Complex Segregation Analysis of Blood Pressure and Heart Rate Measured Before and After a 20-Week Endurance Exercise Training Program: The HERITAGE Family Study

Ping An, Treva Rice, Louis Pérusse, Ingrid B. Borecki, Jacques Gagnon, Arthur S. Leon, James S. Skinner, Jack H. Wilmore, Claude Bouchard, and D. C. Rao

Complex segregation analysis of baseline resting blood pressure (BP) and heart rate (HR) and their responses to training (post-training minus baseline) were performed in a sample of 482 individuals from 99 white families who participated in the HERITAGE Family Study. Resting BP and HR were measured at baseline and after a 20-week training program. Baseline resting BP and HR were age-adjusted and age-BMI–adjusted, and the responses to training were age-adjusted and age-baseline–adjusted, within four gender-by-generation groups. This study also analyzed the responses to training in two subsets of families: (1) the so-called "high" subsample, 45 families (216 individuals) with at least one member whose baseline resting BP is in the high end of the normal BP range (the upper 95th percentile: systolic BP [SBP] ≥ 135 or diastolic BP [DBP] ≥ 80 mm Hg); and (2) the so-called "nonhigh" subsample, the 54 remaining families (266 individuals). Baseline resting SBP was influenced by a multifactorial component (23%), which was independent of body mass index (BMI). Baseline resting DBP was influenced by a putative recessive locus, which accounted for 31% of the variance. In addition to the major gene effect, which may impact BMI as well, baseline resting DBP was also influenced by a multifactorial component (29%). Baseline resting HR was influenced by a putative dominant locus independent of BMI, which accounted for 31% of the variance. For the responses to training, no familiality was found in the whole sample or in the nonhigh subsample. However, in the high subsample, resting SBP response to training was influenced by a putative recessive locus, which accounted for 44% of the variance. No familiality was found for resting DBP response to training. Resting HR response to training was influenced by a major effect (accounting for 35% of the variance), with an ambiguous transmission from parents to offspring. Am J Hypertens 2000;13:488–497

KEY WORDS: Heritability, multifactorial effect, major effect, major gene effect.

Elevated resting blood pressure (BP) and heart rate (HR) are associated with cardiovascular diseases (CVD),[1–3] and there is considerable interest in understanding the roles of genetic and familial environmental contributions to the variation in these risk factors. Heritability estimates for baseline resting systolic BP (SBP), diastolic BP (DBP), and HR in the HERITAGE Family Study are 54%, 41%, and 32%, respectively,[4] and reach about 30% to 40% for resting BP and 33% for resting HR in

0895-7061/00/$20.00
PII S0895-7061(99)00275-7

other family studies.[5–10] Major gene effects regulating resting SBP[8,11,12] and DBP[13] were previously evidenced in a few family studies. Findings from several other family studies also suggested that variations in both resting SBP[13–15] and DBP[12,14] were largely multifactorial, whereas Weissbecker[16] found no evidence of familiality for resting DBP. Whether resting HR is regulated by a major gene effect has not been reported in the literature.

Regular exercise is known to reduce blood pressure in individuals.[17–20] According to a recent review, exercise training leads to a reduction of 3/3 mm Hg (SBP/DBP) in normotensive individuals, 3/7 mm Hg in borderline hypertensive persons, and 10/8 mm Hg in hypertensive individuals.[20] The resting HR response to exercise training was examined in the HERITAGE Family Study. There was a small but significant decrease of resting HR (2.6 beats/min) in response to the 20-week endurance exercise training program.[21] Heritability estimates for HR response to training reached 26% in the whole sample, 38% in the so-called "high" subsample (a total of 45 families 216 individuals with at least one family member whose baseline resting BP is in the high end of the normal BP range; ie, the upper 95th percentile: SBP $\geq$ 135 mm Hg or DBP $\geq$ 80 mm Hg), and 0% in the so-called "nonhigh" subsample (a total of 54 remaining families, ie, 266 individuals with no family member whose baseline resting BP is in the upper 95th percentile). Little or no additive (multifactorial or polygenic) genetic determinants were revealed for resting BP responses to training in a previous familial aggregation analysis in this study.[22] It should be noted here that a heritability study (familial correlation) does not necessarily pick up a major gene effect unless it is additive mode of inheritance. Although it has been reported that the resting DBP acute response to arithmetic and bicycle tasks was influenced by a major gene effect,[23] the genetic determinants of resting BP and HR chronic responses to regular exercise training have not been addressed. The current investigation represents the first study assessing a major gene hypothesis for resting BP and HR in response to endurance training.

Complex segregation analysis, based on tests of hypotheses regarding the fit of Mendelian segregation ratios for traits in families, is performed in the current study so that a major gene hypothesis for baseline resting BP and HR and in response to endurance training data could be examined. This study is unique in that resting BP and HR were assessed before (in a sedentary state) and after completing a 20-week standardized endurance exercise training program in intact families.

MATERIALS AND 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 regular exercise to changes in cardiovascular disease and diabetes risk factors. (See Bouchard et al for more details concerning the HERITAGE Family Study sample and protocol.[24])

A total of 482 individuals from 99 white families (including one three-generation family that was then divided into two nuclear families), 233 men, 249 women, were analyzed in this study. Table 1a gives the sample sizes within each of four gender-by-generation groups (fathers, mothers, sons, and daughters) for baseline resting BP and HR and the changes in response to training. Resting BP and HR responses to training were further analyzed in the high and nonhigh subsamples. Detailed sample descriptive information for the high and nonhigh subsamples were also presented (see Table 1b).[22] Black families also were recruited and tested in this study, but their results are not reported here. The study protocol was approved by the Institutional Review Board at each participating clinical center. Recruitment of families was based on extensive media publicity and advertisements.

The following entry criteria were applied to screen subjects for participation. First, individuals had to be between the ages of 17 and 65 years (17–40 years for children and $\leq$ 65 years for parents). Second, all participants were required to be sedentary at baseline. Third, the body mass index (BMI, weight over height squared [kg/m^2]) less than 40 kg/m^2 was required unless a physician certified that the subject was able to meet the demands of the exercise tests and exercise

Received April 26, 1999. Accepted December 6, 1999.

From the Division of Biostatistics, St. Louis, Missouri, and Department of Genetics and Psychiatry, Washington University School of Medicine, St. Louis, Missouri; Division of Kinesiology, Physical Activity Sciences Laboratory; Laboratory of Molecular Endocrinology, CHUL Research Center, Laval University, Québec, Canada; School of Kinesiology and Leisure Studies, University of Minnesota, Minneapolis, Minnesota; Department of Kinesiology, Indiana University, Bloomington, Indiana; Department of Health and Kinesiology, Texas A& M University, College Station, Texas; and Pennington Biomedical Research Center, Louisiana State University, Baton Rouge, Louisiana

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

Address correspondence and reprint requests to Ping An, MD, Division of Biostatistics, Campus Box 8067, Washington University School of Medicine, 660 South Euclid Avenue, St. Louis, MO 63110-1093; e-mail: anping@wubios.wustl.edu

TABLE 1A. MEANS AND SD FOR UNADJUSTED RESTING BP (mm Hg) AND HR (bpm)

Variables	No.	Means	SD	No.	Means	SD
		Fathers			Mothers	
Age (years)	93	53.3*	5.4	91	52.1*	5.1
BMI (kg/m^2)	93	28.3*	4.5	91	27.5*	4.8
Baseline SBP	93	121.3*	12.8	91	116.7*,†	11.9
Baseline DBP	93	72.3*,†	8.4	91	67.5*,†	6.7
Baseline HR	93	63.7*,†	7.5	91	66.5*,†	8.9
SBP change in response to training	91	0.2	6.0	90	1.1	7.3
DBP change in response to training	92	−0.8	4.5	90	0.1	5.1
HR change in response to training	93	−3.4	5.9	90	−2.5	6.2
		Sons			Daughters	
Age (years)	140	25.4*	6.1	158	25.5*	6.4
BMI (kg/m^2)	139	25.7*,†	4.9	158	23.6*,†	4.4
Baseline SBP	140	119.1†	8.6	158	110.5*,†	7.9
Baseline DBP	140	65.4*,†	7.8	158	61.9*,†	6.3
Baseline HR	140	61.2*,†	8.5	157	67.1†	8.2
SBP change in response to training	140	−0.7	5.6	158	0.2	5.7
DBP change in response to training	137	0.3	5.1	158	0.4	5.7
HR change in response to training	140	−3.6	6.3	157	−2.4	6.7

* *Significant ($P < .05$) mean differences for father-son or mother-daughter (within-gender) comparisons;* † *significant ($P < .05$) mean differences for father-mother or son-daughter (within-generation) comparisons.*

training program. Fourth, resting BP levels were ≤ 159 mm Hg for SBP and ≤ 99 mm Hg for DBP in the absence of medications. Finally, participants were required to be in good general physical health to complete the 20-week endurance training program. Further details can be found in Bouchard et al.[24]

Exercise Training Program The training protocol is described in Bouchard et al.[24] Briefly, each individual trained on a cycle ergometer in the laboratory under supervision three times a week for 20 weeks. Participants exercised for 30 min at the heart rate associated with 55% of their baseline maximal oxygen intake during the first 2 weeks. The intensity or duration of exercise was adjusted every 2 weeks thereafter, so that participants were working for 50 min at the heart rate associated with 75% of their baseline maximum oxygen intake during the last 6 weeks of training. The power output was adjusted automatically by a computer so that the desired training heart rate was maintained. 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, a battery of measurements were administered to each family member. Multiple resting BP and HR measurements were made on two separate days, both at baseline and post-training. Resting BP and HR were obtained before 11:00 AM with participants in a 12-h fasted state and with no caffeine-containing beverages or tobacco products for at least 2 h before assessment. Measurements were performed in a quiet room after participants had rested for at least 5 min in a reclining chair with legs elevated and the chair back reclined at about 45°. BP was determined using a properly fitted cuff connected to a Colin STBP-780 automated unit (San Antonio, TX), and HR also was monitored during the BP measurement by ECG. At least four BP and HR readings were taken after the initial 5-min rest period, with 2-min intervals between readings. The first measurement, although recorded on the paper form, was discarded. The procedure was conducted on two separate days for each of baseline and post-training, and the data used here represent the average of up to six measurements (three measurements on each of 2 days).[21] Resting BP and HR changes in response to training were computed as (post-training minus baseline).

Data Adjustments Baseline resting BP and HR were adjusted for the effects of age within each of the four gender-by-generation groups (fathers, mothers, sons, daughters) using a stepwise multiple regression procedure. Briefly, a given measure 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 is independent of age, gender, and generation effects. A similar set of stepwise regressions (by gender and generation groups) also was

TABLE 1B. MEANS AND SD FOR RESTING BP AND HR IN THE HIGH AND NONHIGH SUBSAMPLES

Variables	No.	Means	SD	No.	Means	SD
		Fathers			Mothers	
The high subsample						
Age (years)	42	55.08	5.48	39	53.63	5.40
BMI (kg/m^2)	42	28.89	4.82	39	28.47	5.51
Resting SBP (mm Hg)						
Baseline	42	129.30	12.34	39	122.30*	12.08
Response to training	42	−0.42	7.92	39	1.20	8.11
Resting DBP (mm Hg)						
Baseline	42	76.66	8.72	39	70.52*	6.25
Response to training	42	−.03	5.30	39	0.43	5.78
Resting HR (beats/min)						
Baseline	42	64.34	7.68	39	66.78	8.03
Response to training	42	−3.07	5.27	39	−1.51	5.75
		Sons			Daughters	
Age (years)	65	26.79†	7.02	70	27.81†	6.45
BMI (kg/m^2)	65	26.53†	5.90	70	23.65*†	4.26
Resting SBP (mm Hg)						
Baseline	65	121.37†	8.60	70	112.38*†	7.46
Response to training	65	−1.24	5.43	70	1.40*	5.40
Resting DBP (mm Hg)						
Baseline	65	67.31†	8.84	70	62.82*†	6.18
Response to training	65	0.63	5.12	70	0.88	6.01
Resting HR (beats/min)						
Baseline	65	62.50	8.44	70	65.10*	6.98
Response to training	65	−2.53	5.77	70	−0.63*	7.23
		Fathers			Mothers	
The nonhigh subsample						
Age (years)	50	52.08‡	4.63	51	50.87‡	4.52
BMI (kg/m^2)	50	27.87	4.27	51	26.92‡	4.05
Resting SBP (mm Hg)						
Baseline	50	114.68‡	9.00	51	112.43‡	10.13
Response to training	50	0.83	6.11	51	0.97	6.73
Resting DBP (mm Hg)						
Baseline	50	68.75‡	6.27	51	65.02*‡	6.08
Response to training	50	−0.77	4.36	51	−0.12	4.47
Resting HR (beats/min)						
Baseline	50	63.00	7.39	51	66.60*	9.37
Response to training	50	−4.09	6.06	51	−3.27	6.49
		Sons			Daughters	
Age (years)	76	24.36†‡	5.34	89	23.73†‡	5.68
BMI (kg/m^2)	76	25.03†‡	3.78	89	23.49*†	4.56
Resting SBP (mm Hg)						
Baseline	76	117.04†‡	8.17	89	108.83*†‡	7.81
Response to training	76	−0.10‡	5.72	89	−0.77†‡	5.78
Resting DBP (mm Hg)						
Baseline	76	63.69†‡	6.36	89	60.93*†‡	6.26
Response to training	76	0.05	6.08	89	0.01	5.32
Resting HR (beats/min)						
Baseline	76	60.04†‡	8.62	89	69.06*†‡	9.61
Response to training	76	−4.30‡	6.85	89	−3.47‡	6.56

** Significant (P < .05) gender (within-generation) group differences; † significant (P < .05) generation (within-gender) group differences; ‡ significant (P < .05) subsample differences (the high v the nonhigh).*

BMI = body mass index; SBP = systolic blood pressure; DBP = diastolic blood pressure.

performed by regressing baseline resting BP and HR on a polynomial in age (age, age^2, and age^3) and BMI (linear). Resting BP and HR responses to training were adjusted for the effects of polynomial in age and the baseline (linear) within each of the four gender-by-generation groups. Each of the adjusted phenotypes used in the genetic analysis was finally standardized to a mean of zero and a SD of one.

Statistical Analysis Group differences were judged by a comparison of standard errors (SE). Segregation analysis, as implemented in the computer program POINTER, was performed using the unified mixed model.[25–27] 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 two alleles (A and a). The a allele is associated with higher trait values. Included in the model are seven parameters: the overall variance (V); the overall mean (u); the frequency of the a allele (q); the displacement between the two homozygous means (t); the relative position of the heterozygous mean or dominance (d); and the multifactorial heritability in offspring (H) and in parents (HZ). The transmission pattern of the major gene from parents to offspring is characterized by three 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 $\tau_3 = 0$. When the three τ values are equal, no transmission of the major effect is obtained. The following three conditions are usually required to infer a major gene[25]: (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 environmental (no transmission) hypothesis (equal τ's).

Competing (nested) models are tested for significance using the likelihood ratio test (LRT), which is the difference in minus twice the log-likelihood (−2 ln L) obtained under the two models. The likelihood ratio is approximately distributed as a χ^2, with the degrees of freedom being equal to the difference in the number of parameters estimated in the two models. In addition to the LRT, Akaike's Information Criterion (AIC), which is −2 ln L plus twice the number of estimated parameters, was used to compare nonnested models. The best model is the one with the smallest AIC.[28]

RESULTS

In this study, coefficients of variation for repeated measures were 4%, 6%, and 8% for resting SBP, DBP, and HR respectively, and intraclass correlations were 0.84, 0.79, and 0.73 for resting SBP, DBP, and HR, respectively.[29]

Means and standard deviation (SD) of the unadjusted baseline resting BP and HR and the changes in response to training are given in Table 1a. In general, baseline BP levels were significantly higher in men than in women, and significantly higher in parents than in offspring, whereas baseline HR was significantly higher in women than in men. There were no group differences for BP and HR changes in response to training. Although the overall means of BP changes in response to training were close to zero, HR change in response to training in each of the four groups generally evidenced a 2 to 4 beats/min reduction. Additionally, sample sizes, unadjusted means, SD, and group comparisons of resting BP and HR measures in the high (45 families) and nonhigh (remaining 54 families) subsamples are given in Table 1b.[22] The high subset of families was characterized by significantly higher age (in parents and offspring) and baseline resting BP (in parents) than the nonhigh subsample. Resting SBP and HR changes in response to training (in offspring) in the high subsample were also significantly different from those in the nonhigh subsample.

Significant age terms and percentages of variance accounted for in each of the gender-by-generation groups were given in the following. For baseline resting BP, age^3 accounted for 18.7% of the mean SBP variation in mothers, and age accounted for 11.7% and 5.5% of the mean DBP variation for sons and daughters, respectively. For baseline resting HR, age accounted for 3.4% of the variance for sons. Baseline resting BP and HR were separately adjusted for the effects of age and BMI. For SBP, BMI accounted for 8.0% of the variance in fathers, and age^3 accounted for 18.7% of the mean variation in mothers. For DBP, BMI accounted for 14.3% of the variance in fathers, age accounted for 11.6% of the variance in sons, and BMI and age^3 accounted for 10.1% of the variance in daughters. For HR, BMI accounted for 8.3% of the variance in sons. No other age or BMI terms were significant in any other groups, and no age or BMI effects in the variance (heteroscedasticity) were detected.

Resting BP and HR responses to training were adjusted for the effects of age and the effects of age and baseline levels. In general, age was not a significant predictor of the changes in response to training except for HR in fathers (age and age^2 accounting for 9.5% of the mean variation) and sons (age^3 accounting for 4.3%). Baseline levels were, however, significant predictors of BP and HR changes in response to training in each of the four groups, accounting for 8.0% to 35.7% of the overall variance.

Segregation analysis results are summarized in Tables 2 and 3, and the parameter estimates under the most parsimonious models are given in Table 4. For

TABLE 2. SEGREGATION ANALYSIS OF BASELINE RESTING BP AND HR

Hypotheses	d.f.	−2 ln L	χ^2	P	AIC
Age-BMI-adjusted SBP					
1. General	0	810.75			824.75
2. No multifactorial (H=Z=0)	2	818.52	7.77	.02*	828.52
3. No major effect (d=t=q=0)	3	813.50	2.75	.43	821.50#
4. No familial effect (H=Z=d=t=q=0)	5	863.96	53.21	<.01*	867.96
5. No generation diff. (d=t=q=0, Z=1)	4	819.27	8.52	.07	825.27
Age-adjusted DBP					
1. General	0	819.59			833.59
2. No multifactorial (H=Z=0)	2	819.75	0.16	.92	829.75
3. No major effect (d=t=q=0)	3	824.40	4.81	.19	832.40
4. No familial effect (H=Z=d=t=q=0)	5	843.68	24.09	<.01*	847.68
5. No generation diff. (d=t=q=0, Z=1)	4	824.57	4.98	.29	830.57
6. Recessive (H=Z=0, d=0)	3	819.75	0.16	.98	827.75#
7. Additive (H=Z=0, d=0.5)	3	823.53	3.94	.27	831.53
8. Dominant (H=Z=0, d=1)	3	826.47	6.88	.08	834.47
9. Free τ's (H=Z=0)	3	823.69	3.94	.27	839.69
10. Equal τ's (H=Z=0, $\tau_1=\tau_2=\tau_3$=1-q)	3	843.57	19.88	<.01*	853.57
Age-BMI-adjusted DBP					
1. General	0	822.38			836.38
2. No multifactorial (H=Z=0)	2	823.43	1.05	.59	833.43
3. No major effect (d=t=q=0)	3	824.60	2.22	.53	832.60
4. No familial effect (H=Z=d=t=q=0)	5	843.68	21.30	<.01*	847.68
5. No generation diff. (d=t=q=0, Z=1)	4	824.63	2.25	.69	830.63
6. Recessive (H=Z=0, d=0)	3	823.43	1.05	.79	831.43
7. Additive (H=Z=0, d=0.5)	3	824.60	2.22	.53	832.60
8. Dominant (H=Z=0, d=1)	3	827.75	5.37	.15	835.75
9. Free τ's (H=Z=0)	3	825.21	1.78	.62	841.21
10. Equal τ's (H=Z=0, $\tau_1=\tau_2=\tau_3$=1-q)	3	842.96	19.57	<.01*	852.96
Age-BMI-adjusted HR					
1. General	0	819.99			833.99
2. No multifactorial (H=Z=0)	2	819.99	0.00	1.00	829.99
3. No major effect (d=t=q=0)	3	823.23	3.24	.36	831.23
4. No familial effect (H=Z=d=t=q=0)	5	839.83	19.84	<.01*	843.83
5. No generation diff. (d=t=q=0, Z=1)	4	823.23	3.24	.52	829.23
6. Recessive (H=Z=0, d=0)	3	823.20	3.21	.36	831.20
7. Additive (H=Z=0, d=0.5)	3	821.99	2.00	.57	829.99
8. Dominant (H=Z=0, d=1)	3	819.99	0.00	1.00	827.99#
9. Free τ's (H=Z=0)	3	815.16	4.83	.18	831.16
10. Equal τ's (H=Z=0, $\tau_1=\tau_2=\tau_3$=1-q)	3	838.05	22.89	<.01*	848.05

* *Statistical significance ($P < .05$); # most parsimonious models.*

baseline resting SBP (Table 2), the results for age-adjusted and age-BMI–adjusted data were similar. Therefore, only the results for the age-BMI–adjusted phenotype were given. A multifactorial effect influenced SBP levels, and the test for no generation difference in the multifactorial factor was borderline (model 5: $\chi^2_4 = 8.52$, $P = .07$). According to the AIC, the hypothesis of no major effect (model 3) best fit the data. The heritability in parents (HZ) was 23% (see footnote of Table 4).

For age-adjusted baseline resting DBP (Table 2), the tests of the transmission probabilities were performed with d unrestricted. Mendelian τ's were not rejected (model 2 − model 9: $\chi^2_3 = 3.94$, $P = 0.27$), whereas the constrained equal τ's hypothesis was rejected (model 10 − model 9: $\chi^2_3 = 19.88$, $P < .01$). According to the AIC, the recessive Mendelian hypothesis (model 6) was the most parsimonious model. The putative recessive locus accounted for 31% of the variance (see Table 4), and an estimated 69% (q^2) of the sample was homozygous recessive, leading to higher values of DBP. For age-BMI–adjusted baseline resting DBP, whereas either a major gene only model or a multifactorial component only model fit the data, the AIC suggested that the multifactorial effect with no generation differ-

TABLE 3. SEGREGATION ANALYSIS OF RESTING BP AND HR RESPONSES TO TRAINING IN THE HIGH SUBSAMPLE*

Hypotheses	d.f.	−2 ln L	χ^2	P	AIC
Age-adjusted SBP†					
1. General	0	373.47			387.47
2. No multifactorial (H=Z=0)	2	373.74	0.27	.87	383.74
3. No major effect (d=t=q=0)	3	381.47	8.00	.046‡	389.47
4. No familial effect (H=Z=d=t=q=0)	5	388.15	14.68	.01‡	392.15
5. Recessive (H=Z=0, d=0)	3	374.34	0.87	.83	382.34#
6. Additive (H=Z=0, d=0.5)	3	381.67	8.20	.04‡	389.67
7. Dominant (H=Z=0, d=1)	3	380.68	7.21	.07	388.68
8. Free τ's (H=Z=0)	3	366.62	7.12	.07	382.62
9. Equal τ's (H=Z=0, $\tau_1=\tau_2=\tau_3$=1-q)	3	377.75	11.13	.01‡	385.75
Age-baseline-adjusted HR§					
1. General	0	382.99			396.99
2. No multifactorial (H=Z=0)	2	384.53	1.54	.46	394.53#
3. No major effect (d=t=q=0)	3	391.55	8.56	.04‡	399.55
4. No familial effect (H=Z=d=t=q=0)	5	397.93	14.94	.01‡	401.93
5. Recessive (H=Z=0, d=0)	3	388.11	5.12	.16	396.11
6. Additive (H=Z=0, d=0.5)	3	388.58	5.59	.13	396.58
7. Dominant (H=Z=0, d=1)	3	389.81	6.82	.08	397.81
8. Free τ's (H=Z=0)	3	383.18	1.35	.72	399.18
9. Equal τ's (H=Z=0, $\tau_1=\tau_2=\tau_3$=1-q)	3	388.79	5.61	.13	396.79

** For age-adjusted (χ^2_5 = 4.93, P = .42) or age-baseline-adjusted (χ^2_5 = 0.94, P = .97) DBP response to training, the test for no familial effect (model 4) was not rejected; † For age-baseline-adjusted SBP response to training, the test for no familial effect (model 4) was not rejected (χ^2_5 = 6.68, P = .25); § For age-adjusted HR response to training, the test for no familial effect (model 4) was not rejected (χ^2_5 = 8.18, P = .15); ‡Statistical significance (p = 0.05); # Most parsimonious models.*

ence model was the most parsimonious. The multifactorial heritability (see Table 4) was 29%.

For baseline resting HR, results from age-adjusted and age-BMI–adjusted data were similar, and only the results for the age-BMI phenotype are given in Table 2. The major gene model with a dominant mode of inheritance was the most parsimonious. The putative locus accounted for 31% of the variance (Table 4). An estimated 41% ($1-q^2$) of the sample were homozygous dominant, leading to lower HR values.

For resting BP and HR responses to training, no evidence of familiality was found in the whole sample or in the nonhigh subsample. However, in the high subsample, there was some evidence of familial influences for SBP and HR (Table 3). For the age-adjusted SBP response to training, either of the recessive or dominant modes fit the data, and the tests on the transmission probabilities were performed with d unrestricted. The recessive Mendelian hypothesis (model 5) provided the most parsimonious fit. This putative recessive locus accounted for 44% of the variance (Table 4), and 19% (q^2) of these high normal families were

TABLE 4. PARSIMONIOUS SEGREGATION MODELS FOR RESTING BP AND HR

Variables	d	t	q	H	Z	%*	q^2
Baseline							
SBP	[0]#	[0]	[0]	0.70 ± 0.09†	0.33 ± 0.12	0	0
DBP‡	[0]	1.20 ± 0.09	0.83 ± 0.03	[0]	[0]	31	69
DBP§	[0]	[0]	[0]	0.29 ± 0.05	[1]	0	0
HR	[1]	1.13 ± 0.09	0.36 ± 0.05	[0]	[0]	31	13
Response¶							
SBP¶	[0]	1.73 ± 0.19	0.44 ± 0.06	[0]	[0]	44	19
HR‖	0.27 ± 0.06	3.09 ± 0.48	0.19 ± 0.05	[0]	[0]	35	4

** Percentages accounted for by the major effect; † Heritability in parents (HZ) = 0.70*0.33 = 0.23 (23%); ‡ Age-adjusted baseline DBP; § Age-BMI-adjusted baseline DBP; ¶ Age-adjusted SBP response to training in the high subsample; ‖ Age-baseline-adjusted HR response to training in the high subsample. # Numbers in brackets were fixed to 0 or 1.*

SBP = systolic blood pressure; DBP = diastolic blood pressure; HR = heart rate.

homozygous recessive. For age-baseline-adjusted SBP response to training, no evidence of familiality was found. Likewise, for DBP and age-adjusted HR responses to training, no evidence of familiality was found (see footnote to Table 3). For age-baseline-adjusted HR response to training, neither of the Mendelian τ's ($\chi^2_3 = 1.35$, $P = .72$) nor the constrained equal τ's hypotheses were rejected ($\chi^2_3 = 5.61$, $P = .13$), suggesting an ambiguity of transmission from parents to offspring. The hypothesis of no multifactorial effect best fit the data according to the AIC. The major effect, influencing HR response to training, accounted for 35% of the variance.

DISCUSSION

This paper examined a major gene hypothesis for resting BP and HR in sedentary white families at baseline and in response to a 20-week endurance exercise training program. As physical activity level was controlled for at baseline, it would be interesting to compare the findings from these physically inactive families at baseline with reports from other samples, which presumably included a mixture of active and inactive families.

In the present study, segregation analysis suggested that baseline resting SBP is solely influenced by a multifactorial effect with generation differences (heritabilities of 23% in parents and 70% in offspring). These estimates (if averaged) compare favorably with that (54%) in this study[4] and with those reported in other family studies (30–40%).[9] Adjustment of the data for the effect of BMI did not modify the result, suggesting the additive familial factors underlying baseline resting SBP levels may at least in part be independent of those underlying the BMI in these sedentary families. The lack of a major locus effect on baseline SBP in these sedentary, nonobese, normotensive families is in agreement with three previous family studies.[13–15] In contrast, evidence of a major gene effect on resting SBP levels was reported in three other family studies.[8,11,12] Carter and Kannel found a rare major gene for low SBP.[8] The major locus evidence was supported when genotype-dependent effects of age and gender were allowed[11] or when a bivariate segregation analysis with BMI was performed.[12]

Baseline resting DBP levels were under the influence of a putative recessive gene in this study. The major locus effect accounted for 31% of the phenotypic variance, and an estimated 69% of the sample may carry the homozygous aa genotype, which leads to higher levels of baseline resting DBP. However, when the data were adjusted for the effects of BMI, this major gene effect was removed, and only a multifactorial effect remained, accounting for 29% of the variance. Based on this pattern, we may speculate the presence of a possible pleiotropic effect influencing baseline resting DBP levels and BMI. Moreover, it is interesting to note that the multifactorial effect became detectable only after the effect of BMI was removed. An interpretation of this pattern is that in sedentary families, resting DBP is primarily influenced by a major locus with pleiotropic effects on the BMI, and after removal of this locus a residual multifactorial effect (which may be polygenic or common environmental in nature) is revealed. A previous HERITAGE Family Study report using familial aggregation methods yielded a heritability of 41% for baseline resting DBP,[4] and in other family studies the estimates were in the range of 30% to 40%.[9] Previous segregation studies of resting DBP yielded contrasting results. Although Rice et al did not find support for a major gene,[14] Cheng et al did find a putative recessive locus that increased in effect with age.[13] Schiecken et al found no genetic relation between DBP and body size using multivariate path analysis in twin pairs,[30] and no previous segregation analyses have come to our attention reporting a pleiotropic effect for DBP and BMI.

For resting HR at baseline, the current segregation analysis evidenced a Mendelian dominant gene with no additional influences due to a multifactorial component. The major gene effect accounted for 31% of the phenotypic variance. Adjustment of the data for the effects of BMI did not modify the result. Recently, An et al found evidence of familial aggregation (heritability of 32%) for baseline resting HR levels in this study.[4]

No familial effect was found for resting BP and HR in response to training in the whole sample or in the nonhigh subsample. Nevertheless, in the high subsample, there was a familial effect for resting SBP and HR in response to training. For age-adjusted resting SBP in response to training, a Mendelian recessive gene was detected, which accounted for 44% of the variance. This finding is supported by Hagberg et al, who recently studied 18 sedentary obese hypertensive older men, and reported that some apolipoprotein E (apoE), angiotensin-converting enzyme (ACE), and lipoprotein lipase (LPL) genotypes were in favor to influencing SBP response to endurance training.[31] Besides, it is interesting to note that no familiality was found after the response to training data were further adjusted for the effects of baseline resting SBP levels. This Mendelian recessive gene for the response to training appears to specifically regulate baseline resting SBP component. It is perplexing that this major gene was not detectable at baseline in the whole sample but emerged in the high subsample for its response to training. One explanation is that although the multifactorial effect is obviously predominant (54%, or 23% in parents and 70% in offspring) for baseline resting SBP in the whole sample, the major gene effect could have demonstrated relatively less stronger ge-

netic influence than that in the high subsample, mostly, high normal families.

Although no familial effect was found for resting DBP in response to training and for age-adjusted resting HR in response to training, a major effect with ambiguous transmission from parents to offspring was revealed for age-baseline–adjusted resting HR in response to training. The major effect for resting HR in response to training, independent of baseline resting HR levels, accounted for 35% of the phenotypic variance. The source of this effect may be familial environmental or genetic in origin. Resting DBP acute responses to arithmetic and bicycle tasks were reported to be under the influence of major genes, whereas no major effect was found for SBP acute responses to the two laboratory stressors.[23] In this study, the heritability of resting HR in response to training was 0% in the nonhigh subsample, but it reached 38% in the high subsample,[22] appearing to be compatible with the major effect found in the current study.

In conclusion, putative major loci were detected for baseline resting DBP and HR in 99 white families participated in the HERITAGE Family Study. More interestingly, evidence of a major gene effect was found for the first time influencing resting SBP in response to training in the high subset of 45 families. To identify these putative loci, marker data are currently being assayed in this study.

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