Familial Resemblance of Plasma Lipids, Lipoproteins and Postheparin Lipoprotein and Hepatic Lipases in the HERITAGE Family Study

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Abstract The familial aggregation of lipids and lipoproteins and plasma postheparin triglyceride lipases was investigated in 86 Caucasian families participating in the HERITAGE Family study, a study investigating the role of genetic factors in the adaptation to exercise training and its relationships with cardiovascular disease risk factors. Accordingly, sedentary subjects were recruited, tested for a battery of measurements, exercise trained for 20 weeks, and were re-measured. The present report includes plasma levels of total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol and triglycerides, and postheparin plasma lipoprotein lipase (LPL) and hepatic lipase (HL) activities measured in 437 sedentary individuals (171 parents and 266 adult offspring) before training. Significant familial resemblance was observed for all the age-adjusted phenotypes. The pattern of familial correlations reveals no spouse correlations but significant parent-offspring and sibling correlations for total cholesterol, HDL-cholesterol and LDL-cholesterol with heritability (h^2) estimates of 62%, 83%, and 50%, respectively. For plasma triglyceride concentrations (h^2=55%) and HL activity (h^2=40%), significant spouse correlations were found in addition to parent-offspring and sibling correlations, suggesting that common familial environment in addition to genetic factors contribute to the familial resemblance. For plasma LPL activity, there was no spouse correlation, but sex differences were found in the familial correlations with higher heritabilities in female pairs (h^2=76%) compared to male pairs (h^2=30%) and opposite-sex pairs (h^2=44%). These results confirm the findings of previous family studies showing that genetic factors are major determinants of the familial resemblance in plasma lipids and lipoproteins and suggest the presence of sex differences in the heritability of postheparin LPL activity. (***Arterioscler Thromb Vasc Biol.* 1997;17:3263-3269.**)

Key Words • lipoproteins • lipids • cholesterol • lipases • coronary heart disease

Coronary heart disease (CHD) continues to be a major cause of morbidity and premature mortality in Western countries. Among risk factors of CHD, dyslipidemic states have been recognized to be important correlates and predictors of the disease. There is extensive epidemiological evidence showing that a dyslipidemic profile, characterized by high plasma levels of total cholesterol, triglycerides and LDL and reduced concentrations of HDL, is strongly associated with an increased risk of CHD.[1–5] There is also evidence from clinical trials that reduction of plasma cholesterol and LDL-cholesterol levels and increase in HDL-cholesterol concentrations contribute to reduce the risk of CHD,[6–7] even in patients who do not exhibit marked elevation of plasma cholesterol levels.[8]

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Because of their key role in the development of atherosclerosis and CHD, the study of genetic factors in modulating plasma lipid and lipoprotein levels has important clinical implications. Studies have clearly established that genetic factors contribute significantly to interindividual differences in blood lipids and lipoproteins in normolipemic individuals with heritability estimates accounting for about 25% to 80% of the phenotypic variance depending on the phenotype considered.[9–14] In most studies, the genetic effect was more important than environmental effects shared among family members.

LPL and HL are enzymes involved in the hydrolysis of triglyceride-rich lipoproteins and play an important role in the metabolism of lipoproteins and in the regulation of circulating levels of HDL-cholesterol. The LPL is responsible for the delipidation of chylomicrons and very low density lipoproteins and a higher LPL activity in the plasma has been associated with reduced plasma triglyceride levels as well as with an increased HDL-cholesterol levels, particularly for the HDL_2 subfraction.[15,16] In contrast, HL is involved in reverse cholesterol transport and its activity is negatively correlated with plasma HDL-cholesterol levels.[17,18] The evidence for a role of genetic factors in these two lipolytic enzymes has been mainly derived from molecular studies. Thus, mutations in the genes coding for these enzymes have been shown to result in severe forms of dyslipoproteinemia[19,20] and some studies reported associations between polymorphisms in the LPL gene and levels of lipids and lipoproteins.[21–23] Data from one twin study[24] based on 17 MZ and 18 DZ male twin pairs reported no significant

Selected Abbreviations and Acronyms

HDL = high-density lipoprotein
LDL = low-density lipoprotein
LPL = lipoprotein lipase
HL = hepatic lipase
CHD = coronary heart disease
MZ = monozygotic
DZ = dizygotic
BMI = body mass index
VLDL = very low-density lipoprotein

genetic effect for LPL, in contrast to HL that exhibited a high pairwise correlation in MZ twins (r=0.80), but not in DZ twins (r=0.21).

In the present study, the familial factors underlying the variation in lipoproteins and postheparin LPL and HL activities in the HERITAGE Family Study are investigated using a familial correlation model. Genetic and environmental inferences made by an inspection of familial correlations among spouses, siblings and between parents and offspring suggests that genetic factors significantly contribute to the familial aggregation of lipoproteins and postheparin lipase activities with heritability estimates ranging from about 40% to 80% of the age-adjusted phenotypic variance.

Methods

Sample

Subjects of the HERITAGE Family Study were used for the purpose of this study. The HERITAGE study is a multicenter study designed to investigate the effects of regular exercise on several cardiovascular disease and diabetes risk factors and to determine the role of genetic factors in cardiovascular, metabolic, and hormonal responses to endurance exercise training. The specific aims, design, and measurements of the study have been described in detail elswhere.[25] Briefly, Caucasian and Black families are recruited, tested, exercise-trained in four clinical centers with a rigorously controlled standardized training program for 20 weeks and re-tested. Only baseline (before training) data in Caucasian families are reported and analyzed in the present study.

Recruitment of families was based on extensive publicity and advertisement. The following exclusion criteria were used to screen subjects for recruitment. The primary requirement was that the families were sedentary, defined at baseline as no regular physical activity over the previous 6 months. Families with some nonsedentary members were included provided that the nonsedentary individual(s) detrained for at least 6 months. Second, individuals were required to be between the ages of 16 years to 65 years (16 years to 40 years for children, and 65 years or less for parents) in order to avoid maturation (low end) and aging (high end) complications. Third, individuals had to be in good health in order to complete the maximal exercise training. Fourth, individuals with a BMI greater than 40 kg/m^2 were usually excluded because of potential metabolic abnormalities and exercise difficulties associated with extreme obesity. Fifth, individuals with blood pressures greater than 159 mm Hg for systolic and 99 mm Hg for diastolic were also excluded. Finally, individuals with any life-threatening condition or disease that could be aggravated by cycle exercise were excluded. More details on exclusion criteria can be found elsewhere.[25] In the current study, data on a total of 437 individuals belonging to 86 Caucasian families were available.

Measures

Fasting blood samples were drawn at each Clinical Center and prepared according to a standard protocol. For women, samples were obtained in the early follicular phase. Samples were then sent to the lipid core laboratory at the Lipid Research Center of the Laval University Medical Center for determinations of plasma lipids, lipoproteins and postheparin lipolytic activities. Cholesterol levels in whole plasma and in lipoprotein fractions and plasma triglyceride levels were measured by enzymatic methods using the Technicon RA-1000 analyzer. Plasma VLDL were isolated by ultracentrifugation[26] and the HDL fraction was obtained after precipitation of LDL in the infranatant with heparin and $MnCl_2$.[27] Plasma LPL and HL activities were also measured in the subjects after a 12-hour overnight fast and 10 minutes after intravenous injection of heparin (60 IU/kg body weight). The postheparin lipase activities were measured using a modification of the method of Nilsson-Ehle and Ekman[28] as previously described.[29] The two lipolytic enzyme activities were expressed as nmoles of oleic acid released per ml of plasma per min.

Because of the multicenter nature of the HERITAGE study, extensive quality assurance and quality control measures were implemented to ensure that data were of the highest quality.[30] The reproducibility of lipids, lipoproteins, and postheparin lipase assays was determined using an intracenter quality control study[30] by generating split samples from 60 nonHERITAGE subjects (15 in each of the clinical center) that were assayed in a blind fashion by the lipid core laboratory. The reproducibility of repeated assays based on split samples was found to be very high, with intraclass correlation coefficients over 0.95. Coefficients of variation for repeated assays ranged from about 1% to 5% for the variables of the present study.

Age Adjustments

Before any data adjustments, triglyceride values were log transformed. Each measure was then adjusted for the effects of age using a stepwise multiple regression procedure, separately in each of the 4 sex by generation groups. In summary, a given measure was regressed on a polynomial in age in a stepwise manner, retaining only those terms that were significant at the 5% level. The phenotype used in the genetic analysis was defined as the age-adjusted and standardized residual score from the regression analysis. The percentages of variance accounted for by age in each of the sex by generation groups ranged from 3% to 24% for total cholesterol, 1% to 2% for HDL-cholesterol, 2% to 21% for LDL-cholesterol, 2% to 10% for HL, and 2% to 9% for LPL. For triglycerides, significant age effects were found only in sons and accounted for 15% of the variance.

Familial Correlation Model

The model was based on 4 groups of individuals [fathers (*f*), mothers (*m*), sons (*s*), and daughters (*d*)], giving rise to 8 interindividual correlations in 3 familial classes [1 spouse (*fm*), 4 parent-offspring (*fs*, *fd*, *ms*, *md*), and 3 sibling (*ss*, *dd*, *sd*)]. The maximum likelihood computer program SEGPATH[31] fitted the model directly to the family data under the assumption that the phenotypes within a family jointly follow a multivariate normal distribution. Null hypotheses were tested using the likelihood ratio test, which is the difference in minus twice the log-likelihoods (-2 ln L) obtained under the two different nested models. The likelihood ratio is approximately distributed as a χ^2 with the degrees of freedom being the difference in the number of parameters estimated in the two competing hypotheses. In addition to the likelihood ratio test, Akaike's[32] Information Criterion (AIC), which is -2 ln L plus twice the number of estimated parameters, was used to judge the fit of nonnested models. The "best" model by AIC is the one with the smallest value.

The general model (model 1) and several reduced models (models 2 to 12) testing specific null hypotheses were fitted to the data. A detailed description of each of these models is given in the appendix along with the parameter constraints involved in each reduced model and the resulting degrees of freedom.

TABLE 1. Descriptive Statistics of Plasma Lipid and Lipoprotein Levels and Lipase Activities in Each of the Sex and Generation Groups

Variable	n	Fathers	n	Mothers	n	Sons	n	Daughters
Age (years)	86	52.9±5.2	85	51.7±5.2	128	24.7±5.9	138	24.3±5.9
Total cholesterol (mmol/L)	86	5.11±0.85	85	4.96±0.79	128	4.25±0.84	138	4.15±0.85
HDL-cholesterol (mmol/L)	86	0.91±0.22	85	1.18±0.27	128	0.93±0.19	138	1.12±0.23
LDL-cholesterol (mmol/L)	86	3.47±0.79	85	3.32±0.69	128	2.86±0.89	138	2.72±0.77
Triglycerides (mmol/L)	86	1.96±1.05	85	1.43±0.66	128	1.32±0.77	138	1.08±0.49
HL (nmol/mL/min)	85	223.87±60.08	80	177.42±67.01	126	257.02±58.54	135	175.45±57.73
LPL (nmol/mL/min)	85	51.89±27.57	80	70.61±36.18	123	46.81±27.10	135	58.25±27.72

Data are mean±SD.

Briefly, two broad classes of reduced models were considered. First, null hypotheses on sex and generation differences in the familial correlations included no sex differences in the offspring (model 2), no sex differences in parents or offspring (model 3), and no sex nor generation differences (model 4). Other sex-specific models involved same versus opposite sex correlations with (model 5) and without (model 6) constraint on the spouse correlation and male versus female versus opposite-sex correlations with (model 7) and without (model 8) constraint in the spouse correlation. The spouse correlation is therefore allowed to vary in models 6 and 8, while it is not in models 5 and 7. Second, null hypotheses testing the strength of the familial resemblance were also conducted by familial class, including no spouse resemblance (model 9), no parent-offspring resemblance (model 10), no sibling resemblance (model 11), and no familial resemblance at all (model 12). Each null hypothesis was tested by a likelihood ratio comparison to the general model. The most parsimonious model was derived by combining all nonrejected null hypotheses. The AIC was used to select the "best" sex hypothesis from among the nonnested sex models. Also, when the AIC for the parsimonious model was larger than that for a null hypothesis, then the hypothesis with the smallest P-value was added back into the model until an acceptable fit was obtained.

Results

Table 1 shows the sample sizes, means, and standard deviations for age and for each of the lipid and lipase measures, separately in each of the sex and generation groups (fathers, mothers, sons, and daughters). Based on a comparison of standard errors, sex differences generally are in the direction of higher mean levels in males and generation differences are reflected in higher concentrations in parents. The exceptions involve total cholesterol (no sex differences), HDL-cholesterol (higher means in females than in males, and no generation difference between fathers and sons), and LDL-cholesterol (no sex difference).

The model-fitting results are given in Table 2 for plasma lipid and lipoprotein levels and in Table 3 for HL and LPL activities. The results for lipids and lipoproteins (Table 2) indicate the presence of significant familial aggregation for all lipid variables (model 12 rejected for all variables) with significant ($P<.001$) parent-offspring and sibling correlations. Except for triglycerides, the hypothesis of no spouse resemblance (model 9) could not be rejected, suggesting that genetic factors are probably more important than familial environment in determining interindividual differences in lipids and lipoproteins. Except for HDL-cholesterol, all the hypotheses involving sex and generation differences in the familial correlations could not be rejected ($.20 \leq P \leq .97$). For HDL-cholesterol, the models 5 and 7, where the spouse correlation is included and equated to the opposite-sex familial correlations, were rejected. Based on the AIC value, the best sex differences hypothesis was model 4 for cholesterol (AIC=5.51), LDL-cholesterol (AIC=7.82) and triglycerides (AIC=7.40) and model 3 for HDL-cholesterol (AIC=7.34). The most

TABLE 2. Summary of Results from Fitting Reduced Models for Plasma Lipids and Lipoproteins

	Total Cholesterol		HDL-Cholesterol		LDL-Cholesterol		Triglycerides	
Model	*P*	AIC	*P*	AIC	*P*	AIC	*P*	AIC
1. General		16.00		16.00		16.00		16.00
2. No sex difference in offspring	.97	8.57	.87	9.22	.78	9.76	.62	10.67
3. No sex difference in parents or offspring	.95	7.11	.93	7.34	.81	8.29	.72	8.86
4. No sex nor generation differences	.96	5.51	.29	11.37	.70	7.82	.76	7.40
5. Same sex vs opposite sex with fm	.39	10.34	.005	16.58	.28	11.44	.65	8.22
6. Same sex vs opposite sex without fm	.95	7.09	.23	12.82	.61	9.58	.69	9.04
7. Male vs female vs opposite sex with fm	.32	11.89	.003	18.56	.20	13.24	.60	9.63
8. Male vs female vs opposite sex without fm	.97	8.55	.15	14.82	.51	11.32	.64	10.51
9. No spouse resemblance	.28	15.19	.31	15.05	.66	14.19	.041	18.19
10. No parent-offspring resemblance	<.001	46.59	<.001	47.93	<.001	30.91	<.001	40.58
11. No sibling resemblance	<.001	44.14	<.001	73.64	<.001	37.03	<.001	29.79
12. No familial resemblance	<.001	74.59	<.001	101.95	<.001	50.46	<.001	55.21
Most parsimonious (models 4 and 9)	.86	5.27						
Most parsimonious (models 3 and 9)			.30	6.39				
Most parsimonious (models 4 and 9)					.73	6.41		
Most parsimonious (model 4)							.76	7.40

P from the likelihood ratio χ^2 test; a significant value ($P<.05$) indicates rejection of the hypothesis. AIC=Akaike's Information Criterion; the most parsimonious model is the one with the smallest AIC.

TABLE 3. Summary of Results from Fitting Reduced Models for Post-heparin HL and LPL Activities

	HL		LPL	
Model	*P*	AIC	*P*	AIC
1. General		16.00		16.00
2. No sex difference in offspring	.62	10.67	.20	14.02
3. No sex difference in parents or offspring	.70	8.97	.28	12.29
4. No sex nor generation differences	.81	6.98	.26	11.69
5. Same sex vs opposite sex with fm	.089	14.98	.15	13.48
6. Same sex vs opposite sex without fm	.95	7.16	.21	13.18
7. Male vs female vs opposite sex with fm	.05	16.95	.43	10.90
8. Male vs female vs opposite sex without fm	.90	9.06	.67	10.37
9. No spouse resemblance	.07	17.31	.31	15.03
10. No parent-offspring resemblance	<.001	29.49	<.001	40.61
11. No sibling resemblance	.011	21.07	.005	22.83
12. No familial resemblance	<.001	35.32	<.001	44.06
Most parsimonious (model 4)	.81	6.98		
Most parsimonious (models 8 and 9)			.74	8.74

parsimonious models were therefore the combination of models 4 and 9 for total cholesterol (AIC=5.27) and LDL-cholesterol (AIC=6.41), combination of models 3 and 9 for HDL-cholesterol (AIC=6.39) and model 4 for triglycerides.

Results for HL and LPL are presented in Table 3. As for lipids and lipoproteins, familial resemblance was noted with significant parent-offspring and sibling correlations ($P<.001$) and nonsignificant ($P>.05$) spouse correlations. For hepatic lipase, all of the hypotheses testing for no sex differences fit the data, although those that equate the spouse correlation with the other familial opposite-sex correlations (models 5 and 7) fit less well. Among the sex difference hypotheses, model 4 gave the best fit with an AIC=6.98. Although the parsimonious hypothesis derived by combining models 4 (no sex nor generation differences) and 9 (no spouse correlation) were found to fit the data by likelihood ratio ($P=.485$), the AIC for this combined model (8.48, results not shown) was larger than that for model 4 alone (AIC=6.98) which allows for an additional spouse correlation. Therefore, the most parsimonious model chosen for hepatic lipase was model 4 involving two correlations, one between spouses and one for the combined parent-offspring and sibling resemblance.

For lipoprotein lipase, none of hypotheses testing for no sex differences in the correlations were rejected, and the best one by AIC (10.37) was model 8 allowing for male-male, female-female, and opposite-sex correlations without any restriction the spouse correlation. Therefore, the most parsimonious model was the combination of models 8 and 9 (AIC=8.74), which allows for male-male, female-female, and opposite-sex familial correlations and no spouse resemblance.

Maximum likelihood parameter estimates (correlations ± standard errors) under both the general and the most parsimonious models are given in Table 4. The familial correlations for these lipid and lipase measures generally reflect a simple pattern of significant parent-offspring and sibling correlations and no significant spouse resemblance, suggesting a primarily genetic etiology. Spouse resemblance is significant for triglyceride and hepatic lipase, suggesting that there may be some common environmental factors in addition to genetic factors influencing these traits. For HDL-cholesterol sibling resemblance is larger than that for parent-offspring pairs, suggesting some additional shared sibship factors influencing HDL levels. Finally, the familial resemblance for lipoprotein lipase appears to be sex-specific (female pairs > opposite-sex > male pairs).

The maximum heritabilities derived from the most parsimonious models are also given in Table 4. These estimates include both genetic and common environmental sources of variance and are adjusted for the degree of spouse resemblance if significant. The estimates range from 40% for HL to 83% for HDL-cholesterol. For LPL, which exhibited significant sex differences in the familial correlations, the heritability estimates reach 30% when derived from male correlations (father-son and son-son), 44% when derived from opposite sex correlation (father-daughter, mother-son and son-daughter), and 76% when derived from female correlations (mother-daughter and daughter-daughter) with an average heritability of 50%.

Discussion

The results of the present study indicate that both plasma lipid and lipoprotein concentrations and plasma postheparin LPL and HL activities strongly aggregate in families. Although genetic and cultural transmission cannot be quantified separately based only on familial correlations computed in intact nuclear families without any index of familial environment, as in the present study, genetic and environmental inferences can be made by inspection of the pattern of familial correlations. For example, a pattern of significant correlations among siblings and between parents and offspring, but not between spouses (who presumably share no genes by immediate descent) suggest that the familial aggregation is likely to be due to genetic factors. This is exactly what was found in the present study for total plasma cholesterol, HDL-cholesterol and LDL-cholesterol levels. For triglyceride concentrations, significant spouse resemblance was observed in addition to parent-offspring and sibling correlations.

The heritability estimates reported in this study are within the range of those reported in several other family studies[9,10,12,33–40] with average heritabilities (range) of 55% (39% to 71%) for total cholesterol, 52% (28% to 80%) for HDL-cholesterol, 49% (23% to 72%) for

TABLE 4. Maximum Likelihood Estimates of Familial Correlations (±SE) Under the General and Most Parsiminious Models

Correlation	Total Cholesterol	HDL Cholesterol	LDL Cholesterol	Triglycerides	HL	LPL
			General Model			
fm	0.12±0.11	0.11±0.11	0.05±0.11	0.22±0.10	−0.21±0.11	0.11±0.11
fs	0.40±0.08	0.38±0.08	0.30±0.09	0.29±0.09	0.26±0.08	0.17±0.09
fd	0.35±0.08	0.33±0.09	0.30±0.08	0.36±0.08	0.18±0.09	0.32±0.22
ms	0.31±0.09	0.37±0.09	0.24±0.09	0.31±0.09	0.07±0.10	0.19±0.09
md	0.30±0.09	0.39±0.08	0.18±0.10	0.26±0.08	0.25±0.09	0.38±0.08
ss	0.40±0.10	0.57±0.09	0.33±0.11	0.38±0.11	0.19±0.13	0.11±0.13
dd	0.38±0.10	0.46±0.09	0.41±0.10	0.20±0.11	0.25±0.10	0.36±0.11
sd	0.33±0.10	0.50±0.08	0.27±0.11	0.24±0.09	0.17±0.09	0.15±0.09
			Most Parsimonious Model			
fm	[0]	[0]	[0]	0.20±0.10	−0.21±0.10	[0]
fs	0.31±0.03	0.34±0.04	0.25±0.04	0.30±0.05	0.20±0.04	0.15±0.08
fd	[0.31]	[0.34]	[0.25]	[0.30]	[0.20]	0.22±0.06
ms	[0.31]	[0.34]	[0.25]	[0.30]	[0.20]	[0.22]
md	[0.31]	[0.34]	[0.25]	[0.30]	[0.20]	0.38±0.07
ss	[0.31]	0.49±0.06	[0.25]	[0.30]	[0.20]	[0.15]
dd	[0.31]	[0.49]	[0.25]	[0.30]	[0.20]	[0.38]
sd	[0.31]	[0.49]	[0.25]	[0.30]	[0.20]	[0.22]
h^2	62%	83%	50%	55%	40%	30%-76%

Values in brackets are fixed or equal to a preceding value. h^2=Maximal heritability computed as: $(r_{sib}+r_{p\text{-}o})(1+r_{spouse})/(1+r_{spouse}+2\ r_{spouse}\ r_{p\text{-}o})$. For LPL, which had sex differences in the correlations, the following equations were used to compute the heritabilities: for opposite sex pairs: $2[(r_{mother\text{-}son}+r_{father\text{-}daughter}+r_{son\text{-}daughter})/3]$; for male pairs: $2[(r_{father\text{-}son}+r_{son\text{-}son})/2]$; and for female pairs: $2[(r_{mother\text{-}daughter}+r_{daughter\text{-}daughter})/2]$.

LDL-cholesterol, and 32% (13% to 61%) for triglycerides. The heritabilities reported in the present study tend to be higher than the average heritabilities computed from these family studies, which could be explained by two factors. First, the heritabilities reported here should be considered as "maximal" heritabilities as no distinction can be made between genetic and cultural inheritance with the approach used in the present study. Since common familial environment accounts for up to 20% of the variance of plasma lipids and lipoproteins,[9,10,13] one cannot exclude the contribution of cultural inheritance as a determinant of the familial aggregation observed in this study, despite the absence of spouse correlation. Second, subjects in the HERITAGE Family study were recruited to be "sedentary" at baseline, thus providing a unique control over an important environmental factor that could contribute to interindividual differences in blood lipids and lipoproteins, ie, physical activity level. Several studies have shown that plasma lipid and lipoprotein levels are affected by regular exercise and some of the protective effect of physical activity against CHD has been postulated to be mediated by the beneficial effects on the lipid and lipoprotein profile.[41–46] Such a control over the level of physical activity could reduce the phenotypic variance and thus lead to higher heritability estimates.

A unique feature of the present study is the investigation of the familial resemblance in postheparin plasma LPL and HL activities. Our results suggest that interindividual differences in HL and LPL activities are genetically determined as indicated by average heritabilities of 40% and 50%, respectively. Besides molecular studies, the only evidence for a role of genetic factors in lipase activities come from twin studies. In one study based on a small number MZ and DZ male twin pairs, a significant genetic effect was reported for post-heparin plasma HL, but not for LPL.[24] The other studies are based on LPL activity measured in the adipose tissue. In one study in which LPL activity was measured in suprailiac adipose tissue samples obtained from 28 pairs of MZ twins and 25 pairs of DZ twins, Bouchard et al[47] reported a higher correlations in MZ twins (r=0.65) compared to DZ twins (r=0.10), suggesting a highly significant heritability for LPL activity. Evidence from twin studies also suggest that the response of adipose tissue LPL activity to exercise or overfeeding is genetically determined. For example, a greater within pair resemblance in 11 pairs of MZ twins (r=0.87) compared to 10 pairs of DZ twins (r=0.51) was reported in the response of the suprailiac adipose tissue LPL activity to a prolonged (90 minutes) single bout of exercise.[48] These results suggest a role for genetic factors in the acute response of adipose tissue LPL to exercise. Furthermore, a significant MZ intrapair resemblance (r=0.82) was also observed in the response of the adipose tissue (suprailiac depot) LPL activity to short-term (22 days) overfeeding.[49] These twin studies suggest a role for genetic factors in the regulation of adipose tissue LPL activity.

Another novel finding of the present study is the presence of significant sex differences in the familial correlations of LPL, resulting in higher heritabilities in female pairs (h^2=76%), intermediate heritabilities in opposite-sex pairs (h^2=44%) and lower heritabilities in male pairs (h^2=30%). Several studies have shown that women exhibit a lipoprotein profile associated with a reduced risk of CHD, particularly because of their higher plasma levels of HDL-cholesterol. Moreover, post heparin LPL activity was reported to be higher in women that in men[50,51] and to be positively correlated with circulating levels of HDL-cholesterol.[16,52] These observations suggest that the protective lipid profile observed in women could be to some extent explained by the gender differences in LPL activity, as recently shown in a study based on measurements of femoral adipose

APPENDIX. Summary of Hypotheses Testing

Model	df	Parameter Constraints
1. General	4	All 8 correlations estimated
2. No sex difference in offspring	5	fs=fd; ms=md; ss=dd=sd
3. No sex difference in parents or offspring	5	fs=fd=ms=md; ss=dd=sd
4. No sex nor generation differences	6	fs=fd=ms=md=ss=dd=sd
5. Same sex vs opposite sex with fm	6	fs=md=ss=dd; fm=fd=ms=sd
6. Same sex vs opposite sex without fm	5	fs=md=ss=dd; fd=ms=sd
7. Male vs female vs opposite sex with fm	5	fs=ss; md=dd; fm=fd=ms=sd
8. Male vs female vs opposite sex without fm	4	fs=ss; md=dd; fd=ms=sd
9. No spouse resemblance	1	fm=0
10. No parent-offspring resemblance	4	fs=fd=ms=md=0
11. No sibling resemblance	3	ss=dd=sd=0
12. No familial resemblance	8	fm=fs=fd=fs=ms=md=ss=dd=0

df=degrees of freedom; f=father; m=mother; s=son; d=daughter.

tissue LPL activity in a sample of 14 premenopausal women and 17 men.[29] Our finding of higher heritability levels in females compared to males for LPL activity indicates that the genetic factors affecting LPL activity are sex-specific and suggests that the sex differences observed in LPL activity and in HDL-cholesterol levels could be genetically determined.

In summary, the results of the present family study indicate that genetic factors contribute significantly to the familial resemblance observed in plasma lipid and lipoprotein levels and in plasma postheparin LPL and HL activities in sedentary individuals with heritability estimates ranging from 40% to 83%. They also reveal the presence of sex differences in the heritabilities of LPL with higher heritabilities in females compared to males. Further genetic studies testing for the presence of major gene effects and investigating the pleiotropic effects between plasma postheparin triglyceride lipase activities and lipoprotein levels will be needed to better understand the genetic basis of lipid and lipoprotein metabolism.

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