Familiality of triglyceride and LPL response to exercise training: the HERITAGE Study

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Division of Biostatistics and Departments of Genetics and Psychiatry, Washington University School of Medicine, St. Louis, MO; Physical Activity Sciences Laboratory, Laval University, Québec, CANADA; Pennington Biomedical Research Center, Louisiana State University, Baton Rouge, LA; School of Kinesiology and Leisure Studies, University of Minnesota, Minneapolis, MN; Department of Kinesiology, Indiana University, Bloomington, IN; Department of Health and Kinesiology, Texas A&M University, College Station, TX; and Lipid Research Center, Laval University, Québec, CANADA

ABSTRACT

HONG, Y., T. RICE, J. GAGNON, L. PÉRUSSE, M. PROVINCE, C. BOUCHARD, A. S. LEON, J. S. SKINNER, J. H. WILMORE, D. C. RAO, and J-P. DESPRÉS. Familiality of triglyceride and LPL response to exercise training: the HERITAGE Study. *Med. Sci. Sports Exerc.*, Vol. 32, No. 8, pp. 1438–1444, 2000. **Purpose:** The main purpose of the present investigation was to test whether and to what extent familial/genetic factors are involved in the changes of postheparin lipoprotein lipase (ΔPH-LPL) activity and triglyceride (ΔTG) levels in response to exercise training. Additional hypotheses were also tested as to whether there were familial/genetic factors shared by baseline and the corresponding response to exercise training (i.e., by baseline triglyceride (TG_B) and ΔTG and by baseline postheparin lipoprotein lipase ($PH\text{-}LPL_B$) and ΔPH-LPL activity). **Methods:** Serum TG and PH-LPL were measured in 459 subjects from 99 sedentary Caucasian families of the HERITAGE Family study before (baseline) and after completing a 20 wk (3 times per week) exercise training protocol. The training protocol had a target intensity of 75% of the heart rate associated with baseline $\dot{V}O_{2max}$ during the last 6 wk. PH-LPL activity was measured in the study subjects. Both univariate and bivariate familial correlation analyses were applied to the baseline and response data. **Results:** The maximal heritabilities for ΔTG and ΔPH-LPL activity were 22% and 15%, respectively. There were no common familial factors for TG_B and ΔTG, nor were there any for $PH\text{-}LPL_B$ and ΔPH-LPL. However, we found that there were common familial factors underlying ΔTG and ΔPH-LPL; these familial factors seemed to differ across sex and generation groups. **Conclusion:** Although there were no common familial factors underlying the covariation between the baseline triglyceride and PH-LPL activity and the corresponding responses to exercise training (i.e., TG_B with ΔTG or $PH\text{-}LPL_B$ with ΔPH-LPL), the ΔTG and ΔPH-LPL covariation apparently share some common familial determinants. **Key Words:** FAMILIAL CORRELATION, HERITABILITY, PLEIOTROPY, GENETIC EPIDEMIOLOGY

Elevated serum levels of triglycerides (TG) are generally associated with increased risk of coronary heart disease (1). Lipoprotein lipase (LPL) is the major enzyme responsible for the hydrolysis of TG molecules in TG-rich circulating lipoproteins (2,6). The strong phenotypic association between LPL and TG has been well established. Previous studies have indicated that both serum LPL and TG are in part influenced by genetic factors (10–12,17). Hence, it is most likely that the phenotypic association between serum LPL and TG is explained by both genetic and nongenetic factors. Among nongenetic factors, most studies found that leisure-time physical activities and exercise training can increase the levels of LPL but reduce the levels of TG (5,7), although one study has suggested that there was no change in lipid level and LPL activity with exercise training in women (9). The changes in LPL and TG levels in response to training (ΔLPL and ΔTG) are also correlated in some studies (25). However, the nature of the change in serum LPL and TG in response to exercise training, their association, and their associations with the corresponding baseline levels is not fully understood.

In a study of 22 twin pairs, Savard and Bouchard (21) found that changes in adipose tissue postheparin LPL (PH-LPL) activity after a 90-min exercise bout were more similar in monozygotic twin pairs than in dizygotic twin pairs, suggesting that the PH-LPL response to acute exercise (ΔPH-LPL) could be in part genetically determined. Moreover, the regulation of LPL expression in humans with exercise was suggested to be pretranslational (22). However, the extent to which familial/genetic factors influence ΔPH-LPL activity and ΔTG level in response to exercise-training is unknown. It is also unclear whether the familial/genetic factors influence ΔPH-LPL levels also affect ΔTG levels. No information is available as to whether familial/

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genetic mechanisms for baseline (before exercise training) levels of PH-LPL and TG (PH-LPL_B and TG_B) are shared by their corresponding changes in response to exercise training, i.e., whether there is common familial/genetic mechanisms between PH-LPL_B and ΔPH-LPL, and between TG_B and ΔTG.

To address these questions, both univariate and bivariate familial correlation analyses were applied to 459 subjects from 99 normolipidemic sedentary Caucasian families who participated in the HERITAGE Family Study. The HERITAGE Family study was a multicenter exercise-training study involving families. The main objective of the study was to assess the role of genetic factors in the cardiovascular, metabolic, and hormonal responses to aerobic exercise training in previously sedentary families.

METHODS

Study Subjects

The HERITAGE sampling procedure and the inclusion and exclusion criteria have been described in detail elsewhere (3). In brief, parents were required to be 65 yr of age or younger, and offspring between 17 and 40 yr. Subjects were required to be sedentary at baseline, with a body mass index (BMI) less than 40 $kg \cdot m^{-2}$ (exceptions were accepted only with sufficient clinical justification on a case by case basis), resting systolic blood pressure less than 160 mm Hg, and resting diastolic blood pressure less than 100 mm Hg. Other exclusion criteria included: definite or possible coronary heart disease, diabetes requiring insulin or oral hypoglycemic therapy, hypercholesterolemia with history of blood cholesterol levels $\geq$ 350 $mg \cdot dL^{-1}$, or hypertriglyceridemia with a fasting blood triglyceride level $\geq$ 500 $mg \cdot dL^{-1}$ or the use of lipid-lowering drugs. In general, subjects were required to be in good physical health in order to complete the 20-wk training program. A few cases with a BMI of 40 $kg \cdot m^{-2}$ and over were included in the study because they were able to perform the required tests and training program.

In all, 99 nuclear families of Caucasian descent, with both biological parents and at least two biological children completed the protocol. Black families were also recruited, but their results are not reported here. The study was approved by an institutional committee at each site and all the subjects gave written informed consent.

Exercise Protocols

Each subject was trained on a cycle ergometer (SensorMedics Ergo-Metrics 800S, Yorba Linda, CA) three times per week for 20 wk using the same standardized training protocol. Exercise training progressed from 30 min per workload at a heart rate corresponding to 55% of their initial $\dot{V}O_{2max}$ to 50 min per workload at a heart rate corresponding to 75% of their initial $\dot{V}O_{2max}$. The intensity and/or duration was adjusted for each individual every 2 wk so that the subject was working at a target intensity corresponding to 75% of the heart rate associated with $\dot{V}O_{2max}$ at baseline for the last 6 wk. The power output was adjusted automatically to the heart rate response during all training sessions. Each training session was supervised on the site. Subjects must have completed the required 60 training sessions within a maximum of 21 wk. They could not exercise more than four sessions per week or less than one per week, and could not get ahead nor fall behind by more than two sessions. Adherence was monitored several times per week, and if a subject was falling behind, a plan was developed to bring him or her back to schedule as soon as possible. At the conclusion of training, $\dot{V}O_{2max}$ was tested in each subject to ensure adherence to the exercise-training program. The $\dot{V}O_{2max}$ was measured on a cycle ergometer before and after the exercise training program. The $\dot{V}O_{2max}$ response to exercise training ($\Delta\dot{V}O_{2max}$) was defined as the absolute difference between posttraining $\dot{V}O_{2max}$ and the baseline (pretraining) $\dot{V}O_{2max}$. See Bouchard et al. (3) for further details regarding the training protocol.

Measures

All participants underwent a series of tests both before (baseline) and after (posttraining) completing the 20-wk standardized and monitored exercise-training program. Results from the baseline and posttraining tests for PH-LPL activity and triglycerides level are reported in the present study.

Plasma PH-LPL activity and triglycerides. Blood samples for PH-LPL activity measurement were taken from subjects after a 12-h overnight fasting and 10 min after an intravenous injection of heparin (60 $IU \cdot kg^{-1}$ body weight). The postheparin plasma lipase activities were measured using a modification of the method of Nilsson-Ehle and Ekman (15) as previously described (17). The PH-LPL activities were expressed as nmoles of oleic acid released per mL of plasma per minute. Determinations of the PH-LPL activities were highly reproducible, with intraclass correlation coefficients for repeated assays of 0.95 Approximately 2% of subjects were excluded from the analyses because of nonfasting conditions. Plasma triglyceride levels were measured by enzymatic methods using the Technicon RA-10000 analyzer (8). Further, all lipid and lipoprotein measures were adjusted for plasma volumes.

Statistical Analysis

Triglycerides were transformed using a natural logarithm before any data analysis because of a heavily skewed distribution. In addition to pretraining triglycerides and PH-LPL, the response of triglycerides and PH-LPL to training (ΔTG and ΔPH-LPL) was calculated as the simple difference between posttraining and baseline measures.

Age adjustment. Adjustments for the effects of age on PH-LPL, triglycerides, ΔLPL, and ΔTG were carried out separately in the four sex by generation groups (fathers, mothers, sons, and daughters) using a stepwise multiple regression procedure. Age, age^2, and age^3 were included in the regression model. The significance level for retaining the terms in the stepwise regression analysis was 5%. The

standardized residuals from the regression analyses were used in the following familial correlation analyses.

Familial correlation model. The purpose of the familial correlation analysis is to determine whether there is evidence of familial/genetic factors underlying the variation in each trait (univariate correlation analysis) or covariation between two traits (bivariate correlation analysis). In the present study, the two traits refer to TG_B and ΔTG, $PH\text{-}LPL_B$ and ΔPH-LPL, or ΔTG and ΔPH-LPL. In univariate correlation analysis, significant correlations among siblings and/or between parents and offspring but not between spouses suggest that there may be genetic influences on the trait. Significant spouse correlations, in addition to sibling and/or parent-offspring correlations, indicate that at least some of the variation is due to familial environments. In the bivariate correlation analysis, significant cross-trait correlations among siblings (e.g., trait 1 in one sib and trait 2 in the other) and/or between parents and offspring (e.g., trait 1 in parents with trait 2 in offspring) but not between spouses suggest that there may be common genetic influences on the two traits. Significant spouse cross-trait correlations, in addition to sibling and/or parent-offspring cross-trait correlations, indicate that at least some of the familial effects are due to familial environments affecting the two traits. Finally, the intraindividual cross-trait correlations reflect the combined effects of common genes and common familial environments, as well as specific environmental effects that are common to both traits but are not necessarily shared among family members.

The general univariate model was based on four groups of individuals—fathers (f), mothers (m), sons (s), and daughters (d), leading to 8 interindividual correlations (fm, fs, fd, ms, md, ss, sd, dd). The bivariate correlation model is the multivariate extension of the univariate case. In addition to estimating these interindividual correlations for each trait, the bivariate analysis also evaluates the inter- and intraindividual cross-trait correlations. For example, the interindividual cross-trait correlation between father's trait 1 and son's trait 2 (f_1s_2) or the intraindividual cross-trait correlation in fathers (f_{12}) are estimated.

The computer program SEGPATH (18) was used to estimate the familial correlations based on maximum likelihood methods. The statistical method of analysis fits the model directly to the family data, under the assumption that the phenotypes in a family jointly follow a multivariate normal distribution. Details about the correlation models in SEGPATH may be found in Rice et al. (19,20). In summary, 8 correlations are estimated in the univariate analysis, while 34 are estimated in the bivariate analysis. For the bivariate analysis, there are 18 cross-trait correlations: 14 interindividual, for siblings (s_1s_2, s_1d_2, s_2d_1, d_1d_2), parent-offspring (f_1s_2, f_2s_1, f_1d_2, f_2d_1, m_1s_2, m_2s_1, m_1d_2, m_2d_1), and spouse (f_1m_2, f_2m_1); and 4 intraindividual (s_{12}, d_{12}, f_{12}, m_{12}). The remaining 16 are interindividual correlations within a trait, 8 for each of the two traits (e.g., s_1d_1, s_1s_1, d_1d_1, f_1s_1, f_1d_1, m_1s_1, m_1d_1, f_1m_1 for trait 1) (see Appendix 1 for details).

Hypothesis tests. The significance of each set of familial correlations is tested by comparing the log likelihood of a reduced model where some of the correlations are fixed to zero against the log likelihood obtained from the general model where all familial correlations are estimated. The likelihood ratio test, which is the difference between minus twice the log likelihoods, is distributed as a χ^2. The degrees of freedoms (*df*) are given by the difference in the number of parameters estimated in the two nested models. A χ^2 with a *P*-value of less than 0.05 is taken to suggest that the familial correlations set to zero under a null hypothesis are significant. The most parsimonious model is derived from combining nonrejected models. Appendix 2 gives the reduced models tested.

Under the assumptions that sibling and parent-offspring pairs share 1/2 of their genes, as well as some familial environmental effects, and that spouse pairs share only familial environmental effects (provided mating is random with regards to the two traits), the maximal cross-trait heritability can be computed from the most parsimonious models using the following equation:

$$h^2 = (r_{sibling} + r_{parent\text{-}offspring})(1 + r_{spouse})/$$
$$(1 + r_{spouse} + 2r_{spouse}r_{parent\text{-}offspring}),$$

where, r represents the interindividual cross-trait correlations, and the heritability is adjusted for the degree of spouse resemblance, if present. The heritability for each trait can also be estimated using the above equation where r represents interindividual correlations within a trait. It should be noted that this is a generalized or maximal heritability: both genetic and familial environmental (if significant) effects are included.

RESULTS

Table 1 presents the sample sizes, means and SDs for age, body height, body weight, BMI, $PH\text{-}LPL_B$, TG_B, ΔPH-LPL, and ΔTG. Based on a comparison of standard errors (SD/214 n), there are mean group differences across sex and generation groups in all four of these measures. In general, parents have higher levels of TG_B and $PH\text{-}LPL_B$ than offspring. In both generations, men have higher levels of TG_B than women, but women have higher $PH\text{-}LPL_B$ activities than men. As to triglyceride and PH-LPL response to exercise training, the patterns were slightly different. There is a reduction of triglycerides in men, but not women. For ΔPH-LPL, there is a marked increase in fathers, sons, and daughters compared with mothers. Although there is considerable heterogeneity in responsiveness of $\dot{V}O_{2max}$ to exercise training, the mean increase of $\dot{V}O_{2max}$ after exercise training is significant in each of the four sex and generation groups. Information on age, body height, body weight, and BMI were given for comparison of characteristics with other studies.

Before bivariate analyses, univariate analyses of ΔTG and ΔPH-LPL were performed. The results of the hypothesis tests are given in Table 2. The parent-offspring correlations for ΔTG were significant (model 6, $\chi^2 = 11.8$, $P < 0.01$) and the sibling correlations were marginal (model 5,

TABLE 1. Characteristics (mean ± SD) of study variables by sex and generation groups.

	Fathers (N = 86–88)	Mothers (N = 77–87)	Sons (N = 132–135)	Daughters (N = 135–149)
Baseline level				
Age (yr)*	53.3 ± 5.1	52.2 ± 5.0	25.2 ± 6.1	25.6 ± 6.3
Height (m)*†	1.76 ± 0.06	1.62 ± 0.06	1.79 ± 0.06	1.65 ± 6.4
Weight (kg)*†	87.3 ± 15.6	72.4 ± 13.5	82.4 ± 17.0	64.0 ± 13.2
BMI ($kg \cdot m^{-2}$)*	28.3 ± 4.61	27.7 ± 4.82	25.7 ± 4.96	23.6 ± 4.48
TG_B ($mmol \cdot L^{-1}$)*†	1.89 ± 0.94	1.39 ± 0.65	1.32 ± 0.77	1.07 ± 0.50
PH-LPL_B ($nmol \cdot mL^{-1} \cdot min^{-1}$)*†	52.8 ± 26.7	71.5 ± 38.3	47.7 ± 26.7	59.1 ± 28.2
Change of levels after exercise-training				
ΔTG ($mmol \cdot L^{-1}$)†	−0.15 ± 0.52	0.06 ± 0.42	−0.03 ± 0.42	0.03 ± 0.32
ΔPH-LPL ($nmol \cdot mL^{-1} \cdot min^{-1}$)*†	9.79 ± 24.1	0.15 ± 31.8	11.1 ± 27.8	6.28 ± 28.2
$\Delta \dot{V}O_{2max}$ ($mL \cdot min^{-1}$)*†	385.9 ± 209.2	292.4 ± 171.4	492.3 ± 241.9	372.7 ± 192.7

BMI indicates body mass index; TG_B, baseline (pretraining) plasma triglycerides; ΔTG, changes in plasma triglycerides after exercise training; PH-LPL_B, baseline postheparin lipoprotein lipase activity; ΔPH-LPL, changes in PH-LPL activity after exercise training.
* $P < 0.05$ when parents and offspring were compared.
† $P < 0.05$ when men and women were compared.

$\chi^2 = 6.99$, $P = 0.07$), while the spouse correlation was not significant (model 7, $\chi^2 = 0.78$, $P = 0.38$). This suggests that genetic factors partly explain the variation in ΔTG response to exercise training. Based on likelihood ratio tests, the model with no sex and generation differences and no spouse correlation is the most parsimonious model for ΔTG (model 9, $\chi^2 = 10.7$, $P = 0.15$). The common familial correlation among siblings and between parents and offspring pairs was 0.11 from the parsimonious model, yielding a maximal heritability for ΔTG of 22%. For ΔPH-LPL, the parent-offspring and spouse correlations were significant while sibling correlations were not, indicating that some familial factors, perhaps not genes, are involved in the variation of ΔPH-LPL. The common correlation among parent-offspring pairs was 0.16, and the spouse correlation was 0.37, giving a maximal heritability for ΔPH-LPL of 15%. These heritabilities suggest that familial/genetic influence on ΔTG and ΔPH-LPL is modest.

The results of the bivariate hypothesis tests are summarized in Table 3. The hypotheses of no intraindividual cross-trait correlations between TG_B and ΔTG, between PH-LPL_B and ΔPH-LPL, and between ΔTG and ΔPH-LPL were all rejected (model 8 with all P-values of less than 0.01), indicating that the within-person correlations are significant. Second, the interindividual cross-trait correlations between TG_B and ΔTG were not significant in any group (models 5, 6, and 7), suggesting that it is unlikely that there are common familial/genetic factors for levels of TG_B and ΔTG. For PH-LPL_B and ΔPH-LPL, we found significant cross-trait correlations in spouses (model 7), but no cross-trait correlations in siblings and parent-offspring (models 5 and 6), also suggesting that there are no common familial/genetic factors for the covariation between PH-LPL_B and ΔPH-LPL. For ΔTG and ΔPH-LPL, we found significant cross-trait correlations in parent-offspring pairs (model 6), but not in siblings and spouses (models 5 and 7), indicating that there are some familial factors in common to ΔTG and ΔPH-LPL, and these familial factors seem to be age-dependent.

The cross-trait familial correlations and standard errors from both the general model and the most parsimonious model are given in Table 4. The intraindividual cross-trait correlations between TG_B and ΔTG ranged from 0.08 to −0.59, being larger in magnitude in the men than women. The intraindividual cross-trait correlation was −0.45 between PH-LPL_B and ΔPH-LPL, and ranged from −0.18 to −0.30 between ΔTG and ΔPH-LPL. The negative correlations suggest that higher baseline levels are associated with smaller responses, and higher ΔPH-LPL is associated with lower ΔTG, as should be expected. Since the cross-trait familial correlations were nonsignificant for TG_B and ΔTG or for PH-LPL_B and ΔPH-LPL, the cross-trait heritabilities for TG_B and ΔTG and for PH-LPL_B and ΔPH-LPL were zero. However, the cross-trait parent-offspring correlations for ΔTG and ΔPH-LPL were significant based on hypothesis tests if we treated all 8 parent-offspring cross-trait correlations as a group. When these eight correlations were examined separately based on standard error comparisons,

TABLE 2. Results of hypothesis tests for univariate familial correlation analyses of ΔTG and ΔPH-LPL.

Hypotheses	df	ΔTG		ΔPH-LPL	
		χ^2	P	χ^2	P
1. General model		—	—	—	—
2. No sex difference in offspring	4	4.97	0.29	9.49	0.05
3. No sex difference in offspring and parents	5	9.66	0.09	9.62	0.09
4. No sex and generation difference	6	9.69	0.14	11.5	0.07
5. No sibling correlations	3	6.99	0.07	4.70	0.19
6. No parent-offspring correlations	4	11.8	0.02	17.7	<0.01
7. No spouse correlations	1	0.78	0.38	12.4	<0.01
8. No spouse and sibling correlations	4	7.88	0.10	16.4	<0.01
Most parsimonius model					
9. No sex and generation difference and no spouse correlations	7	10.7	0.15		
10. No sex and generation difference and no sibling correlations	7			11.5	0.12

ΔTG indicates changes in plasma triglyceride levels after exercise training; ΔPH-LPL, changes in postheparin lipoprotein lipase activity after exercise training.

TABLE 3. Results of hypothesis tests across sex, generation, and traits for triglycerides and lipoprotein lipase in response to exercise training.

Hypothesis	df	TG_B and ΔTG		PH-LPL_B and ΔPH-LPL		ΔTG and ΔPH-LPL	
		χ^2	P	χ^2	P	χ^2	P
1. General model	—	—	—	—	—	—	—
2. No sex differences in offspring	16	28.3	0.03	20.6	0.19	23.6	0.09
3. No sex differences in offspring or parents	22	53.4	<0.01	28.2	0.17	48.4	<0.01
4. No sex and generation differences	27	59.1	<0.01	32.5	0.21	50.8	<0.01
5. No cross-trait correlations in siblings	4	3.97	0.41	0.85	0.93	2.61	0.62
6. No cross-trait correlations in parent-offspring	8	6.04	0.64	15.6	0.05	20.7	<0.01
7. No cross-trait correlations in spouse	2	2.13	0.34	7.01	0.03	2.68	0.26
8. No cross-trait correlations in intraindividual	4	65.8	<0.01	80.1	<0.01	18.9	<0.01
9. No cross-trait correlations at all	18	88.2	<0.01	125.7	<0.01	54.7	<0.01
10. No sex difference in offspring, no cross-trait correlations in siblings and spouses	19					26.5	0.12
Most parsimonious model							
No interindividual cross-trait correlations	14	13.3	0.50				
No sex and generation difference, no cross-trait correlations in parent-offspring and siblings	28			35.7	0.17		
No sex difference in offspring, no cross-trait correlations in siblings and spouses	19					26.5	0.12

TG_B indicates baseline (pretraining) plasma triglycerides; ΔTG, changes in plasma triglycerides after exercise training; PH-LPL_B, baseline postheparin lipoprotein lipase activity; ΔPH-LPL, changes in PH-LPL activity after exercise training.

two of them (mother-son, mother-daughter) were significant. This suggests that the familial factors common to ΔTG and ΔPH-LPL are minor and that they differ across sex and generation groups.

DISCUSSION

To the best of our knowledge, the present investigation is the first attempt to address the extent to which familial or genetic factors are involved in the responses of LPL activity and blood TG level to exercise training. Previous studies have suggested that there were individual differences in LPL and lipid levels in response to exercise training (14,21). For example, TG levels in subjects with a high BMI responded less strongly than in those with a low BMI (14). After comparing the differences in responses to acute prolonged exercise between monozygotic twin pairs and dizygotic twin pairs, Savard and Bouchard (21) concluded that the individual differences in PH-LPL responses were largely genetic in nature. In the present study, we found that familial factors have significant influences on ΔPH-LPL but this time in response to exercise training. We also found significant genetic influences on ΔTG. The novel findings of the present study are that these influences are quantitatively estimated and that an involvement of familial factors in the covariation between the responsiveness of both triglycerides and PH-LPL to exercise training is found.

Interestingly, we did not find common genetic influences underlying baseline levels and responses for either trait studied even though there are within-individual phenotypic correlations between baseline level and the response in previous studies (25,26) and in this HERITAGE data. Significant intraindividual cross-trait correlations, in the absence of interindividual cross-trait correlations as seen here, do not suggest a contribution from familial factors, but rather from specific environmental factors underlying the

TABLE 4. Parameter estimates ± standard errors from general and most parsimonious models.

Correlations	Between TG_B and ΔTG		Between PH-LPL_B and ΔPH-LPL		Between ΔTG and ΔPH-LPL	
	General	Parsimonious	General	Parsimonious	General	Parsimonious
Siblings						
s_1s_2	−0.07 ± 0.09	[0]	−0.03 ± 0.10	[0]	0.04 ± 0.09	[0]
d_1d_2	0.08 ± 0.09	[0]	−0.08 ± 0.11	[0]	−0.09 ± 0.09	[0]
s_1d_2	−0.05 ± 0.09	[0]	−0.01 ± 0.09	[0]	−0.10 ± 0.07	[0]
s_2d_1	−0.14 ± 0.08	[0]	0.02 ± 0.09	[0]	0.02 ± 0.08	[0]
Parent-offspring						
f_1s_2	−0.01 ± 0.11	[0]	−0.10 ± 0.08	[0]	0.13 ± 0.10	0.11 ± 0.07
f_1d_2	0.01 ± 0.09	[0]	−0.03 ± 0.10	[0]	0.08 ± 0.07	[0.11]
f_2s_1	−0.12 ± 0.09	[0]	−0.05 ± 0.09	[0]	−0.04 ± 0.09	0.01 ± 0.06
f_2d_1	−0.17 ± 0.09	[0]	−0.26 ± 0.09	[0]	0.11 ± 0.09	[0.01]
m_1s_2	−0.05 ± 0.09	[0]	0.01 ± 0.09	[0]	−0.18 ± 0.09	−0.20 ± 0.06
m_1d_2	−0.08 ± 0.08	[0]	−0.25 ± 0.09	[0]	−0.22 ± 0.08	[−0.20]
m_2s_1	0.05 ± 0.08	[0]	0.03 ± 0.10	[0]	0.02 ± 0.08	−0.05 ± 0.06
m_2d_1	0.03 ± 0.11	[0]	−0.23 ± 0.09	[0]	−0.22 ± 0.07	[−0.05]
Spouse						
f_1m_2	0.15 ± 0.11	[0]	−0.23 ± 0.10	−0.17 ± 0.08	−0.08 ± 0.11	[0]
f_2m_1	−0.08 ± 0.11	[0]	−0.22 ± 0.10	[−0.17]	0.15 ± 0.10	[0]
Intraindividual						
f_{12}	−0.46 ± 0.08	−0.42 ± 0.08	−0.45 ± 0.08	−0.45 ± 0.04	−0.28 ± 0.09	−0.30 ± 0.09
m_{12}	0.09 ± 0.10	0.08 ± 0.09	−0.58 ± 0.06	[−0.45]	−0.21 ± 0.10	−0.24 ± 0.10
s_{12}	−0.53 ± 0.06	−0.59 ± 0.06	−0.44 ± 0.07	[−0.45]	−0.11 ± 0.08	−0.18 ± 0.06
d_{12}	−0.17 ± 0.08	−0.18 ± 0.07	−0.47 ± 0.07	[−0.45]	−0.24 ± 0.08	[−0.18]

TG_B indicates baseline (pretraining) plasma triglycerides; ΔTG, changes in plasma triglycerides after exercise training; PH-LPL_B, baseline postheparin lipoprotein lipase activity; ΔPH-LPL, changes in PH-LPL activity after exercise training.

phenotypic relationship. In other words, the familial factors influencing baseline levels are not the same as those influencing the response to exercise training. However, we note that the methodological design used here only indexes additive components. Whether there are nonadditive factors (e.g., major genes) leading to the covariation between baseline and response measures cannot be ruled out, although such effects, if they exist, are not likely to be large. For example, previous studies have suggested that the high density lipoprotein (HDL) cholesterol responsiveness to dietary cholesterol or fat is highly individualized (24) and that a gene may contribute by regulating dietary cholesterol absorption (16). Thus, it is possible that a gene with a small effect may be influencing the responses in TG level and PH-LPL activity to exercise training. Another interesting finding from the present study is that common familial factors for ΔTG and ΔPH-LPL explain only a minor proportion (5%) of the familial influences on either ΔTG or ΔPH-LPL, indicating that other physiological mechanisms are involved in addition to the baseline levels of both phenotypes.

In addition, we found that there was a sex difference in the triglyceride and PH-LPL response to exercise-training. Men responded more than did women, which is in agreement with previous findings (9). The physiological/pathophysiological mechanism underling this difference is not fully understood but it should be noted that females usually have higher levels of LPL activity but lower levels of TG at baseline (23). The changes in $\dot{V}O_{2max}$ may relate to the sex difference in triglyceride and PH-LPL response to exercise training. Due to the fact that there was no correlation between change in TG and LPL and change in $\dot{V}O_{2max}$ in the four sex by generation groups, it is likely that other biological factors instead of the changes in $\dot{V}O_{2max}$ may related to sex differences of LPL and TG after exercise training. Consistent with previous studies (4,14), we found negative within individual correlations between baseline and response measures for TG level and PH-LPL activity with the exception of TG in mothers. The magnitude of the TG (but not PH-LPL) correlations varied by both sex and generation, being stronger in men than women and stronger in offspring than parents. The significant negative correlation between ΔTG and ΔPH-LPL observed in the present investigation suggests that increased levels in PH-LPL activity after exercise training may result in delayed reductions in TG levels after training, which is in agreement with the findings from Kantor et al. (13) for acute exercise. The novel finding in the current study is that some familial determinants underlie this correlated response.

In conclusion, there is evidence of moderate familial influences on TG or PH-LPL in response to regular exercise over a 20-wk period. Moreover, the multifactorial mechanisms associated with these responses may be different from those modulating the respective baseline levels. Finally, there is evidence that some of the familial factors for triglyceride responsiveness to exercise-training are the same as those for PH-LPL responsiveness to exercise-training in sedentary Caucasian adult subjects. All of these results suggest that familial/genetic factors are involved (modestly) in the changes in lipid metabolism during exercise training, as well as a strong involvement additional familial/genetic factors on the baseline lipid levels.

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APPENDIX 1. Correlations in the bivariate familial correlation model.

	Cross-Trait		Within Trait (All Interindividual)	
	Interindividual	**Intraindividual**	**Trait 1**	**Trait 2**
Siblings	s_1s_2, s_1d_2	S_{12}	s_1s_1, s_1d_1	s_2s_2, s_2d_2
	s_2d_1, d_1d_2	D_{12}	d_1d_1	d_2d_2
Parent-offspring	f_1s_2, f_2s_1	—	f_1s_1	f_2s_2
	f_1d_2, f_2d_1	—	f_1d_1	f_2d_2
	m_1s_2, m_2s_1	—	m_1s_1	m_2s_2
	m_1d_2, m_2d_1	—	m_1d_1	m_2d_2
Spouse	f_1m_2, f_2m_1	f_{12}, m_{12}	f_1m_1	f_2m_2

s, sons; d, daughters; f, fathers; m, mothers; 1, trait 1 (e.g., TG); 2, trait 2 (e.g., PH-LPL).

APPENDIX 2. Summary of hypothesis tests.

Hypothesis	***df***	**Parameter Reductions**
1. General	—	All 34 correlations estimated
2. No sex difference in offspring	16	$s_1s_1=d_1d_1=s_1d_1$, $s_1s_2=d_1d_2=s_1d_2=s_2d_1$, $s_2s_2=d_2d_2=s_2d_2$, $f_1s_1=f_1d_1$, $f_1s_2=f_1d_2$, $f_2s_1=f_2d_1$, $f_2s_2=f_2d_2$, $m_1s_1=m_1d_1$, $m_1s_2=m_1d_2$, $m_2s_1=m_2d_1$, $m_2s_2=m_2d_2$, $s_{12}=d_{12}$
3. No sex differences in offspring or parents	22	$s_1s_1=d_1d_1=s_1d_1$, $s_1s_2=d_1d_2=s_1d_2=s_2d_1$, $s_2s_2=d_2d_2=s_2d_2$, $f_1s_1=f_1d_1=m_1s_1=m_1d_1$, $f_1s_2=f_1d_2=m_1s_2=m_1d_2$, $f_2s_1=f_2d_1=m_2s_1=m_2d_1$, $f_2s_2=f_2d_2=m_2s_2=m_2d_2$, $f_1m_2=f_2m_1$, $f_{12}=m_{12}$, $s_{12}=d_{12}$
4. No sex and generation differences	27	$f_1s_1=f_1d_1=m_1s_1=m_1d_1=s_1s_1=d_1d_1=s_1d_1$, $f_1s_2=f_1d_2=m_1s_2=m_1d_2=f_2s_1=f_2d_1=m_2s_1=m_2d_1=s_1s_2=d_1d_2=s_1d_2=s_2d_1$, $f_2s_2=f_2d_2=m_2s_2=m_2d_2=s_2s_2=d_2d_2=s_2d_2$, $f_1m_2=f_2m_1$, $f_{12}=m_{12}=s_{12}=d_{12}$
5. No cross-trait correlations in siblings	4	$s_1s_2=d_1d_2=s_1d_2=s_2d_1=0$
6. No cross-trait correlations in parent-offspring	8	$f_1s_2=f_1d_2=m_1s_2=m_1d_2=f_2s_1=f_2d_1=m_2s_1=m_2d_1=0$
7. No cross-trait correlations between spouses	2	$f_1m_2=f_2m_1=0$
8. No cross-trait correlations in intraindividual	4	$f_{12}=m_{12}=s_{12}=d_{12}=0$
9. No cross-trait correlations at all	18	$s_1s_2=d_1d_2=s_1d_2=s_2d_1=0$, $f_{12}=m_{12}=s_{12}=d_{12}=0$, $f_1s_2=f_1d_2=m_1s_2=m_1d_2=f_2s_1=f_2d_1=m_2s_1=m_2d_1=0$, $f_1m_2=f_2m_1=0$
10. Most parsimonious model		Combination of all or some nonrejected hypotheses above

s, sons; d, daughters; f, fathers; m, mothers; 1, trait 1 (e.g., TG); 2, trait 2 (e.g., PH-LPL).