and advertisements, and details have been published elsewhere [3]. The main inclusion criteria included the following: (1) subjects were healthy in order to complete a 20-week endurance exercise training program; (2) subjects were sedentary at baseline; (3) age ≤ 65 years for parents and between 17 – 40 years for offspring; (4) resting SBP ≤ 159 mm Hg and resting DBP ≤ 99 mm Hg; (5) no antihypertensive or lipid lowering drug therapy. Body mass index (BMI) had to be less than 40 kg/m^2. However, some participants whose BMI were slightly higher than 40 kg/m^2 were approved for participation by supervising physicians, because they were considered to be in good health and were able to complete the required training program. The Institutional Review Boards at five participating centers of HERITAGE approved the study protocol, and written informed consents were obtained from all the participants. In this study, a total of 527 individuals (261 men and 266 women) from 99 White families (86 families with both parents and at least one offspring) and 326 individuals (117 men and 209 women) from 113 Black families (17 families with both parents and at least one offspring) had baseline data. Table **1** gives the sample sizes within the four sex-by-generation groups for Whites and Blacks, respectively.

The exercise-training program has been described in detail previously [23]. Each subject was administered a comprehensive battery of tests prior to the 20-week training program including plasma lipids and lipoproteins. Subjects then completed 60 sessions of endurance exercise (3 sessions per week for a total of 20 weeks) on cycle ergometers that were computer controlled to maintain the subjects' heart rates at levels associated with fixed percentages of their $\dot{V}O_{2max}$. The training program started at 55% $\dot{V}O_{2max}$ for 30 min per session, and gradually increased to 75% $\dot{V}O_{2max}$ for 50 min per session during the last 6 weeks of training. All training sessions were supervised on site and adherence to the protocol was strictly monitored. The full test battery was administered again after completion of the training program.

Blood samples were obtained from an antecubital vein into vacutainers containing EDTA in the morning after a 12-hour fast with participants in a semirecumbent position, twice before (24 hours apart) and twice after (24 and 72 hours after the last exercise session) the training program. The blood samples collected at each clinical center were prepared according to a standard protocol before being sent to the Lipid Research Center of Laval University Medical Center. Cholesterol and TG levels were determined in plasma and in lipoprotein fractions by enzymatic methods using a Technicon RA-500 analyzer (Bayer Corp Inc, Tarrytown, NY, USA) [21]. The HDL fraction was obtained after precipitation of LDL in the infranatant (density > 1.006 g/mL) with heparin and $MnCl_2$ [4]. The cholesterol and TG contents of the infranatant fraction were measured before and after the precipitation step.

Extensive quality control procedures were implemented to ensure high quality lipid data, including repeat of lipid assays in 5% of all samples and analyses of split samples prepared at each clinical center. Results from plasma samples containing chylomicrons were discarded for the analyses as being suggestive of a non-fasting status. To adjust for possible acute and chronic plasma volume changes associated with exercise, plasma total proteins were assayed using the biuret method (Roche Molecular Biochemicals, Dallas, TX, USA) on the initial pre-training sample and on both post-training samples. Post-training plasma lipid values were corrected based on pre-training to post-training plasma total protein levels. The two baseline lipid values were averaged and compared with the average of the two corrected post-training lipid values. The training response is defined as the simple difference between the averaged post-training values and the averaged baseline values.

The reproducibility of baseline HDL-C and LDL-C measures in HERITAGE was shown to be high. The intraclass correlations (ICC) for repeated measures were 0.94, and the analytical errors (ANER) were 0.06 and 0.19 mmol/L for baseline HDL-C and LDL-C, respectively. The coefficients of variation (CV) for repeated measures were 6.2% for baseline HDL-C and 6.5% for baseline LDL-C. The ICC, ANER, and CV for repeated measures of baseline TG were 0.87, 0.21 mmol/L, and 22.9%, respectively [8].

The data adjustments were performed by race within each of the groups of fathers, mothers, sons, and daughters, using a stepwise multiple regression procedure. All HDL-C, LDL-C and TG measurements were adjusted for the effects of age, age^2, age^3, and baseline BMI, while the response to training phenotypes (post-training minus baseline) were adjusted for the effects of age, age^2, age^3, baseline BMI, and the respective baseline values. For each of the regressions, only terms that were significant at the 5% level were retained. The adjusted phenotypes were standardized to zero mean and unit variance for the segregation analysis. Also prior to segregation analysis, data skewness, kurtosis, and outlier(s) were carefully inspected. Outliers were defined as isolated observations beyond 3 SD and at least 1 SD away from the adjacent observation, and were assigned missing for genetic analysis.

Pedigree Analysis Package (PAP) was used to test for a major gene hypothesis [14]. The general model includes a major effect, a multifactorial (polygenic and familial environmental) component, and a non-familial residual. The major gene is assumed to have alleles *A* and *a,* which constitute genotypes *AA, Aa,* and *aa.* The *A* allele leads to low phenotype values. It is assumed that the

locus is in Hardy-Weinberg equilibrium. PAP estimates the *A* allele frequency p and the genotypic means μ_{AA}, μ_{Aa}, and μ_{aa}. The overall mean μ_0 can be derived from the equation $\mu_{AA}p^2 + \mu_{Aa}2\,p(1\text{-}p) + \mu_{aa}(1\text{-}p)^2$. Genotype by environment interactions can be tested allowing for genotype specific covariate effects, which are modeled as regression coefficients. In this study, the effects of sex, age, and BMI are denoted as β_{sex}, β_{age} and β_{BMI}, and the effects can be genotype-specific: $\beta_{(sex)AA}$, $\beta_{(sex)Aa}$, $\beta_{(sex)aa}$, $\beta_{(age)AA}$, $\beta_{(age)Aa}$, $\beta_{(age)aa}$, $\beta_{(BMI)AA}$, $\beta_{(BMI)Aa}$, and $\beta_{(BMI)aa}$. The SD estimated in the model (σ) is assumed to be equal for each genotype, and includes both polygenic and residual variance components. The multifactorial heritability *(H)* estimated in the model is expressed as a function of the common variance (σ^2). The multifactorial heritability is usually expressed as the percentage of the total phenotypic variance (h^2) and can be computed using the equation $(H\sigma^2)/(\sigma^2 + \sigma^2_{mg})$, where σ^2_{mg} is the variance due to the major gene, $(\mu_{AA} - \mu_0)^2\,p^2 + (\mu_{Aa} - \mu_0)^2 2\,p(1\text{-}p) + (\mu_{aa} - \mu_0)^2(1\text{-}p)^2$. In addition to these major locus and multifactorial parameters, there are three transmission probabilities τ_{AA}, τ_{Aa}, and τ_{aa}, each is the probability of an individual transmitting an *A* allele given to genotype shown. These are explicitly modeled in order to test whether the segregation pattern follows Mendelian expectations. Under Mendelian assumptions, the probabilities are 1, 1/2, and 0, respectively. The three τ's are equal if there is no transmission of the major effect. In order to infer a major gene, the following requirements have to be met: (1) rejection of the no major effect hypothesis ($p = 1$, $\mu_{AA} = \mu_{Aa} = \mu_{aa}$); (2) non-rejection of Mendelian τ's; and (3) rejection of equal transmission probabilities [17]. The maximum likelihood method was employed to estimate parameters, and the likelihood ratio test was used to test hypotheses of nested models. Finally, the most parsimonious model was the one with the smallest Akaike's Information Criterion (AIC), which is defined as minus twice the log likelihood plus twice the number of independently estimated parameters [1]. Segregation analyses were thus carried out in Whites and a smaller sample size of Blacks, separately.

Results

Means and SD of unadjusted baseline HDL-C, LDL-C, TG and their changes in response to training are given in Table **1** for Whites and Blacks. Based on comparisons of group means, no generation differences were noted, but sex differences in mean baseline HDL-C were found, with higher levels in women than in men within generation (although the father-mother comparison was nonsignificant in Blacks). Generation differences of mean baseline LDL-C also were significant, with higher levels in parents than in offspring, within sex. Mean baseline TG levels exhibited both sex and generation differences, being significantly higher in men than in women within generation, and significantly higher in parents than in offspring within sex. The mean changes in levels of HDL-C, LDL-C, and TG in response to training were generally modest, without sex and generation differences, except that mean TG response levels in Whites were significantly lower in fathers than in mothers.

In Whites and Blacks, both age and BMI (accounting for 10 – 40% of the variance in fathers, mothers, sons, and daughters) were significant predictors of baseline HDL-C and LDL-C, and BMI (accounting for 10 – 30% of the variance in the four groups) alone was a significant predictor of baseline TG. Baseline HDL-C was not a significant predictor of HDL-C training response in women, but it accounted for about 20% of the variance in Black men. For LDL-C training response, significant percentages of variance accounted for by the baseline LDL-C along with age and BMI were 10 – 20% in the four groups. Baseline TG and BMI were significant predictors of its training response, accounting for 10 – 30% of the variance in the four groups.

For baseline HDL-C in Whites, the hypotheses of no familial resemblance (sporadic model, $p = 1$, $\tau_{AA} = 1$, $\tau_{Aa} = 0.5$, $\tau_{aa} = 0$, $\mu_{AA} = \mu_{Aa} = \mu_{aa}$, σ, $H = 0$), no major effect (solely multifactorial effect model, $p = 1$, $\tau_{AA} = 1$, $\tau_{Aa} = 0.5$, $\tau_{aa} = 0$, $\mu_{AA} = \mu_{Aa} = \mu_{aa}$, σ, H) and no multifactorial effect (solely major effect model, p, $\tau_{AA} = 1$, $\tau_{Aa} = 0.5$, $\tau_{aa} = 0$, μ_{AA}, μ_{Aa}, μ_{aa}, σ, $H = 0$) were all rejected (as vs. mixed Mendelian model, p, $\tau_{AA} = 1$, $\tau_{Aa} = 0.5$, $\tau_{aa} = 0$, μ_{AA}, μ_{Aa}, μ_{aa}, σ, H), suggesting that both the major and multifactorial effects were significant. Tests of the transmission probabilities showed that neither the Mendelian (general model, p, τ_{AA}, τ_{Aa}, τ_{aa}, μ_{AA}, μ_{Aa}, μ_{aa}, σ, H vs. mixed Mendelian, p, $\tau_{AA} = 1$, $\tau_{Aa} = 0.5$, $\tau_{aa} = 0$, μ_{AA}, μ_{Aa}, μ_{aa}, σ, H) nor the environmental (non-transmitted model, $p = \tau_{AA} = \tau_{Aa} = \tau_{aa}$, μ_{AA}, μ_{Aa}, μ_{aa}, σ, H vs. general model, p, τ_{AA}, τ_{Aa}, τ_{aa}, μ_{AA}, μ_{Aa}, μ_{aa}, σ, H) τ's could be rejected. Thus, the transmission from parents to offspring was ambiguous, and there was no evidence of a major gene effect. The major effect and multifactorial component accounted for 32% and 47% of the variance, respectively. For baseline HDL-C in Blacks, both the no familial resemblance and the no major effect hypotheses were rejected, whereas the hypothesis of no multifactorial effect was not rejected, suggesting a solely major effect. Tests of the transmission probabilities resulted in the rejection of the environmental hypothesis but non-rejection of the Mendelian hypothesis. While the dominant hypothesis (p, $\tau_{AA} = 1$, $\tau_{Aa} = 0.5$, $\tau_{aa} = 0$, μ_{AA}, $\mu_{Aa} = \mu_{aa}$, σ, H) was not rejected, the recessive model (p, $\tau_{AA} = 1$, $\tau_{Aa} = 0.5$, $\tau_{aa} = 0$, $\mu_{AA} = \mu_{Aa}$, μ_{aa}, σ, H) was rejected. Although no aggregate effects of age ($\beta_{(age)AA} = \beta_{(age)Aa} = \beta_{(age)aa}$ vs. $\beta_{(age)AA} = \beta_{(age)Aa}$, $\beta_{(age)aa}$), sex ($\beta_{(sex)AA} = \beta_{(sex)Aa} = \beta_{(sex)aa}$ vs. $\beta_{(sex)AA} = \beta_{(sex)Aa}$, $\beta_{(sex)aa}$), and BMI ($\beta_{(BMI)AA} = \beta_{(BMI)Aa} = \beta_{(BMI)aa}$ vs. $\beta_{(BMI)AA} = \beta_{(BMI)Aa}$, $\beta_{(BMI)aa}$) were expected due to prior phenotypic adjustments, we tested for possible interactions with major genotypes. No significant age, sex and BMI interactions with genotypes were found. The most parsimonious hypothesis was the dominant hypothesis (Table **2**). The dominant major gene effect explained 45% of the phenotypic variance.

For baseline LDL-C in Whites, both major and multifactorial effects were significant. Test of the transmission probabilities showed that the Mendelian τ's were not rejected, while the equal τ's hypothesis was rejected. Whereas the recessive model was not rejected, the dominant model was rejected. No significant age, sex, and BMI interactions with genotypes were found. The most parsimonious hypothesis was the recessive model (Table **2**). The recessive gene accounted for 27% of the phenotypic variance, with 12% of the sample carrying the homozygous *aa* genotype, whereas the multifactorial effect accounted for 42% of the variance. For baseline LDL-C in Blacks, there was a significant familial component, but there were no distinctive major and multifactorial effects possibly due to insufficient sample size. A multifactorial component and shared environmental factors may appreciably contribute to the familiality found here.

Table **1** Data description for unadjusted plasma HDL-C, LDL-C, and TG (all in mmol/L)

Variables	*No.*	*Means*	*SD*	*No.*	*Means*	*SD*
Whites		**Fathers**			**Mothers**	
– *Age (years)*	99	53.5*#	5.3	95	52.0*#	5.1
– *BMI (kg/m²)*	98	28.4	4.4	94	27.6#	5.0
– *HDL-C: baseline*	97	0.91*	0.21	94	1.19*	0.28
– *HDL-C: response*	92	0.03	0.10	91	0.05	0.12
– *LDL-C: baseline*	97	3.49#	0.78	94	3.29#	0.69
– *LDL-C: response*	92	–0.04	0.41	91	0.02	0.35
– *TG: baseline*	97	1.93*#	1.00	94	1.43*#	0.69
– *TG: response*	92	–0.15*	0.52	91	0.05*	0.45
		Sons			**Daughters**	
– *Age (years)*	162	25.3#	6.0	171	25.4#	6.3
– *BMI (kg/m²)*	160	25.6*#	4.9	168	23.7*#	4.5
– *HDL-C: baseline*	157	0.93*	0.19	170	1.12*	0.25
– *HDL-C: response*	139	0.04	0.09	157	0.05	0.14
– *LDL-C: baseline*	157	2.79#	0.78	170	2.72#	0.73
– *LDL-C:rResponse*	139	–0.002	0.32	157	0.004	0.40
– *TG: baseline*	157	1.32*#	0.75	170	1.07*#	0.50
– *TG: response*	139	–0.02	0.41	157	0.03	0.34
Blacks		**Fathers**			**Mothers**	
– *Age (years)*	29	50.0*#	7.2	60	46.6*#	6.6
– *BMI (kg/m²)*	29	27.5	5.2	59	29.4	5.2
– *HDL-C: baseline*	29	1.01	0.52	58	1.17	0.32
– *HDL-C: response*	24	0.03	0.10	49	0.02	0.13
– *LDL-C: baseline*	29	3.28#	0.80	58	3.11#	0.79
– *LDL-C: response*	24	–0.08	0.35	49	–0.03	0.34
– *TG: baseline*	29	1.50*#	0.87	58	1.08*#	0.58
– *TG: response*	24	0.07	0.84	49	–0.03	0.24
		Sons			**Daughters**	
– *Age (years)*	88	27.0#	7.2	149	27.6#	7.5
– *BMI (kg/m²)*	86	27.4	5.8	147	27.9	7.0
– *HDL-C: baseline*	85	0.98*	0.22	143	1.11*	0.26
– *HDL-C: response*	64	0.02	0.11	113	0.04	0.15
– *LDL-C: baseline*	85	2.83#	0.82	143	2.66#	0.67
– *LDL-C: response*	64	0.03	0.40	113	0.04	0.36
– *TG: baseline*	85	1.15*#	0.72	143	0.83*#	0.33
– *TG: response*	64	–0.01	0.49	113	–0.05	0.25

* Significant ($p < 0.05$) mean differences for father-mother or son-daughter (within generation) comparisons. # Significant ($p < 0.05$) mean differences for father-son or mother-daughter (within sex) comparisons.

For baseline TG in both races, all of the hypotheses of no familial resemblance, no major effect, and no multifactorial effect were rejected, suggesting significance of both the major and multifactorial effects. In Whites, both the Mendelian and environmental τ's were rejected, the major effect did not follow Mendelian expectations, and thus could not resolve as a major gene effect. The major effect and multifactorial component accounted for 72% and 14% of the variance, respectively. In Blacks, both the Mendelian and environmental τ's were not rejected. The major effect, with an ambiguous transmission from parents to offspring, could not be inferred as a major gene effect. The major effect accounted for 73% of the variance. Together, a major gene effect for baseline TG was not found in both races.

For HDL-C training response in Whites, both the no familial resemblance and the no major effect hypotheses were rejected, and the hypothesis of no multifactorial effect was not rejected, suggesting a single locus model. Tests of the transmission probabilities resulted in the rejection of the environmental hypothesis but non-rejection of the Mendelian hypothesis. While the recessive hypothesis was not rejected, the dominant model was at the borderline significance. No significant age, sex, and BMI interactions with genotypes were found. The most parsimonious hy-

Table **2** Evidence of major genes for baseline HDL-C (Blacks), HDL-C training response (Whites), and baseline LDL-C (Whites) based on most parsimonious hypotheses

Parameters *	*HDL-C baseline, Blacks*	*HDL-C response, Whites*	*LDL-C baseline, Whites*
p	0.89	0.84	0.66
τ_{AA}	(1)	(1)	(1)
τ_{Aa}	(0.5)	(0.5)	(0.5)
τ_{aa}	(0)	(0)	(0)
μ_{AA}	– 0.38	– 0.05	– 0.18
μ_{Aa}	1.24	(– 0.05)	(– 0.18)
μ_{aa}	(1.24)	2.80	1.49
σ	0.74	0.93	0.87
H	(0)	0.19	0.58
Mode of inheritance	dominant	recessive	recessive
Percent variance (%)			
– *major gene effect*	45	19	27
– *multifactorial effect*	0	16	42
– *environment*	55	65	31

* p, the A allele frequency; $\tau_{AA} = 1$, $\tau_{Aa} = 0.5$, $\tau_{aa} = 0$, Mendelian transmission probabilities; μ_{AA}, μ_{Aa}, μ_{aa}, genotypic means; σ, SD; H, multifactorial heritability

Table **3** Result summary for segregation analysis of HDL-C, LDL-C, and TG at baseline and in response to training

Phenotypes	*Major effect (Whites)*	*Multi-factorial (Whites)*	*Major effect (Blacks)*	*Multi-factorial (Blacks)*
HDL-C				
– *baseline*	yes	yes	major gene	no
– *response*	major gene	yes	no	no
LDL-C				
– *baseline*	major gene	yes	no	yes
– *response*	no	yes	no	no
TG				
– *baseline*	yes	yes	yes	yes
– *response*	yes	yes	yes	no

pothesis was the recessive hypothesis (Table **2**). The recessive major gene explained 19% of the phenotypic variance, with 3% of the sample having homozygous *aa* genotype, and the multifactorial effect accounted for 16% of the phenotypic variance. No familial component for HDL-C training response was found significant in Blacks.

For LDL-C training response, no distinctive major effect was found in Whites, and no familiality was evidenced in Blacks. For TG training response, a major effect (along with a multifactorial effect in Whites but not in Blacks) was significant in each of Whites and Blacks. Whereas the Mendelian τ's were rejected, the environmental τ's were not rejected. This would suggest that the major effect might be environmental in origin. The major effect accounted for 32% and 47% of the variance in Whites and Blacks, respectively.

Discussion

In the current study, baseline variation in HDL-C levels was influenced by a major effect as well as a multifactorial effect in Whites. Since we could not reject an environmental transmission of the major effect, we were unable to conclude that this major effect was caused by a gene. Interestingly, a major dominant gene effect was firmly resolved in a relatively smaller sample of Blacks. Previously, five family studies found evidence for a major gene effect on HDL-C, but the mode of inheritance varied in different samples; it was recessive in 3074 nuclear families in the multiethnic Jerusalem Lipid Research Center Study [10] and 1082 families from the NHLBI Family Heart Study [8] dominant in 55 Utah pedigrees [13], but neither dominant nor recessive in a large multigenerational kindred in the Bogalusa Heart Study [2], and codominant in 25 large Mexican American families from the San Antonio Family Heart Study (SAFHS) [19]. Mahaney and colleagues performed a multipoint genome-wide linkage scan in Mexican Americans, and mapped a major gene influencing HDL-C on chromosome 16 q [20].

Regular endurance exercise training can raise HDL-C levels in hypertriglyceridemic individuals but has relatively little effect on HDL-C levels in subjects with isolated low HDL-C levels [24]. According to a recent report based on the HERITAGE cohort, it may be particularly helpful in men with centralized obesity and concomitant low HDL-C and elevated TG levels [6]. In the present study, we found a major gene effect (that did not replicate in Blacks though) along with a multifactorial component (heritability of 16%) for HDL-C training response in Whites. The major gene appeared to have a recessive mode of inheritance, and accounted for 19% of the phenotypic variance. A relatively small percentage (3%) of the sample carried the homozygous genotype leading to higher HDL-C increases in response to training.

We also found that baseline LDL-C levels are under the influence of both major gene and multifactorial ($h^2 = 42\%$) effects in Whites (but not in Blacks). The recessive gene, accounting for 27% of the phenotypic variance, was independent of the effects of sex, age, and BMI, with no evidence of genotype interactions with sex, age, and BMI. An estimated 12% of the sample was homozygous for a genotype leading to elevated LDL-C levels. Evidence of a major gene for LDL-C levels has been obtained previously in two large family studies. Friedlander and Kark found a recessive major gene ($q = 0.108$) along with a significant polygenic component in a random sample of more than 3074 nuclear families in the Jerusalem Lipid Research Clinic Study [11]. More recently, Coon and colleagues found a recessive major gene effect ($q = 0.52$, explaining 24% of the variation) with a polygenic heritability of 28% in 1039 Caucasian families of the NHLBI Family Heart Study [5]. Our current finding of a recessive major gene for elevated baseline LDL-C levels is consistent with the results from these two studies. In addition, evidence of major effects for baseline

TG and its training response in both races was obtained, but the transmission of these major effects between generations could not be resolved as Mendelian. There were two previous reports of major genes for baseline TG levels in 176 families from Seattle [12] and in 55 families from the United Kingdom [7].

In summary, as shown in Table **3**, major gene effects for baseline plasma HDL-C (in Blacks) and LDL-C (in Whites) levels were found. More interestingly, a major recessive gene for changes in plasma HDL-C levels in response to regular endurance exercise was revealed for the first time in White families from the HERITAGE Family Study. A genome-wide linkage scan to identify quantitative trait loci for these traits, especially HDL-C training response, is warranted in this and other studies.

Acknowledgement

The HERITAGE Family Study is supported by the National Heart, Lung, and Blood Institute through the following grants: HL45670 (C. Bouchard, PI), HL47323 (A. S. Leon, PI), HL47317 (D. C. Rao, PI), HL47327 (J. S. Skinner, PI), and HL47321 (J. H. Wilmore, PI). A. S. Leon is supported in part by the Henry L. Taylor Professorship in Exercise Science and Health Enhancement. C. Bouchard is partially supported by the George A. Bray Chair in Nutrition.

References

[1] Akaike H. A new look at statistical model identification. IEEE Transaction on Automatic Control 1974; 19: 716 – 723

[2] Amos CI, Wilson AF, Rosenbaum PA, Srinivasan SR, Webber LS, Elston RC, Berenson GS. An approach to the multivariate analysis of high-density lipoprotein cholesterol in a large kindred: The Bogalusa Heart Study. Genet Epidemiol 1986; 3: 255 – 267

[3] Bouchard C, Leon AS, Rao DC, Skinner JS, Wilmore JH, Gagnon J. The HERITAGE Family Study. Aims, design, and measurement protocol. Med Sci Sports Exerc 1995; 27: 721 – 729

[4] Burstein, M, Samaille J. Sur un dosage rapide du cholestérol lié aux b-lipoprotéines du sérum. J Clin Chim Acta 1960; 5: 609 – 610

[5] Coon H, Leppert MF, Kronenberg F, Province MA, Myers RH, Arnett DK, Eckfeldt JH, Heiss G, Williams RR, Hunt SC. Evidence for a major gene accounting for mild elevation in LDL cholesterol: The NHLBI Family Heart Study. Ann Hum Genet 1999; 63: 401 – 412

[6] Couillard C, Després JP, Lamarche B, Bergeron J, Gagnon J, Leon AS, Rao DC, Skinner JS, Wilmore JH, Bouchard C. Effects of endurance exercise training on plasma HDL cholesterol levels depend on levels of triglycerides: Evidence from men of the Health, Risk Factors, Exercise Training and Genetics (HERITAGE) Family Study. Arterioscler Thromb Vasc Biol 2001; 21: 1226 – 1232

[7] Cullen P, Farren B, Scott J, Farrall M. Complex segregation analysis provides evidence for a major gene acting on serum triglyceride levels in 55 British families with familial combined hyperlipidemia. Arterioscler Thromb 1994; 14: 1233 – 1249

[8] Després JP, Gagnon J, Bergeron J, Couillard C, El-Moalem HE, Daw WE, Leon AS, Rao DC, Skinner JS, Wilmore JH, Bouchard C. Plasma post-heparin lipase activities in the HERITAGE Family Study: the reproducibility, gender differences and associations with lipoprotein levels. Clin Biochem 1999; 32: 157 – 165

[9] Durstine JL, Grandjean PW, Davis PG, Ferguson MA, Alderson NL, DuBose KD. Blood lipid and lipoprotein adaptations to exercise: a quantitative analysis. Sports Med 2001; 31: 1033 – 1062

[10] Friedlander Y, Kark JD, Stein Y. Complex segregation analysis of low levels of plasma high-density lipoprotein cholesterol in a sample of nuclear families in Jerusalem. Genet Epidemiol 1986; 3: 285 – 297

[11] Friedlander Y, Kark JD. Complex segregation analysis of plasma and lipoprotein variables in a Jerusalem sample of nuclear families. Hum Hered 1987; 37: 7 – 19

[12] Goldstein JL, Schrott HG, Hazzard WR, Bierman EL, Motulsky AG. Hyperlipidemia in coronary heart disease, II: Genetic analysis of lipid levels in 176 families and delineation of a new disorder, combined hyperlipidemia. J Clin Invest 1973; 52: 1544 – 1568

[13] Hasstedt SJ, Ash KO, Williams RR. A re-examination of major locus hypotheses for high density lipoprotein cholesterol level using 2170 persons screened in 55 Utah pedigrees. Am J Med Genet 1986; 24: 57 – 67

[14] Hasstedt SJ. Pedigree Analysis Package, Rev 4.0. Salt Lake City: Department of Human Genetics, University of Utah, 1994

[15] Katzmarzyk PT, Leon AS, Rankinen T, Gagnon J, Skinner JS, Wilmore JH, Rao DC, Bouchard C. Changes in blood lipids consequent to aerobic exercise training related to changes in body fatness and aerobic fitness. Metabolism 2001; 50: 841 – 848

[16] Kronenberg F, Coon H, Ellison RC, Borecki I, Arnett DK, Province MA, Eckfeldt JH, Hopkins PN, Hunt SC. Segregation analysis of HDL cholesterol in the NHLBI Family Heart Study and in Utah pedigrees. Eur J Hum Genet 2002; 10: 367 – 374

[17] Lalouel JM, Rao DC, Morton NE, Elston RC. A unified model for complex segregation analysis. Am J Hum Genet 1983; 35: 816 – 826

[18] Leon AS, Rice T, Mandel S, Després JP, Bergeron J, Gagnon J, Rao DC, Skinner JS, Wilmore JH, Bouchard C. Blood lipid response to 20 weeks of supervised exercise in a large biracial population: The HERITAGE Family Study. Metabolism 2000; 49: 513 – 520

[19] Mahaney MC, Blangero J, Rainwater DL, Comuzzie AG, VandeBerg JL, Stern MP, MacCluer JW, Hixson JE. A major locus influencing plasma high-density lipoprotein cholesterol levels in the San Antonio Family Heart Study. Arterioscler Thromb Vasc Biol 1995; 15: 1730 – 1739

[20] Mahaney MC, Rainwater DL, Vandeberg JL, Blangero J, Almacy L, Comuzzie AG, Stern MP, MacCluer JW, Hixson JE. A major gene influencing normal quantitative variation in high-density lipoprotein cholesterol (HDL-C) maps to chromosome 16 q in Mexican Americans. Am J Hum Biol 1999; 11: 122

[21] Moorjani S, Dupont A, Labrie F, Lupien PJ, Brun D, Gagné C, Giguère M, Bélanger A. Increase in plasma high-density lipoprotein concentration following complete androgen blockage in men with prostatic carcinoma. Metabolism 1987; 36: 244 – 250

[22] Ross R. The pathogenesis of atherosclerosis – An update. N Engl J Med 1986; 314: 488 – 500

[23] Skinner JS, Wilmore KM, Krasnoff JB, Jaskolski A, Jaskolska A, Gagnon J, Province MA, Leon AS, Rao DC, Wilmore JH, Bouchard C. Adaptation to a standardized training program and changes in fitness in a large, heterogeneous population: the HERITAGE Family Study. Med Sci Sports Exerc 2000; 32: 157 – 161

[24] Thompson PD, Rader DJ. Does exercise increase HDL cholesterol in those who need it the most? Arterioscler Thromb Vasc Biol 2001; 21: 1097 – 1098