Segregation Analysis of Apolipoproteins A-1 and B-100 Measured Before and After an Exercise Training Program

The HERITAGE Family Study

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Abstract—Complex segregation analyses of apolipoproteins (apo) A-1 and B-100 were performed in a sample of 520 individuals from 99 white families who participated in the HERITAGE Family Study. In these sedentary families, plasma apo A-1 and B-100 concentrations were measured before and after a 20-week endurance exercise training program. Baseline apo A-1 and B-100 were adjusted for the effects of age (age-adjusted baseline apo A-1 and B-100) and for the effects of age and BMI (age-BMI–adjusted baseline apo A-1 and B-100). The change in response to training was computed as a simple Δ (posttraining minus baseline) and was adjusted for age and the baseline (age-baseline–adjusted apo A-1 and B-100 responses to training). In the present study, a major gene could not be inferred for baseline apo A-1. Rather, we found a major effect along with a multifactorial effect accounting for 8% to 9% and 51% to 56% of the variance, respectively. In addition, no clear evidence supported a major-gene effect for its response to training, whereas the transmission of a major effect from parents to offspring was ambiguous, ie, genetic in nature or familial environmental in origin. The major effect accounted for 15% of the variance, with an additional 21% and 58% of the variance being accounted for by a multifactorial effect in parents and offspring, respectively. It is interesting to have obtained evidence of a putative recessive major locus for baseline apo B-100, which accounted for 50% to 56% of the variance, with an additional 25% to 29% of the variance due to a multifactorial effect. In contrast, no major effect for its response to training was identified, although a multifactorial effect was found that accounted for 27% of the variance. The novel findings arising from the present study are summarized as follows. Baseline apo A-1 and its response to training were influenced by a major effect and a multifactorial effect. Baseline apo B-100 was influenced by a putative major recessive gene with a multifactorial component, but its response to training was influenced solely by a multifactorial component in these sedentary families. **(*Arterioscler Thromb Vasc Biol*. 2000;20:807-814.)**

Key Words: commingling ■ major gene effect ■ major effect ■ multifactorial effect

Some evidence indicates that elevated plasma and total LDL cholesterol (LDL-C) levels are major etiologic factors for developing atherosclerosis and coronary heart disease, whereas elevated HDL cholesterol (HDL-C) concentrations appear to provide protective effects against premature coronary heart disease. Apolipoprotein (apo) A-1 is one of the major protein components of HDL. It activates lecithin:cholesterol acyltransferase (LCAT), a plasma enzyme that catalyzes the esterification of cholesterol on the HDL particle surface, making possible reverse cholesterol transport from peripheral tissues.[1] Apo B-100 is predominant in LDL and VLDL, which transport cholesterol and triglycerides to peripheral tissues in the fasting state. Apo B-100, the sole lipoprotein in LDL, serves as the ligand for binding to cell LDL receptors in the liver and other tissues.[2]

The clinical significance of apo A-1 and B-100 has led to extensive studies for 2 decades focusing on the level and nature of genetic influences.[3,4] The familial aggregation of apo A-1 is well documented, with genetic heritability estimates reported to range from 53% to 66% in twin studies[5,6] and to reach 43% in families selected through probands with premature myocardial infarction and in families randomly selected from the general population.[7] For apo B-100, Hamsten et al[7] used path analysis in families and reported genetic heritabilities of 14% in parents and 51% in offspring. Results obtained from segregation analyses have suggested major-gene effects for both apo A-1[8–16] and apo B-100.[2,12,17–20] More recent studies have reported a second major locus determining apo A-1 levels.[21,22] In contrast to these positive findings,

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TABLE 1. Mean, SD, and SEM for Baseline Apo A-1 and B-100 (mg/dL) and the Changes in Response to Training

Variable	No.	Mean	SD (SEM)	Variable	No.	Means	SD (SEM)
	Fathers				Mothers		
Age, y*	98	53.3	5.3 (0.5)	Age, y*	94	52.1	5.0 (0.5)
BMI, kg/m^2*	97	28.4	4.4 (0.5)	BMI, kg/m^2*	93	27.5	4.8 (0.5)
Baseline				Baseline			
Apo A-1	98	116.3†	16.7 (1.7)	Apo A-1*	94	127.4†	16.2 (1.7)
Apo B-100*	93	104.8†	21.4 (2.2)	Apo B-100*	91	91.7†	21.5 (2.3)
Response to training				Response to training			
Apo A-1	93	1.8	9.2 (1.0)	Apo A-1	91	3.4	11.4 (1.2)
Apo B-100	93	−1.9†	11.9 (1.2)	Apo B-100	91	2.6†	8.6 (0.9)
	Sons				Daughters		
Age, y*	157	25.4	6.0 (0.5)	Age, y*	171	25.4	6.3 (0.5)
BMI, kg/m^2*	155	25.6†	4.9 (0.4)	BMI, kg/m^2*	169	23.7†	4.4 (0.3)
Baseline				Baseline			
Apo A-1	157	112.6†	15.2 (1.2)	Apo A-1*	171	118.1†	16.7 (1.3)
Apo B-100*	140	81.6	23.2 (2.0)	Apo B-100*	159	76.8	21.2 (1.7)
Response to training				Response to training			
Apo A-1	140	4.4	11.0 (0.9)	Apo A-1	159	4.6	13.0 (1.0)
Apo B-100	140	−0.2	9.3 (0.8)	Apo B-100	159	1.5	12.0 (1.0)

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

there also have been contradictory reports for apo A-1[9,18,23] and apo B-100.[24,25]

Prospective epidemiological studies have provided evidence that apolipoprotein levels can be affected by physical activity and fitness levels.[26] In particular, apo A-1 levels have been reported to increase and apo B-100 levels to decrease[27,28] in response to exercise training. However, no studies indicated whether there is a familial basis for the changes in response to exercise training.

Physical activity level was controlled for in the HEalth, RIsk factors, exercise Training and GEnetics (HERITAGE) Family Study by requiring all participants to be sedentary at baseline, ie, having not engaged in regular physical activity over the previous 6 months. Apo A-1 and B-100 were measured before and after a 20-week endurance exercise training program. The present study is unique in that the contribution of physical activity level to the baseline apo A-1 and B-100 variability is somewhat reduced, because the HERITAGE Family Study participants were required to be sedentary at entry. Furthermore, this study is unique in that apo A-1 and B-100 levels were assessed before and after exercise training in intact families, so that genetic hypotheses regarding the response to exercise training can be evaluated.

Methods

Sample

The HERITAGE Family Study was designed to investigate the role of the genotype in cardiovascular, metabolic, and hormonal responses to aerobic exercise training and the contribution of exercise training to changes in several cardiovascular disease and diabetes risk factors. See Bouchard et al[29] for more details concerning the HERITAGE Family Study sample and protocol.

A total of 520 individuals from 99 white families (255 men, 265 women) were analyzed in this study. Participants with incomplete baseline or postexercise training apo A-1 and B-100 measures were excluded from these analyses. Table 1 gives the sample sizes within each of 4 sex-by-generation subgroups (fathers, mothers, sons, and daughters) for the baseline measurements and the changes in response to exercise training. Black families were also recruited for the HERITAGE Family Study but were not included in these analyses because of inadequate sample size. Recruitment of families was based on extensive media publicity and advertisements at the 4 participating clinical centers.

The following criteria were applied to screen subjects for participation. First, individuals had to be between the ages of 17 and 65 years (17 and 40 years for children and ≤65 years for parents). Second, all participants were required to be sedentary at baseline. Third, individuals with a body mass index [BMI, weight (kg)/height (m)^2] >40 kg/m^2 were excluded unless it was determined during baseline testing that they were able to meet the demands of the exercise tests and exercise training program. Fourth, resting blood pressure (BP) levels could not exceed 159 mm Hg for systolic BP and 99 mm Hg for diastolic BP without medications. Finally, participants were required to be in good general physical health to complete the 20-week exercise training program. Further exclusion criteria can be found in Bouchard et al.[29]

Exercise Training Program

The training protocol is thoroughly outlined in Bouchard et al.[29] Briefly, each individual trained on a cycle ergometer in the laboratory under supervision 3 times a week for 20 weeks. The intensity and duration of exercise were adjusted for each individual every 2 weeks so that each participant was working at a heart rate associated with 75% of their maximum oxygen uptake volume for 50 minutes at the last 6 weeks of training. The power output was adjusted automatically via built-in computers in the cycle ergometer to meet the designed heart rate response to exercise training. All training sessions were supervised on site, and adherence to the protocol was strictly monitored.

Measurements

Before and after the 20-week standardized exercise training program, blood samples were taken from an antecubital vein into vacuum tubes containing EDTA to measure lipid levels, including plasma apo A-1 and B-100 concentrations. The blood samples were col-

lected in the morning in a 12-hour fasting state with the participants in a semirecumbent position and were drawn twice before (24 hours apart) and twice after (24 and 72 hours after the last exercise session) a 20-week endurance exercise training program. The blood samples collected at each clinical center were prepared according to a standard protocol before being sent to the core laboratory in Québec and were adjusted for possible hemodilution by protein assays (total proteins were assayed by the Biuret method (Roche Molecular Biochemicals, Boehringer Mannheim Corp). Apo A-1 and B-100 concentrations were tested in plasma by the rocket immunoelectrophoretic method of Laurell.[30] See Després et al[31] for more details on the internal and external quality control of plasma apo A-1 and B-100 assays.

Data Adjustments

Baseline apo A-1 and B-100 were adjusted for the effects of age, separately within each of the 4 sex-by-generation groups, by a stepwise multiple-regression procedure. Briefly, a given measurement was regressed on a polynomial in age (linear, quadratic, and cubic) in a stepwise manner, retaining only those terms that were significant at the 5% level. Thus, the residual score from this regression should be independent of age, sex, and generation effects. Similar sets of stepwise regressions (by sex and generation groups) were performed on baseline apo A-1 and B-100 with a polynomial in age (age, age^2, and age^3) and BMI (linear). The apo A-1 and B-100 changes in response to exercise training were adjusted for the effects of polynomial in age and baseline apo A-1 and B-100 (linear), respectively, separately within each of the 4 sex-by-generation groups. Each of the adjusted phenotypes used in the genetic analysis was finally standardized to a mean of zero and an SD of 1 within each of the 4 sex-by-generation groups.

Commingling

The method of commingling analysis as described in MacLean et al[32] and implemented in the computer program SKUMIX[33] was used. A mixture of up to 3 distributions in Hardy-Weinberg proportions can be fitted optionally, including p, a Box-Cox power transformation parameter. There are 5 additional parameters in the model, including the common variance in each component (E); the overall mean (u) in the entire sample; q, which determines the relative proportion (q^2) of component distribution with the highest mean; the displacement between the 2 extreme component means (t); and the relative position of the mean of the middle component (d). These parameters were estimated by the maximum-likelihood method. Hypothesis tests for nested models were carried out with the likelihood ratio test. The test criterion, which is the difference in minus twice the log-likelihoods (-2 ln L) obtained under 2 models, is distributed asymptotically as a χ^2, with the degrees of freedom being equal to the difference in the number of parameters estimated in the competing models. Nonnested models are compared by Akaike's information criterion (AIC), which is -2 ln L plus twice the number of estimated parameters, and the "best" model is the one with the smallest AIC.[34]

Segregation Model

Segregation analysis, as implemented in the computer program POINTER,[32–35] was performed with the unified mixed model.[36] This model assumes that a phenotype is composed of the independent and additive contributions from a major effect, a heritable multifactorial background, and a unique environmental residual. The major effect is assumed to result from the segregation at a single locus with 2 alleles (*A* and *a*). The *a* allele is defined as associated with higher trait value. Included in the model are 7 parameters: the overall variance (V); the overall mean (u); the frequency of the *a* allele (q); the displacement between the 2 homozygous means (t); the relative position of the heterozygous mean, or dominance (d); and the multifactorial heritability in offspring (H) and in parents (HZ). In this study, we used conditional likelihood (ie, conditioned the likelihood on the parental values). We note that u, q, t, and d are parameterized identically to those in SKUMIX. The transmission pattern of the major gene from parents to offspring is characterized by 3 parameters: τ_1 is the probability that an *AA* individual transmits allele *A* to the offspring; τ_2 is the probability that *Aa* transmits *A*; and τ_3 is the probability that *aa* transmits *A*. Under Mendelian transmission, $\tau_1=1$, $\tau_2=0.5$, and $\tau_3=0$, and when the 3 τ values are equal, no transmission of the major effect is obtained. The following 3 conditions are usually necessary to infer a major gene[35]: (1) rejection of the no-major-effect hypothesis (q=t=d=0); (2) nonrejection of the Mendelian transmission hypothesis (Mendelian τ's); and (3) rejection of the no-transmission hypothesis (equal τ's). Competing models are tested for significance by the likelihood ratio test.

Results

In the present study, reproducibility of baseline apo A-1 and B-100 measures is very high, with coefficients of variation for repeated measures being 4.9% and 6.2% for baseline apo A-1 and B-100, respectively, and intraclass correlations for repeated measures being 0.89 and 0.95 for baseline apo A-1 and B-100, respectively.[31] Means and SD of baseline and apo A-1 and B-100 changes in response to exercise training are given in Table 1. Group differences may be judged by use of the SEM comparisons. There were significant generation differences in the means of both baseline apo A-1 and B-100, with higher levels in parents than in offspring within sex, but not in men for mean of baseline apo A-1 levels. In each of the generations, means of baseline apo A-1 were significantly higher in women than in men, whereas means of baseline apo B-100 were higher in men than in women (not significant in offspring). For apo A-1 and B-100 changes in response to exercise training, there were no generation differences in the means for men or women and no sex differences in the means for parents or offspring, except that mean apo B-100 changes in response to exercise training were significantly higher in mothers than in fathers.

For age-adjusted baseline apo A-1, there were no significant age effects in mothers and offspring. For age-adjusted baseline apo B-100, age was not a significant predictor in parents or daughters. For age-BMI–adjusted baseline apo A-1 and B-100, BMI accounted for a larger percentage of variance than did age. For age- and baseline-adjusted apo A-1 and apo B-100 changes in response to exercise training, baseline apo A-1 was a significant predictor in parents and sons, and baseline apo B-100 was a more important predictor in offspring than in parents. See Table 2 for detailed percentages of variance accounted for by the effects of age, BMI, and the baseline apo A-1 and B-100 levels.

The commingling analysis results suggested that the best models consist of 2 normal distributions for age-adjusted baseline apo A-1 (E=0.99436, u=0.02302, d=0, t=3.71293, q=0.08008, P=1), age-BMI–adjusted baseline apo A-1 (E=0.98692, u=0.02389, d=0, t=3.77115, q=0.08229, P=1), and age-baseline–adjusted apo A-1 change in response to exercise training (E=0.99613, u=0.01238, d=0, t=3.26704, q=0.10320, P=1); 3 skewed distributions for age-adjusted baseline apo B-100 (E=0.37407, u=0.10469, d=0.43438, t=3.58885, q=0.16647, P=2.21982) and age-BMI–adjusted baseline apo B-100 (E=0.43936, u=0.07154, d=0.44020, t=3.02684, q=0.19375, P=1.86593); and 2 skewed distributions for age-baseline–adjusted apo B-100 change in response to exercise training (E=0.76250, u=0.05458, d=0, t=2.51142, q=0.22426, P=1.71526). The finding of multiple distributions is compatible with a major-gene hypothesis; however, commingling may also arise through other causes. Thus, segregation analysis was used to

TABLE 2. Data Adjustment for the Effects of Age, BMI, and Baseline Levels of Apo A-1 and B-100

Effects Allowed; Group	Significant Terms ($P<0.05$)	% Variance
(1) Age-adjusted baseline apo A-1		
Fathers	Age^2	4.0
Mothers	None	None
Sons	None	None
Daughters	None	None
(2) Age-adjusted baseline apo B-100		
Fathers	None	None
Mothers	None	None
Sons	Age	21.7
Daughters	None	None
(3) Age-BMI–adjusted baseline apo A-1		
Fathers	BMI, age^3	11.7
Mothers	BMI	5.1
Sons	None	None
Daughters	None	None
(4) Age-BMI–adjusted baseline apo B-100		
Fathers	None	None
Mothers	BMI	6.1
Sons	Age, BMI	34.9
Daughters	BMI	6.5
(5) Age-baseline–adjusted apo A-1 response		
Fathers	Baseline apo A-1	15.8
Mothers	Baseline apo A-1	6.5
Sons	Age, Baseline apo A-1	24.6
Daughters	None	None
(6) Age-baseline–adjusted apo B-100 response		
Fathers	Age^2	8.8
Mothers	Age, age^2	10.1
Sons	Age, baseline apo B-100	9.7
Daughters	Baseline apo B-100	9.9

determine whether these major effects segregated in families according to Mendelian expectations.

Segregation analysis results are summarized in Tables 3 and 4 for baseline and apo A-1 and B changes in response to exercise training, respectively. The parameter estimates under each of the most parsimonious segregation models are given in Table 5. For age-adjusted baseline apo A-1, hypothesis tests for models 2, 3, and 4 were significant, suggesting that there were significant multifactorial, major, and familial effects. Both additive (model 7) and dominant (model 8) hypotheses were rejected, whereas the recessive (model 6) mode of inheritance fit the data. Tests of transmission probabilities were carried out under the parsimonious Mendelian hypothesis (no generation difference in the multifactorial component and a recessive mode of inheritance for the major-gene component). Although there was a major effect, neither the hypothesis of Mendelian τ's (model 12, free τ's, "most general" model in Tables 3 and 4) (model 9−model 12: $\chi_3^2=0.46$, $P=0.928$) nor the hypothesis of equal τ's (model 11, τ's$=1-$q, "nontransmitted" model in Tables 3 and 4) (model 11−model 12: $\chi_3^2=0.09$, $P=0.993$) was rejected. According to AIC, the most parsimonious hypothesis was the equal τ's model (AIC$=884.38$). Thus, the transmission of the major effect was ambiguous. The major effect accounted for 9% of the variance, and an additional 56% of the variance was due to a multifactorial effect. Similar results were obtained for the age-BMI–adjusted apo A-1: the major effect accounted for 8% of the variance, and an additional 51% of the variance was due to a multifactorial effect.

For age-adjusted baseline apo B-100, models 2 to 4 were rejected, suggesting that there was familial resemblance (both major and a multifactorial component). The recessive hypothesis (model 6) was accepted, whereas both additive and dominant hypotheses (models 7 and 8) were rejected. Transmission probability tests were performed under the parsimonious Mendelian hypothesis (model 9, no generation difference in the multifactorial component and a recessive mode of inheritance for the major-gene component), and the 3 required conditions to infer a major-gene hypothesis were satisfied: First, major effect was significant (model 3−model 1: $\chi_3^2=33.57$, $P<0.001$); second, the hypothesis of Mendelian τ's was not rejected (model 9−model 12: $\chi_3^2=0.23$, $P=0.891$); finally, the equal τ's hypothesis was rejected (model 11−model 12: $\chi_3^2=8.30$, $P=0.040$). The putative homogeneous major gene accounted for 56% of the phenotypic variance, and 25% (q^2) of the sample carried the homozygous recessive genotype. An additional 25% of the variance was due to a multifactorial effect. For the age-BMI–adjusted baseline apo B-100, a similar pattern resulted, except that the restricted-equal-τ's ($\tau_1=\tau_2=\tau_3=1-$q) hypothesis (model 11) was borderline ($\chi_3^2=7.47$, $P=0.058$). The putative major gene accounted for 50% of the phenotypic variance, and 21% (q^2) of the sample carried the homozygous recessive genotype. An additional 29% of the variance was due to a multifactorial effect.

For age-baseline–adjusted apo A-1 change in response to exercise training, each of the multifactorial, major, and familial effects was suggested. Transmission probability tests were carried out under the parsimonious Mendelian hypothesis (generation differences in the multifactorial component and a recessive major-locus component). Neither the Mendelian τ's nor the equal τ's hypothesis was rejected, suggesting an ambiguous transmission of the major effect from parents to offspring. Although the AIC suggests that the Mendelian hypothesis fits best (AIC$=835.59$), evidence obtained was not clear enough to infer a major-locus effect.[35] The major effect accounted for 15% of the phenotypic variance, with an additional 21% and 58% of the variance due to a multifactorial effect in parents and offspring, respectively. For the age-baseline–adjusted apo B-100 change in response to exercise training, neither the major effect (model 3) nor the multifactorial component (model 2) was significant, but there was evidence for familial resemblance (model 4). At least 1 of these effects is needed. The AIC suggests that the best model is for a multifactorial-only effect (model 5). As given in Table 5, 27% of the variance was due to a multifactorial effect, and no major effect was found.

TABLE 3. Segregation Analysis Log-Likelihoods for Baseline Apo A-1 and Baseline Apo B-100

		Age*				Age+BMI			
Model	*df*	−2 ln L	χ^2	*P*	AIC	−2 ln L	χ^2	*P*	AIC
Baseline apo A-1									
1. General mendelian	0	873.94	...	...	887.94	879.20	...	...	893.20
2. No multifactorial (H=Z=0)	2	898.79	24.85	<0.001†	908.79	903.14	23.94	<0.001†	913.14
3. No major effect (d=t=q=0)	3	886.83	12.89	<0.005†	894.83	891.49	12.29	0.006†	899.79
4. No familial (d=t=q=H=Z=0)	5	964.57	90.63	<0.001†	968.57	964.57	85.37	<0.001†	968.57
5. No generation difference (Z=1)	1	873.96	0.02	0.888	885.96	879.63	0.43	0.512	891.63
6. Recessive (d=0)	1	874.75	0.81	0.368	886.75	881.10	1.90	0.168	893.10
7. Additive (d=0.5)	1	881.54	7.60	0.006†	893.54	885.89	6.69	0.010†	897.89
8. Dominant (d=1)	1	881.55	7.61	0.006†	893.55	885.96	6.76	0.009†	897.96
9. Models 5+6 (d=0, Z=1)	2	874.75	0.81	0.667	884.75	881.32	2.12	0.346	891.32
10. Nontransmitted (d=0, Z=1)	2	874.32	0.03	0.985	886.32	880.57	0.05	0.975	892.57
11. Model 10 plus π's=1−q	3	874.38	0.09	0.993	884.38‡	880.60	0.08	0.994	890.60‡
12. Most general (d=0, Z=1)	3	874.29	0.46	0.928	890.29	880.52	0.80	0.849	896.52
Baseline apo B-100									
1. General mendelian	0	830.04	...	...	844.04	827.22	...	...	841.22
2. No multifactorial (H=Z=0)	2	857.93	27.89	<0.001†	867.93	854.39	27.17	<0.001†	864.39
3. No major effect (d=t=q=0)	3	863.61	33.57	<0.001†	871.61	854.88	27.66	<0.001†	862.88
4. No familial (d=t=q=H=Z=0)	5	937.47	107.43	<0.001†	941.47	932.18	104.96	<0.001†	936.18
5. No generation difference (Z=1)	1	830.26	0.22	0.639	842.26	827.27	0.05	0.823	839.27
6. Recessive (d=0)	1	830.06	0.02	0.888	842.06	827.23	0.01	0.920	938.23
7. Additive (d=0.5)	1	855.28	25.24	<0.001†	867.28	850.86	23.64	<0.001†	862.86
8. Dominant (d=1)	1	853.61	23.57	<0.001†	865.61	850.81	23.59	<0.001†	862.81
9. Models 5+6 (d=0, Z=1)	2	830.27	0.23	0.891	840.27‡	827.27	0.05	0.975	837.27‡
10. Nontransmitted (d=0, Z=1)	2	837.32	8.12	0.017†	849.32	833.64	7.13	0.028†	845.64
11. Model 10 plus π's =1−q	3	837.50	8.30	0.040†	847.50	833.86	7.47	0.058	843.86
12. Most general (d=0, Z=1)	3	829.20	1.07	0.784	845.20	826.39	0.88	0.830	842.39

*Adjusted for age only.
†Significant ($P<0.05$).
‡The most parsimonious models.

Discussion

The primary purpose of this investigation was to understand whether the segregation patterns of baseline apo A-1 and B-100 in these sedentary white families, as well as their responses to a 20-week endurance exercise training program, supported a major-gene hypothesis. The present investigation represents the first study to assess the major-locus hypothesis for apo A-1 and B-100 changes in response to exercise training.

In this study, correlation coefficients for baseline apo A-1 and B-100 were ≈0.35 ($P<0.05$) in parent-offspring and siblings, in contrast to ≈0.10 ($P>0.05$) in spouses, which suggested the presence of familiality. They were somewhat lower for the response to training measures, which were ≈0.15 to 0.30 in parent-offspring and siblings.

Varied results from previous segregation studies of apo A-1 have been reported within the last 2 decades. Studies in a large pedigree with excess coronary heart disease[18] and in a large pedigree ascertained through cases of early myocardial infarction[23] found no evidence of a major gene and even no genetic transmission of apo A-1, whereas findings from other studies supported the hypothesis of a major[9,13,14,22] dominant[10,11,21] or recessive[12] gene, which accounted for 27% to 58% of the phenotypic variance, with an additional component resulting from a polygenic or multifactorial effect (up to 65% variance). Among these studies, Moll et al[9] used 283 pedigrees that were randomly selected from the population with respect to disease status and risk factors for coronary artery disease, identified heterogeneous etiologies, and found evidence of a polygenic effect versus a single locus effect from 2 subsets (126 pedigrees supporting nontransmitted environmental factor versus 157 pedigrees supporting genetic etiology) of their data, respectively. Moreover, in other studies, a major-locus hypothesis was not conclusive, unless it was paired with HDL-C[10] or a second major locus was involved.[22] Recently, Livshits et al[15] found a major locus influencing plasma apo A-1 levels also influencing plasma HDL_3-C concentrations in a random sample of 228 Israeli pedigrees; however, Juo et al[16] used 137 selected families ascertained through probands undergoing elective diagnostic coronary angiography at the Johns Hopkins Hospital and reported no common major locus for these phenotypes. In

TABLE 4. Segregation Analysis Log-Likelihoods for Age-Baseline–Adjusted Apo A-1 and B-100 Changes in Response to Exercise Training

		A-1				B-100			
Model	*df*	−2 ln L	χ^2	*P*	AIC	−2 ln L	χ^2	*P*	AIC
1. General mendelian	0	823.59	...	...	837.59	857.72	...	...	871.72
2. No multifactorial	2	847.99	24.40	<0.001*	857.99	859.61	1.89	0.389	869.61
3. No major effect	3	841.63	18.04	<0.001*	849.63	859.54	1.82	0.611	867.54
4. No familial effect	5	874.14	50.55	<0.001*	878.14	873.02	15.30	0.010*	877.02
5. No generation difference	1	830.30	6.71	0.010*	842.30				
(d=t=q=0, Z=1)	4					859.63	1.91	0.752	865.63§
6. Recessive	1	823.59	0.00	1.000	835.59†				
7. Additive	1	840.84	17.25	<0.001*	852.84				
8. Dominant	1	840.94	17.35	<0.001*	852.94				
9. Model 6	1	823.59	0.00	1.000	835.59				
10. Recessive (H=Z=0)	3					861.27	3.55	0.314	869.27
11. Nontransmitted (d=0)	3	827.87	4.44	0.218	839.87	870.67	9.19	0.027*	878.67
12. Most general (d=0)	3	823.43	0.16	0.984	841.43	861.48	0.21	0.976	875.48
13. Additive (H=Z=0)	3					860.36	2.64	0.451	868.36
14. Nontransmitted (d=0.5)	3					870.74	11.58	0.009*	878.74
15. Most general (d=0.5)	3					859.16	1.20	0.753	873.16
16. Dominant (H=Z=0)	3					862.05	4.33	0.228	870.05
17. Nontransmitted (d=1)	3					870.67	12.64	0.005*	878.67
18. Most general (d=1)	3					858.03	4.02	0.259	872.03

*Significant ($P<0.05$).
†The most parsimonious models.

addition, 2 recent studies used the GAW8 Berkeley data set,[21] and the 137 selected families from the Johns Hopkins Hospital[22] have provided evidence of 2 major loci affecting apo A-1 levels.

Findings from the present study for age-adjusted and age-BMI–adjusted baseline apo A-1 provided no evidence for a major locus controlling baseline apo A-1 levels, although there was a noteworthy pattern of a major effect with ambiguous transmission from parents to offspring. The major effect accounted for 8% to 9% of the variance and was accompanied by a substantial multifactorial heritability (51% to 56%). These results are similar to the findings from the first data subset (ie, 126 population-based pedigrees supporting the nontransmitted environmental factor) by Moll et al[9] and are quite comparable to findings from a single locus model by Juo et al.[22] Because BMI adjustments of the data did not significantly affect the results, a pleiotropic effect (ie, a single common gene underlying both baseline apo A-1 and BMI) may not be operating. The non-Mendelian nature of the major effect could be due to environmental factors, or it may

TABLE 5. Most Parsimonious Segregation Models for Apo A-1 and B-100 (d=0)

Variables	V	u	t	q	H	Z
Baseline*						
Apo A-1§	1.11±0.08	0.04±0.10	2.92±0.71	0.11±0.04	0.56±0.06	[1]
Apo B-100‖	1.07±0.23	0.14±0.25	1.78±0.20	0.50±0.12	0.25±0.21	[1]
Baseline†						
Apo A-1§	1.04±0.07	0.04±0.09	3.10±0.60	0.10±0.03	0.51±0.05	[1]
Apo B-100‖	1.02±0.05	0.10±0.08	1.75±0.11	0.46±0.03	0.29±0.06	[1]
Response‡						
Apo A-1	1.12±0.10	0.05±0.07	3.68±0.40	0.11±0.03	0.58±0.09	0.21±0.09
Apo B-100	1.09±0.07	−0.01±0.06	[0]	[0]	0.27±0.06	[1]

*Age-adjusted baseline apo A-1 and B-100.
†Age-BMI–adjusted baseline apo A-1 and B-100.
‡Age-baseline–adjusted apo A-1 and B-100 changes in response to exercise training.
§Mendelian transmission ($\pi_1=1$, $\pi_2=0.5$, $\pi_3=0$).
‖Non-Mendelian transmission of major effect or environmental ($\pi_1=\pi_2=\pi_3=1-q=0.89\approx0.90$).
Numbers in brackets were fixed to 1 or 0.

be the result of gene-environment interactions that were not modeled. In fact, a second major gene affecting apo A-1 levels, as suggested by a previous investigation,[22] was not modeled in the present study and offers 1 possible explanation for the non-Mendelian pattern found here. Other environmental factors potentially affecting levels of apo A-1 include smoking, alcohol consumption, use of exogenous sex hormones, and possible gene-environment interactions that were not considered in this study. In addition, results for the age-baseline–adjusted apo A-1 change in response to training provided no clear evidence to infer a major locus. The major effect, whose transmission from parents to offspring was ambiguous (genetic in nature or environmental in origin), accounted for 15% of the adjusted variance. An additional 21% and 58% of the phenotypic variance was due to a multifactorial component in parents and offspring, respectively. Again, in addition to potential factors discussed above, limited sample size might also be an explanation that prevented the second distribution component from being detectable in this study.

For apo B-100, studies in a large Amish pedigree ascertained through a 13-year-old boy who died suddenly of advanced coronary atherosclerosis[24] and in a sample of 102 families volunteered for a free health checkup in the Preventive Center of Vandoeuvre-lès-Nancy of France[25] found no evidence of a major-gene effect, but a multifactorial component was significant. In contrast, 6 studies reported positive findings of a major gene influencing apo B-100 levels.[2,12,17–20] Among the findings from these 6 investigations, studies in a large pedigree ascertained through cases of early myocardial infarction[17] in a large pedigree with excess coronary heart disease[18] in 83 pedigrees ascertained though probands identified by the Lipid Clinic of the Clinical Research Institute of Montreal[19] and in 40 Dutch families ascertained through familial combined hyperlipidemia probands[20] suggested a codominant major gene that accounted for 35% to 66% of the phenotypic variance. An additional 8% of variance was due to a multifactorial component.[19] A study in a random sample of 367 population-based Israeli pedigrees suggested a recessive major gene that accounted for 32% of the variance, with a polygenic effect accounting for an additional 26% of the variance.[12] The other study, in 263 families ascertained through children with a family history of coronary artery disease at the Children's Hospital of Philadelphia, suggested that the mode of inheritance was unresolved between codominant and recessive, with a major locus accounting for 79% of the total variance.[2]

Results from the present study for age-adjusted and age-BMI–adjusted baseline apo B-100 supported the hypothesis of a major recessive locus regulating baseline apo B-100 levels in these sedentary families. The putative locus accounted for 50% to 56% of the phenotypic variance, and the multifactorial component accounted for an additional 25% to 29% of the variance. Our results did not support a codominant hypothesis predominant in previous reports but were consistent with findings by Livshits et al.[12] The recessive major locus accounted for a higher percentage of the phenotypic variance in the present study (50% to 56% in the present study versus 32% by Livshits et al[12]), and there was a similar effect due to a multifactorial component (25% to 29% in the present study versus 26%). However, results for the age-baseline–adjusted apo B-100 change in response to exercise training suggested a multifactorial component and failed to demonstrate a major-gene effect. Thus, the major gene may be specific to baseline levels, and it is not clear whether the same gene also regulates response to training. The percentage accounted for by the multifactorial component for the apo B-100 change in response to exercise training was 27%. Again, there are no available reports of familial basis of apo B-100 change in response to exercise training.

In summary, evidence of a major gene with a recessive mode of inheritance was found for baseline apo B-100 that accounted for 56% of the phenotypic variance in a sample of 99 white families of the HERITAGE Family Study. In addition, a major effect with a multifactorial component for baseline apo A-1 and its response to training and a multifactorial effect for apo B-100 response to training were detected. These results are generally in accordance with findings from previous studies, suggesting that the factors underlying the phenotype levels in these sedentary families are similar to those in the general population. In particular, this is the first study that documented familial basis of apo A-1 and B-100 changes in response to endurance exercise training.

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