Evidence of Major Genes for Exercise Heart Rate and Blood Pressure at Baseline and in Response to 20 Weeks of Endurance Training: The HERITAGE Family Study

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Abstract

Major gene effects on exercise heart rate (HR) and blood pressure (BP) measured at 50 W and 80% maximal oxygen uptake ($\dot{V}O_2$max) were assessed in 99 White families in the HERITAGE Family Study. Exercise HR and BP were measured both before and after 20 weeks of endurance training. The baseline phenotypes were adjusted for the effects of age and BMI, whereas the training responses (post-training minus baseline) were adjusted for the effects of age, BMI and the corresponding baseline values, within four sex-by-generation groups. Baseline exercise HR at 50 W was under the influence of a major recessive gene and a multifactorial component, which accounted for 30% and 27% of the variance, respectively. The training response was found to be under the influence of a major dominant gene, which accounted for 27% of the variance. These significant major gene effects were independent of the effects of cigarette smoking, baseline $\dot{V}O_2$max, and the resting HR levels. No significant interactions were found between genotype and age, sex, or BMI. No major gene effect was found for exercise BP. Instead, we found the baseline exercise BP at 50 W and 80% $\dot{V}O_2$max and the training response at 50 W were solely influenced by multifactorial effects, which accounted for about 50%, 40% and 20% of the variance, respectively. No familial resemblance was found for training responses in exercise HR or BP at 80% $\dot{V}O_2$max. Segregation analysis also was carried out for exercise HR in Whites pooled with a small sample of Blacks in HERITAGE. Similar major effects were found, but the transmission from parents to offspring did not follow Mendelian expectations, suggesting sample heterogeneity. In conclusion, submaximal exercise HR at baseline and in response to endurance training was influenced by putative major genes, with no evidence of interactions with sex, age or BMI, in contrast to a multifactorial etiology for exercise BP.

Key words
Major gene effect · multifactorial effect · 50 W · 80% $\dot{V}O_2$max · Whites · Blacks

Introduction

Elevated resting heart rate (HR) levels are associated with an increased frequency of sudden death, and recently, it has been reported in the Framingham Heart Study that high resting HR also predicts hypertensive and all-cause mortality [9,11]. Elevated resting blood pressure (BP) has long been recognized as an independent risk factor for cardiovascular disease, and interestingly, an exaggerated BP response to acute treadmill exercise is independently associated with increased risk of future hypertension, which may be important in determining cardiovascular disease risk [14]. Beneficial reductions in HR and BP levels in response to a period of regular endurance training have been observed [21]. Further studies of genetic and environmental impacts on

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the responses to regular endurance training are potentially of physiological and clinical significance.

Genetic factors influence exercise HR and BP levels. It has been reported that DBP response to acute exercise was influenced by a significant genetic component in a study of 81 Utah pedigrees [7]. Extensive genetic epidemiological analyses of exercise HR and BP were recently performed in the HERITAGE Family Study (HERITAGE). The maximal heritabilities for submaximal exercise HR, systolic BP (SBP), and diastolic BP (DBP) at an absolute power output of 50 W reached 59%, 45% and 55%, respectively. The estimates reached 46%, 25% and 42%, respectively, during submaximal exercise at a relative power output of 60% maximal oxygen uptake ($\dot{V}O_2$max) [13]. For the changes in response to 20 weeks of endurance training (post-training minus baseline), the heritabilities were 34% and 29% for exercise HR at 50 W and 60% $\dot{V}O_2$max, respectively, and 22% for exercise SBP at 50 W, whereas there was no significant familial resemblance for exercise SBP at 60% $\dot{V}O_2$max, for exercise DBP during submaximal exercise, and for exercise HR and BP measured at a high exercise intensity of 80% $\dot{V}O_2$max [4]. The present study aims to assess whether baseline exercise HR and BP (each measured at 50 W and 80% $\dot{V}O_2$max) and their changes in response to a period of endurance training are influenced by major gene effects.

Material and Methods

Subjects in the HERITAGE Family Study were recruited through extensive media publicity and advertisements. Critical screening criteria for participation were: 1) subjects were healthy so as to complete 20 weeks of endurance training; 2) subjects were sedentary at baseline without regular strenuous exercise lasting more than 30 min for at least 6 months before study entry; 3) age ≤ 65 y for parents and between 17 – 40 for offspring; 4) resting SBP ≤ 159 mm Hg and resting DBP ≤ 99 mm Hg; BMI < 40 kg/m^2; 5) no antihypertensive drug therapy. Several subjects whose BMI were slightly higher than 40 kg/m^2 were approved for participation by supervising physicians, because they were considered to be in good health and were judged to be able to complete the required training program. The Institutional Review Boards at five participating centers of HERITAGE approved the study protocol, and written informed consents were obtained from all the participants. In this study, a total of 528 individuals (262 men and 266 women) from 99 White families and a total of 326 individuals (117 men and 209 women) from 113 Black family units completed the training, and had complete pre- and post-training exercise HR and BP measurements. Table **1** and Table **2** give the sample sizes within the four sex-by-generation groups for Whites and Blacks, respectively. In the present study, segregation analyses were carried out in Whites, and then in a pooled sample with Blacks aimed to confirm a major gene effect, if any, in Whites only sample. Blacks were not analyzed alone because of a smaller sample size and limited statistical power for detecting a major gene effect.

Each subject was administered a comprehensive battery of tests prior to the 20-week training program including HR and BP phenotypes measured at rest and during exercise (50 W and 80% $\dot{V}O_2$max). Subjects then completed 60 sessions of endurance exercise training (3 sessions per week for a total of 20 weeks) on cycle ergometers that were computer-controlled to maintain the subjects' HR at levels associated with fixed percentages of their $\dot{V}O_2$max. The training program started at 55% $\dot{V}O_2$max for 30 min per session, and gradually increased to 75% $\dot{V}O_2$max for 50 min per session during the last 6 weeks of training. All training sessions were supervised on site and adherence to the protocol was strictly monitored. The full test battery was administered again after completion of the training program. Details have been published previously [5].

HR and BP measurement techniques and exercise test methodology have been explicitly described [19,21]. Identical controls were used to measure exercise HR and BP before and after the training program, and testing was performed but not limited to the early morning hours. Exercise HR and BP measurements were obtained on two separate days after subjects reached a steady state during 8 – 12 min of pedaling at 50 W with two measurements on each day. Exercise HR and BP phenotypes were also obtained after 2 – 3 min of pedaling at the workload of 80% $\dot{V}O_2$max with only one measurement during each exercise test. The same protocol was used before and after the training program, but post-training exercise HR and BP measurements were made at 24 h and 72 h after the last training session. Both baseline and post-training phenotypes at 50 W were therefore means of four separate measurements, i.e., two exercise tests and two exercise HR or BP measurements during each exercise test. Both baseline and post-training phenotypes at 80% $\dot{V}O_2$max were solely measured once, i.e., one exercise test and one exercise HR or BP measurement during each test. The training response was determined by a simple difference of the averaged values of the post-training and the averaged values of the baseline levels. Baseline exercise HR and BP measurements at 50 W were highly reproducible for repeated measurements. The intraclass correlations were 0.89, 0.82 and 0.79 for exercise HR, SBP and DBP, respectively, and the coefficients of variation were 5.1, 6.0 and 7.8 for exercise HR, SBP and DBP, respectively [20].

The data adjustments were performed within each of the groups of fathers, mothers, sons and daughters, using a stepwise multiple regression procedure. Baseline exercise HR and BP levels were adjusted for the effects of age, age^2, age^3 and BMI, whereas the changes in response to training were adjusted for the effects of age, age^2, age^3, BMI and the respective baseline values. For each of the regressions, only terms that were significant at the 5% level were retained. The adjusted phenotypes were standardized to zero mean and unit variance for the segregation analysis.

Pedigree Analysis Package (PAP) was used to assess the major gene hypothesis [10]. The general model includes a major effect, a multifactorial component and a non-familial component. The major gene is assumed to have alleles *A* and *a*, which constitute genotypes *AA*, *Aa* and *aa*. The *A* allele leads to low phenotype values. It is assumed that the locus is in Hardy-Weinberg equilibrium. PAP estimates the *A* allele frequency *p* and the genotypic means μ_{AA}, μ_{Aa} and μ_{aa}. The overall mean μ_0 can be derived from the equation $\mu_{AA}p^2 + \mu_{Aa}2p(1-p) + \mu_{aa}(1-p)^2$. The effect of the genotype may be modified by covariates, which are modeled as regression coefficients βs. In this study, the effects of sex, age and BMI are noted as β_{sex}, β_{age} and β_{BMI}, and the effects can be gen-

Table **1** Means and SD for exercise HR and BP at 50W and 80% of $\dot{V}O_2$max in Whites

Variables	*No.*	*Means*	*SD*	*No.*	*Means*	*SD*
		Fathers			**Mothers**	
Age (*years*)	99	53.5*,#	5.3	95	52.0*,#	5.1
HR (*beats/min*):						
50 W, Baseline	97	105.5*	12.3	94	128.0*	16.6
50W, Response	91	–8.6*	8.6	90	–14.2*	11.2
80%, Baseline	97	150.9#	17.1	89	154.6#	14.9
80%, Response	90	–2.6	10.7	84	–4.0#	12.0
SBP (*mmHg*):						
50 W, Baseline	97	154.4#	21.3	94	157.7#	24.8
50 W, Response	91	–8.5#	11.7	90	–11.9#	14.5
80%, Baseline	95	196.0*,#	19.8	84	178.4*,#	20.3
80%, Response	87	5.1	16.6	76	2.2	18.0
DBP (*mmHg*):						
50 W, Baseline	97	78.1#	11.5	94	78.6#	9.7
50 W, Response	91	–3.8	6.8	90	–5.8#	7.0
80%, Baseline	96	84.1#	12.6	84	81.7#	10.5
80%, Response	88	–3.8	9.4	77	–4.5	8.8
		Sons			**Daughters**	
Age (years)	163	25.2#	6.0	171	25.4#	6.3
HR (beats/min):						
50 W, Baseline	159	107.1*	11.1	165	128.2*	14.5
50 W, Response	138	–8.8*	8.3	153	–12.5*	10.3
80%, Baseline	156	172.9#	12.8	165	175.0#	13.1
80%, Response	135	–4.9*	9.8	148	–0.7*,#	9.5
SBP (mmHg):						
50 W, Baseline	158	141.1*,#	13.4	165	134.6*,#	12.0
50 W, Response	137	–4.5#	10.0	153	–5.4#	9.2
80%, Baseline	155	186.7*,#	17.5	162	161.2*,#	17.1
80%, Response	133	5.2	16.0	139	5.7	15.2
DBP (mmHg):						
50 W, Baseline	158	68.7*,#	10.0	165	65.6*,#	8.7
50 W, Response	137	–2.5	6.5	153	–2.6#	6.8
80%, Baseline	153	72.1#	11.2	164	70.6#	10.6
80%, Response	130	–2.9	11.0	143	–1.8	11.0

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

otype-specific: $\beta_{(sex)AA}$, $\beta_{(sex)Aa}$, $\beta_{(sex)aa}$, $\beta_{(age)AA}$, $\beta_{(age)Aa}$, $\beta_{(age)aa}$, $\beta_{(BMI)AA}$, $\beta_{(BMI)Aa}$ and $\beta_{(BMI)aa}$. The common SD estimated in the model (σ) is assumed to be equal for each genotype, and includes both polygenic and residual variance components. The multifactorial heritability (H) estimated in the model is expressed as a function of the common variance (σ^2). The multifactorial heritability expressed as the percentage of the total phenotypic variance (h^2) can be computed using the equation $(H\sigma^2)/(\sigma^2 + \sigma^2_{mg})$, where σ^2_{mg} is the variance due to the major gene, $(\mu_{AA} - \mu_0)^2p^2 + (\mu_{Aa} - \mu_0)^2 2p(1-p) + (\mu_{aa} - \mu_0)^2(1-p)^2$. In addition to these major locus and multifactorial parameters, the transmission probabilities τ_{AA}, τ_{Aa} and τ_{aa} are explicitly modeled in order to test whether the major effect follows Mendelian expectations. Under Mendelian assumptions, the probabilities are 1, 0.5 and 0, respectively. The three τ's are equal if there is no transmission of the major effect. In order to infer a major gene, the following requirements have to be met: 1) rejection of the no major effect hypothesis ($p = 1$, $\mu_{AA} = \mu_{Aa} = \mu_{aa}$); 2) non-rejection of Mendelian τ's; and 3) rejection of equal transmission probabilities [12]. The maximum likelihood method was employed to estimate parameters, and the likelihood ratio test was used to test hypotheses of nested models. Finally, the most parsimonious model was the one with the smallest Akaike's Information Criterion (AIC), which is the minus twice the log likelihood plus twice the number of independently estimated parameters [1].

Results

Means and SD of unadjusted exercise HR and BP at 50 W and 80% $\dot{V}O_2$max are presented in Table **1** based on a total of 528 Whites. The percentages of variance over the four generation by sex groups accounted for by the significant effects of covariates in exercise HR were: 5% (age) at 50 W; 7–26% (age, BMI) at 80%

Table **2** Means and SD for exercise HR and BP at 50 W and 80 % of $\dot{V}O_2$max in Blacks

Variables	*No.*	*Means*	*SD*	*No.*	*Means*	*SD*
		Fathers			**Mothers**	
Age (years)	29	50.0*,#	7.2	60	46.6*,#	6.6
HR (beats/min):						
50 W, Baseline	29	112.6*	15.3	58	136.4*	16.7
50 W, Response	24	–11.3	12.4	48	–15.5	10.5
80 %, Baseline	29	146.3*,#	19.5	49	155.5*,#	17.1
80 %, Response	24	–2.5	13.4	41	1.1	12.6
SBP (mmHg):						
50 W, Baseline	29	170.6#	18.2	58	173.2#	23.8
50 W, Response	24	–16.2#	12.9	48	–15.8#	12.2
80 %, Baseline	29	203.0	24.9	48	191.5#	24.8
80 %, Response	24	3.4	23.6	40	–1.9	19.5
DBP (mmHg):						
50 W, Baseline	29	89.2#	7.3	58	89.1#	10.9
50 W, Response	24	–7.6	6.3	48	–7.5	6.3
80 %, Baseline	29	92.9#	9.6	48	89.7#	12.0
80 %, Response	24	–6.6	10.0	40	–4.9	11.8
		Sons			**Daughters**	
Age (years)	88	27.0#	7.2	149	27.6#	7.5
HR (beats/min):						
50 W, Baseline	87	108.6*	9.7	147	134.1*	16.0
50 W, Response	64	–7.5*	7.9	118	-13.4*	10.8
80 %, Baseline	87	163.1#	13.7	145	166.2#	15.5
80 %, Response	64	–0.7	12.5	117	-2.7	11.3
SBP (mmHg):						
50 W, Baseline	87	149.6#	13.2	144	148.9#	16.3
50 W, Response	64	–5.4*,#	11.1	115	-10.0*,#	11.5
80 %, Baseline	85	195.2*	21.7	132	170.5*,#	19.9
80 %, Response	60	0.4	19.0	103	-1.8	16.0
DBP (mmHg):						
50 W, Baseline	87	77.2#	9.7	144	75.6#	9.4
50 W, Response	64	–4.8	6.6	115	-5.8	7.4
80 %, Baseline	84	81.3#	12.8	135	82.2#	11.9
80 %, Response	60	–3.1	12.4	108	-6.1	11.4

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

$\dot{V}O_2$max; 34 – 51 % and 13 – 36 % (baseline, age, BMI) for the training responses at 50 W and 80 % $\dot{V}O_2$max, respectively. For exercise SBP, these values were: 7 – 38 % and 12 – 15 % (age, BMI) at 50 W and 80 % $\dot{V}O_2$max, respectively; 16 – 39 % (baseline, BMI) for the training response at 50 W; 7 – 22 % (baseline, age) for the training response at 80 % $\dot{V}O_2$max. For exercise DBP, they were: 10 – 19 % (age, BMI) at 50 W; 10 – 13 % (age) at 80 % $\dot{V}O_2$max; 24 – 35 % (baseline, age, BMI) for the training response at 50 W; 18 – 33 % (baseline) for the training response at 80 % $\dot{V}O_2$max. Means and SD of unadjusted exercise HR and BP at 50 W and 80 % $\dot{V}O_2$max are given in Table **2** based on a total of 326 Black participants. Similar percentages of variance accounted for by covariates were found in Blacks.

Segregation analysis results for baseline exercise HR at 50 W in Whites are presented in Table **3**. All the hypotheses of no familial resemblance (2), no major effect (3), and no multifactorial effect (4) were rejected, suggesting that both the major and the multifactorial effects were significant. Whereas the dominant model (6) was rejected, a recessive mode of inheritance (model 5) was not. Tests on the transmission probabilities were carried out, and whereas the environmental hypothesis (model 8, equal τ's) was rejected, that of the Mendelian τ's (model 7, free τ's) was not. Model 5 was the most parsimonious according to the AIC (16.22). The putative recessive gene accounted for 30 % of the phenotypic variance, while the multifactorial effect and the random environmental effect accounted for 27 % and 43 % of the variance, respectively. Furthermore, while we expected no effects of sex, age or BMI because of prior phenotypic adjustments, we did test for the possibility of interactions with major genotypes. However, no significant covariate interactions with specific genotypes were found (details not presented). For baseline exercise HR at 80 % $\dot{V}O_2$max in Whites, while there was evidence for familial resemblance, neither the hypothesis of no multifactorial

Table **3** Segregation analysis of exercise HR at 50 W in Whites

Model[#]	*(1)*	*(2)*	*(3)*	*(4)*	*(5)*	*(6)*	*(7)*	*(8)*
Baseline								
P	0.591	(1)	(1)	0.663	0.588	0.884	0.586	0.759
τ_{AA}	(1)	(1)	(1)	(1)	(1)	(1)	(1)*	(0.759)
τ_{Aa}	(0.5)	(0.5)	(0.5)	(0.5)	(0.5)	(0.5)	0.586	(0.759)
τ_{aa}	(0)	(0)	(0)	(0)	(0)	(0)	(0)*	(0.759)
μ_{AA}	–0.175	0.011	0.011	–0.608	–0.246	–0.246	–0.107	–0.067
μ_{Aa}	–0.293	(0.011)	(0.011)	0.244	(–0.246)	0.954	–0.329	–0.067
μ_{aa}	1.228	(0.011)	(0.011)	1.449	1.219	(0.954)	1.268	1.302
σ	0.837	1.017	0.997	0.757	0.838	0.874	0.839	0.946
H	0.411	(0)	0.477	(0)	0.381	0.314	0.434	0.522
–2 ln L	1386.69	1458.57	1394.90	1391.18	1386.81	1392.14	1386.16	1393.64
Comp.	–	2 – 1	3 – 1	4 – 1	5 – 1	6 – 1	1 – 7	8 – 7
d. f.	–	4	3	1	1	1	1	1
χ^2	–	71.88	8.21	4.49	0.12	5.45	0.53	7.48
P	–	< 0.001	0.042	0.034	0.729	0.020	0.467	0.006
AIC	18.10	81.98	20.31	20.59	16.22	21.55	19.57	25.05
Response								
P	0.916	(1)	(1)	0.904	0.636	0.942	0.927	0.871
τ_{AA}	(1)	(1)	(1)	(1)	(1)	(1)	(1)*	(0.871)
τ_{Aa}	(0.5)	(0.5)	(0.5)	(0.5)	(.5)	(0.5)	0.390	(0.871)
τ_{aa}	(0)	(0)	(0)	(0)	(0)	(0)	(0)*	(0.871)
μ_{AA}	–0.201	0.002	–0.002	–0.239	–0.217	–0.169	–0.192	–0.328
μ_{Aa}	1.221	(0.002)	(–0.002)	1.061	(–0.217)	1.199	1.205	1.031
μ_{aa}	–0.824	(0.002)	(–0.002)	1.067	1.169	(1.199)	–0.886	1.032
σ	0.856	0.996	0.994	0.852	0.856	0.887	0.862	0.809
H	0.152	(0)	0.295	(0)	0.148	0.103	0.143	0.398
–2 ln L	1302.43	1330.22	1312.41	1305.56	1305.68	1304.73	1302.06	1306.47
Comp.	–	2 – 1	3 – 1	4 – 1	5 – 1	6 – 1	1 – 7	8 – 7
d. f.	–	4	3	1	1	1	1	1
χ^2	–	27.79	9.98	3.13	3.25	2.30	0.37	4.41
P	–	< 0.001*	0.019*	0.077	0.071	0.129	0.543	0.036
AIC	14.78	34.57	18.76	15.91	16.03	15.08	16.41	18.82

[#](1) Mixed Mendelian ($\tau_{AA} = 1$, $\tau_{Aa} = 0.5$, $\tau_{aa} = 0$); (2) Sporadic (p = 1, $\tau_{AA} = 1$, $\tau_{Aa} = 0.5$, $\tau_{aa} = 0$, $\mu_{AA} = \mu_{Aa} = \mu_{aa}$, $H = 0$); (3) Multifactorial effect only ($p = 1$, $\tau_{AA} = 1$, $\tau_{Aa} = 0.5$, $\tau_{aa} = 0$, $\mu_{AA} = \mu_{Aa} = \mu_{aa}$); (4) Major effect only ($\tau_{AA} = 1$, $\tau_{Aa} = 0.5$, $\tau_{aa} = 0$, $H = 0$); *(5) Recessive* ($\tau_{AA} = 1$, $\tau_{Aa} = 0.5$, $\tau_{aa} = 0$, $\mu_{AA} = \mu_{Aa}$); (6) Dominant ($\tau_{AA} = 1$, $\tau_{Aa} = 0.5$, $\tau_{aa} = 0$, $\mu_{Aa} = \mu_{aa}$); (7) Revised general ($\tau_{AA} = 1$, $\tau_{aa} = 0$); (8) Environmental ($p = \tau_{AA} = \tau_{Aa} = \tau_{aa}$) *The parameters τ_{AA} and τ_{aa} reached bounds and they were therefore fixed as $\tau_{AA} = 1$ and $\tau_{aa} = 0$ under revised general model (7).

effect nor that of no major effect could be rejected. The latter, however, was the most parsimonious according to the AIC, and the multifactorial effect accounted for 44% of the variance.

Segregation analysis results for HR training response at 50 W in Whites are also given in Table **3**. Both the no familial resemblance and the no major effect hypotheses were rejected, while the test of no multifactorial effect model was at borderline significance (p = 0.077). The dominant model was not rejected (p = 0.129), and the recessive hypothesis was at the borderline of significance (p = 0.071), indicating an ambiguous mode of inheritance. While the no transmission of major effect was rejected, Mendelian τ's were not. According to the AIC (14.78), the mixed Mendelian model (1) was the most parsimonious. The major gene accounted for 27% of the variance, and the multifactorial and the random environmental effects accounted for 11% and 62% of the variance, respectively. No significant covariate interactions with specific genotypes were found (details not presented). For exercise HR training response at 80% $\dot{V}O_2$max in Whites, there was no evidence of familial resemblance.

Segregation analyses of exercise BP in Whites at both work rates at baseline and in response to training revealed no major gene effects. Instead, these phenotypes appeared to be solely influenced by multifactorial effects, except that no familial influence was found for exercise BP training responses at 80% $\dot{V}O_2$max. The multifactorial components accounted for 40 – 50% of the variance for baseline exercise BP at both work rates and 20% of the variance for the training responses at 50 W (details not presented).

Major genes for submaximal exercise HR were also assessed in Blacks. However, as can be expected, models did not converge appropriately due to a small sample size. They were alternatively assessed in a pooled data of Whites and Blacks (Table **4**). Although major effects were significant for submaximal exercise

Table **4** Segregation analysis of exercise HR at 50 W in pooled data of Whites and Blacks

Models	*(1)*	*(2)*	*(3)*	*(4)*	*(5)*	*(6)*	*(7)*	*(8)*
Baseline								
P	0.592	(1)	(1)	0.671	0.626	0.889	0.803	0.950
τ_{AA}	(1)	(1)	(1)	(1)	(1)	(1)	0.947	(0.950)
τ_{Aa}	(0.5)	(0.5)	(0.5)	(0.5)	(0.5)	(0.5)	0.610	(0.950)
τ_{aa}	(0)	(0)	(0)	(0)	(0)	(0)	(0)*	(0.950)
μ_{AA}	-0.391	0.010	–0.001	–0.632	–0.227	–0.266	–0.465	–0.155
μ_{Aa}	-0.168	(0.010)	(–0.001)	0.265	(–0.227)	1.160	0.702	1.397
μ_{aa}	1.281	(0.010)	(–0.001)	1.533	1.367	(1.160)	2.118	1.397
σ	0.814	1.009	0.998	0.721	0.840	0.835	0.730	0.885
H	0.380	(0)	0.520	(0)	0.489	0.317	0.320	0.612
-2 ln L	2131.85	2233.44	2150.04	2136.90	2131.87	2136.30	2131.59	2135.31
Compare	–	2 – 1	3 – 1	4 – 1	5 – 1	6 – 1	1 – 7	8 – 7
d.f.	–	4	3	1	1	1	2	2
χ^2	–	101.59	18.19	5.05	0.020	4.45	0.26	3.72
P	–	< 0.001	< 0.001	0.025	0.888	0.035	0.878	0.156
AIC	12.26	105.85	24.45	15.31	*10.28*	14.71	16.00	15.72
Response								
p	0.527	(1)	(1)	0.553	0.511	0.882	0.855	0.845
τ_{AA}	(1)	(1)	(1)	(1)	(1)	(1)	0.818	(0.845)
τ_{Aa}	(0.5)	(0.5)	(0.5)	(0.5)	(0.5)	(0.5)	0.996	(0.845)
τ_{aa}	(0)	(0)	(0)	(0)	(0)	(0)	0*	(0.845)
μ_{AA}	0.122	0.002	0.012	–0.631	–0.315	–0.255	–0.339	–0.371
μ_{Aa}	–0.536	(0.002)	(0.012)	–0.055	(–0.315)	0.954	0.870	0.953
μ_{aa}	1.103	(0.002)	(0.012)	1.155	1.047	(0.954)	1.324	0.953
σ	0.768	1.002	0.999	0.785	0.818	0.868	0.831	0.808
H	0.406	(0)	0.357	(0)	0.215	0.173	0.503	0.532
–2 ln L	1945.84	1992.41	1959.67	1952.95	1950.70	1954.99	1951.18	1951.82
Compare	–	2 – 1	3 – 1	4 – 1	5 – 1	6 – 1	7 – 1	8 – 7
d.f.	–	4	3	1	1	1	2	2
χ^2	–	46.57	13.83	7.11	4.86	9.15	5.34	0.64
P	–	< 0.001	0.003	0.008	0.027	0.002	0.069	0.726
AIC	12.00	50.57	19.83	17.11	14.86	19.15	21.34	17.98

* The parameter τ_{aa} reached a bound and was therefore fixed to zero ($\tau_{aa} = 0$) in the revised general model (7).

HR both at baseline and in response to training, a Mendelian transmission pattern from parents to offspring could not be demonstrated.

Discussion

We found evidence for a major recessive gene influencing baseline submaximal exercise HR in Whites. The major gene effect was independent of age, sex and BMI. In addition, segregation analysis was also performed using data adjusted for the effects of cigarette smoking, baseline $\dot{V}O_2$max and resting HR levels, and similar results were obtained (data not shown); therefore, the evidence supporting a major gene is independent of these factors. The putative major gene accounted for 30% of the variance, with another 27% of the variance attributable to residual polygenic and familial environmental factors. Tests of possible interactions of genotype with sex, age and BMI were negative. A major gene effect for the training response in submaximal exercise HR was also found, but the mode of inheritance is unclear. The major gene accounted for 27% of the variance, with the multifactorial effect accounting for 11% of the variance. Since the data have been adjusted for the effects of baseline HR values, these effects may be actually caused by different genes. Similarly, the data were adjusted for the effects of smoking, baseline $\dot{V}O_2$max and resting HR values (data not shown), and the conclusions regarding major gene effects were generally not impacted by these covariate adjustments.

Results arising from a series of genetic analyses in HERITAGE have documented that resting HR is under the influence of both a major gene effect and a multifactorial effect (heritability of 30%) [2,3,18]. A genetic influence on submaximal exercise HR has also been found (heritability of 40%) [4,13]. The major recessive gene detected in the present data for baseline submaximal exercise HR appears to be different from the major dominant gene detected in the same dataset for baseline resting HR, as the former was unaffected by the adjustment for baseline values. We also noted that putative major genes for submaximal exercise HR were found solely in Whites, and not in Blacks nor in the pooled

data. A small sample size and sample heterogeneity may account for the failure to demonstrate a similar effect in Blacks. To our knowledge, this is the first study to investigate the mode of inheritance of submaximal exercise HR phenotypes.

It is known that resting BP levels are under substantial genetic control [2,6,8,15–17]. In the current study, it appeared that submaximal exercise BP levels were also influenced by familial multifactorial effects, which accounted for 50% of the variance in baseline BP and 20% of the variance in the BP training response. In a previous study based on the same data but using a different model, comparable estimates of the maximal heritability were found, 45–55% for the baseline BP and 22% for the training response [4,13]. No major gene effect was detected either for baseline resting or exercise SBP in these data [3]. In contrast, whereas there was no evidence for a major gene effect on baseline exercise DBP in the present study, we previously reported a putative recessive gene for baseline resting DBP [3].

It has been observed that familial influences on exercise HR and SBP training responses tend to decline from modest levels of heritability (20–30%) to non-significant estimates, with increasing exercise intensities [4,13]. A similar trend was evident in the current study. The multifactorial heritabilities for the training response phenotypes went from modest (about 20%) at 50 W to negligible at 80% $\dot{V}O_2$max.

In conclusion, HR changes in response to acute submaximal exercise and to regular endurance training appear to be under the influence of putative major genes. Exercise BP phenotypes are mainly affected by multifactorial components. Genome-wide linkage and association studies are underway to identify the responsible genes.

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