Genomic Scan for Exercise Blood Pressure in the Health, Risk Factors, Exercise Training and Genetics (HERITAGE) Family Study

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Abstract—A genome-wide linkage scan was performed for genes affecting submaximal exercise systolic blood pressure (SBP) and diastolic blood pressure (DBP) in the sedentary state and their responses to a standardized endurance training program. A total of 344 polymorphic markers were used, and 344 pairs of siblings from 99 white nuclear families and 102 sibling pairs from 105 black family units were available for the study. All subjects were healthy but sedentary at baseline. SBP and DBP were measured during exercise tests at 2 different intensities: 50 W (SBP50 and DBP50) and 80% of maximal oxygen consumption (SBP80 and DBP80). Baseline blood pressure phenotypes were adjusted for age, gender, and body mass index, and the training responses (after training minus baseline [Δ]) were adjusted for age, gender, baseline body mass index, and baseline blood pressure. Two analytical strategies were used: a multipoint variance-components linkage analysis using all the family data and a single-point linkage analysis using pairs of siblings. In whites, promising linkages (lod score >1.75) were detected for baseline SBP80 on 10q23-q24 and for ΔSBP50 on 8q21. In addition, several chromosomal regions with suggestive evidence of linkage (lod score 1.0 to 1.75) were observed for SBP50 (22q11.2-q13), DBP50 (6q23-q27), SBP80 (2p24, 2q21, 14q11.1-q12, and 16q21), DBP80 (6q13-q21), ΔSBP50 (7p12-p13), and ΔDBP50 (5q31-q32). In blacks, DBP50, DBP80, and ΔDBP80 showed promising quantitative trait loci on 18p11.2, 11q13-q21, and 10q21-q23, respectively. Suggestive linkages were evident for DBP50 on 2p22-p25, 11p15.5, and 18q21.1; for SBP80 on 6q21-q21, 6q31-q36, 12q12-q13, 15q12-q13, and 17q11-q12; and for DBP80 on 8q24, 10q21-q24, and 12p13. All the detected chromosomal regions include several potential candidate genes and therefore warrant further studies in the Health, Risk Factors, Exercise Training and Genetics (HERITAGE) cohort and other studies. **(*Hypertension*. 2001;38:30-37.)**

Key Words: genes ■ blood pressure ■ exercise ■ linkage

Contribution of genetic factors to the regulation of resting blood pressure (BP) and the development of hypertension has been well established. Estimates of the resting BP heritability have varied from ≈25%, as derived from family studies, up to ≈70%, as derived from twin studies.[1] The majority of the studies support a multifactorial model of inheritance with polygenic effects, although major gene effects contributing to BP variability have been reported.[2–4] The search for genes affecting BP and hypertension has relied mainly on association and linkage studies using molecular markers at or near potential candidate gene loci. Several candidate genes have been tested, but the results have been mainly inconclusive, and the contribution of the genes showing positive associations has been moderate at best.[5] An alternative strategy is to perform a genome-wide scan with the use of a large panel of polymorphic markers covering all chromosomes. This approach allows the detection of chromosomal regions that most likely harbor genes affecting the phenotype of interest. So far, 7 genomic scans for resting BP phenotypes[6–12] and 1 scan for postural BP changes[13] have been reported, and the number of promising quantitative trait loci (QTLs) has ranged from 1 to 6 per study.

Several studies have shown the BP-lowering effect of regular endurance training, especially in subjects with high-normal BP levels and mild-to-moderate hypertension. In normotensive subjects, an exaggerated BP response to acute exercise has been suggested to predict the future risk of hypertension.[14,15] Only a few studies have investigated the role of genetic factors in the regulation of BP response to exercise. For the acute exercise response, a segregation

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analysis study of 864 subjects from 81 pedigrees showed a mixed recessive model of transmission for diastolic BP (DBP) response to a cycle ergometer exercise test, with a gene frequency of 0.21. The phenotypic variances explained by the major gene and polygenic effects were 34% and 17%, respectively.[16] In the Health, Risk Factors, Exercise Training and Genetics (HERITAGE) Family Study, maximal heritability for acute systolic BP (SBP) response to submaximal exercise at 50 W in whites was 50%.[17] The contribution of genetic factors to acute SBP and DBP responses to an incremental cycle ergometer test were also investigated in a cohort of 148 monozygotic and 111 dizygotic twin pairs with a mean age of 11 years.[18] Significant genetic effects were found for SBP and DBP, and the results suggested that the genetic effects found at rest also influenced the exercise phenotypes, although the effects tended to decline with higher exercise intensities.

On the basis of these heritability estimates, it is reasonable to start looking for genomic regions and individual genes that are responsible for the genetic effects on exercise BP phenotypes. Using the data from the HERITAGE Family Study, we performed a genome-wide linkage scan for submaximal exercise SBP and DBP measured in the sedentary state and also in response to a 20-week endurance training program.

Methods

Subjects

The study cohort consists of 492 white subjects (239 males and 253 females) from 99 nuclear families and 270 black subjects (91 males and 179 females) from 105 family units. The complete training response data were available for 471 whites (228 men and 243 women) and 249 blacks (87 men and 162 women). The maximum number of sibling pairs available was 344 and 102 in whites and blacks, respectively. The study design and inclusion criteria have been described previously.[19] To be eligible, the individuals were required to be in good health, ie, to be free of diabetes, cardiovascular diseases, or other chronic diseases that would prevent their participation in an exercise training program. Subjects were also required to be sedentary, which was defined as not having engaged in regular physical activity over the previous 6 months. Individuals with resting SBP >159 mm Hg and/or DBP >99 mm Hg were excluded. According to the Joint National Committee VI classification,[20] 67%, 22%, and 8% of whites and 42%, 30%, and 20% of blacks had optimal, normal, and high-normal resting BPs, respectively. The study protocol had been approved by each of the institutional review boards of the HERITAGE Family Study research consortium. Written informed consent was obtained from each participant.

Blood Pressure

Before and after the 20-week training program, each subject completed 3 cycle ergometer (SensorMedics Ergo-Metrics 800S) exercise tests conducted on separate days: a maximal exercise test (Max), a submaximal exercise test (Submax), and a submaximal/maximal exercise test (Submax/Max).[21] The Submax test was performed at 50 W and at 60% of the initial maximal oxygen consumption (VO_2max). Subjects exercised for 8 to 12 minutes at each work rate, with a 4-minute period of seated rest between exercise periods. Finally, the Submax/Max test was started with the Submax protocol. After exercising at 60% VO_2max, subjects also exercised for 3 minutes at 80% VO_2max. The test then progressed to a maximal level of exertion. BP was obtained by using Colin STBP-780 automated units. Earphones allowed the technician to confirm the BP values selected by the detection algorithm of the instrument. For the present analyses, SBP and DBP measured at 2 different Submax intensity levels were selected. SBP and DBP at 50 W (SBP50 and DBP50, respectively) represent a moderate intensity level, whereas SBP and DBP at 80% VO_2max (SBP80 and DBP80, respectively) reflect high-intensity exercise. BP was measured twice at each workload in both Submax tests, both before and after the training period, whereas only 1 BP recording was obtained at 80% VO_2max. Thus, both the pretraining and posttraining 50 W phenotypes are the means of 4 measurements, whereas the 80% VO_2max phenotypes represent a single measurement. BP training responses (Δ) were calculated as posttraining BP minus pretraining BP.

Exercise Training Program

The exercise training program has been described in detail previously.[21] Briefly, the exercise intensity of the 20-week training program was customized for each participant on the basis of the heart rate–VO_2 relationship measured at baseline. During the first 2 weeks, the subjects trained at a heart rate corresponding to 55% of the baseline VO_2max for 30 minutes per session. Duration and intensity of the training sessions were gradually increased to 50 minutes and 75% of the heart rate associated with baseline VO_2max; these levels were then sustained for the last 6 weeks. Training frequency was 3 times per week, and all training was performed on cycle ergometers in the laboratory. Heart rate was monitored during all training sessions by a computerized cycle ergometer system (Universal FitNet System), which adjusted ergometer resistance to maintain the target heart rate. Trained exercise specialists supervised all exercise sessions.

Data Adjustment

Baseline BP measurements were adjusted for the effects of gender, generation, and age by using stepwise multiple regression.[22] Training response phenotypes were also adjusted for baseline value of the phenotype. In summary, a BP phenotype was regressed on up to a third-degree polynomial in age (separately within race-by-gender-by-generation subgroups). Only significant terms (5% level) were retained (ie, the model did not need to be saturated). The residual from this regression (or the raw score if no age terms were significant) was then standardized to 0 mean and unit variance and constituted the analysis variable. Similarly, a second set of BP variables (both baseline and training responses) was constructed by removing the effects of baseline body mass index (BMI) and the polynomial in age. For the training response phenotypes, we also checked the effect of training-induced changes in BMI (ΔBMI) on BP training responses. ΔBMI had no significant contribution in regression models and, therefore, was not included in the final models.

Molecular Studies

A total of 344 markers with an average spacing of 9.7 cM were used. Polymerase chain reaction conditions and genotyping methods have been fully outlined previously.[23] Automatic DNA sequencers from LI-COR were used to detect the polymerase chain reaction products, and genotypes were scored automatically by using SAGA software. Incompatibilities of mendelian inheritance were checked, and markers showing incompatibilities were regenotyped completely (<10% were retyped). Microsatellite markers were selected mainly from the Marshfield panel, version 8a, as were some candidate genes for obesity and comorbidities, including hypertension. Map locations were taken mainly from the Genetic Location DataBase of Southampton, UK (which can be accessed online at http://cedar.genetics.soton.ac.uk) and from other sources for a few markers (published articles and the Marshfield Institute map can be accessed online at http://www.marshmed.org/genetics).

Linkage Analyses

Linkage analysis was performed by using a multipoint variance components model as implemented in SEGPATH.[24,25] According to this model, a phenotype is influenced by the additive effects of a trait locus (g), a residual familial background modeled as a pseudopolygenic component, and a residual nonfamilial component (r). The

TABLE 1. Baseline BP Phenotypes and Their Responses to Training

		Blacks			Whites		
Variable	Group	No.	Mean	SD	No.	Mean	SD
Basic characteristics							
Age, y	Fathers	25	50.9	7.3	95	53.5	5.2
	Mothers	50	46.9	6.6	93	52.1	5.0
	Sons	66	28.4	7.1	144	25.4	6.1
	Daughters	128	27.8	7.6	160	25.6	6.4
Resting SBP at baseline, mm Hg	Fathers	25	125.0	12.9	94	121.8	13.2
	Mothers	49	128.6	13.9	93	116.7	11.8
	Sons	65	124.3	8.8	144	119.3	8.8
	Daughters	127	119.8	11.5	159	110.4	7.8
Resting DBP at baseline, mm Hg	Fathers	25	75.2	8.7	94	72.6	8.6
	Mothers	49	77.1	8.0	93	67.6	6.6
	Sons	65	72.0	6.6	144	65.6	8.1
	Daughters	127	70.9	8.5	159	61.8	6.4
Baseline, mm Hg							
SBP50	Fathers	25	172.0	18.7	95	154.5	21.4
	Mothers	51	173.0	23.9	93	157.8	24.9
	Sons	66	148.0	13.1	145	141.2	13.6
	Daughters	129	148.3	16.3	160	134.4	12.0
DBP50	Fathers	25	88.6	7.5	95	78.2	11.5
	Mothers	51	88.3	11.0	93	78.5	9.8
	Sons	66	76.9	9.7	145	68.7	9.7
	Daughters	129	75.3	9.4	160	65.2	8.4
SBP80	Fathers	25	205.1	25.0	91	196.6	19.5
	Mothers	41	191.5	25.5	83	178.5	20.4
	Sons	64	194.0	21.0	142	186.9	17.6
	Daughters	119	169.8	19.8	152	161.1	17.1
DBP80	Fathers	25	93.1	9.4	92	84.5	12.2
	Mothers	41	89.2	12.3	83	81.7	10.6
	Sons	63	81.0	12.6	141	72.5	11.3
	Daughters	120	82.0	11.8	154	70.4	10.6
Training response, mm Hg							
ΔSBP50	Fathers	25	−16.1	12.6	91	−8.4	11.7
	Mothers	48	−15.8	12.2	90	−11.9	14.5
	Sons	64	−5.4	11.1	138	−4.7	10.1
	Daughters	115	−10.0	11.5	153	−5.3	9.2
ΔDBP50	Fathers	25	−7.4	6.3	91	−3.8	6.8
	Mothers	48	−7.5	6.3	90	−5.8	7.0
	Sons	64	−4.8	6.6	138	−2.5	6.5
	Daughters	115	−5.8	7.4	153	−2.5	6.7
ΔSBP80	Fathers	25	+3.2	23.1	85	+5.0	16.6
	Mothers	39	−1.9	19.5	76	+2.2	18.0
	Sons	60	+0.4	19.0	132	+5.0	16.1
	Daughters	103	−1.8	16.0	134	+5.8	15.2
ΔDBP80	Fathers	25	−6.1	10.1	86	−3.8	9.4
	Mothers	39	−4.9	11.8	77	−4.4	8.8
	Sons	60	−3.1	12.4	129	−2.9	10.9
	Daughters	106	−6.1	11.4	138	−1.9	11.0

TABLE 2. Promising ($P<0.0023$) and Suggestive ($P<0.01$) Multipoint (SEGPATH) Linkages and Corresponding Single-Point (SIBPAL) Linkages With Submax BP Phenotypes in the Sedentary State and in Response to Endurance Training in Whites

Marker	Chromosome	Map Position, Mb	Trait	SEGPATH Lod	SEGPATH *P*	SIBPAL *P*
D2S2952	2p24	7.277	SBP80	1.70	0.0026	0.005
D2S1334	2q21	144.536	SBP80	1.63	0.0031	0.356
ADRB2	5q31-q32	156.379	ΔDBP50	1.38	0.0058	0.025
D5S640	5q31-q33	158.081	ΔDBP50	1.47	0.0046	0.020
D6S1270	6q13-q21	77.721	DBP80	1.55	0.0037	0.014
D6S462	6q13-q21	95.096	DBP80	1.45	0.0049	0.114
GATA184A08	6q23-q25	146.000	DBP50	1.40	0.0056	0.009
D6S2436	6q24-q27	158.466	DBP50	1.52	0.0041	0.061
IGFBP3	7p12-p13	50.897	ΔSBP50	1.35	0.0063	0.039
D8S373	8q21	154.102	ΔSBP50	2.36	0.0005	0.010
D10S2470	10q21-q24	92.113	SBP80	1.25	0.0082	0.037
D10S677	10q23-q24	96.068	SBP80	1.84	0.0018	0.152
D10S1239	10q23-q25	106.000	SBP80	1.48	0.0045	0.107
D14S283	14q11.1-q12	22.320	SBP80	1.59	0.0034	0.049
ANG	14q11.1-q11.2	25.417	SBP80	1.30	0.0072	0.021
D15S211	15q24-q25	86.370	DBP80	1.72	0.0024	*
D16S748	16p13.3	7.103	SBP80	1.19	0.0097	0.027
D16S753	16p12	39.008	SBP80	1.23	0.0087	0.135
D16S261	16q21	53.319	SBP80	1.70	0.0026	0.003
D22S304	22q12-q13	42.324	SBP50	1.22	0.0088	0.020
IL2RB	22q11.2-q13	43.211	SBP50	1.27	0.0078	0.013

All baseline phenotypes are adjusted for age, gender, and baseline BMI. Training response (Δ) phenotypes are adjusted also for baseline value of the response phenotype.

*Could not be analyzed with SIBPAL because of a high number of alleles (n=26) of the marker.

ADRB2 indicates adrenergic receptor-β2; IGFBP3, insulin-like growth factor binding protein 3; ANG, angiotensin; and IL2RB, interleukin 2 receptor-β.

effects of the trait locus and the pseudopolygenic component on the phenotype represent the heritabilities, h^2_g and h^2_r, respectively. Allele-sharing probabilities (at each marker location for each sibling pair) were used as input data for the linkage component of the SEGPATH model. These multipoint probabilities were derived by using the program MAPMAKER/SIBS.[26] Other parameters in the model include spouse and additional sibling resemblance and the mean and variance in the offspring. The linkage hypothesis is tested by restricting the trait locus heritability to 0. A likelihood ratio test contrasts the null hypothesis ($h^2_g=0$) with the alternative (h^2_g estimated). The difference in -2 ln L (minus twice the log likelihood) between the null and alternate hypotheses is asymptotically distributed as a 50:50 mixture of a χ_1^2 and a point mass at 0, and the *P* value is half that associated with the χ^2 value.[27] The lod score is $\chi^2/(2 \cdot \log_e 10)$. The α-level used here to identify promising results ($P<0.0023$, corresponding to a lod score of 1.75) represents, on average, 1 false positive per scan for experiments involving ≈400 markers.[28]

In addition to the multipoint linkage analyses, a single-point linkage analysis was performed with the sib-pair linkage procedure[29,30] as implemented in the SIBPAL program of the SAGE Statistical Package.[31] Briefly, the squared sib-pair phenotypic difference was regressed on the expected proportion of marker alleles identical-by-descent at the locus. A 1-sided *t* test was then used to test whether the regression coefficient is <0. A significant inverse relationship between the squared sib-pair phenotypic difference and allele sharing at the marker locus was taken as evidence of linkage. Both the multipoint and single-point analyses were conducted separately for blacks and whites.

Results

The means and standard deviations for SBPs and DBPs at 50 W and 80% of VO_2max at baseline and their responses to endurance training in 4 gender-by-generation subgroups in blacks and whites are presented in Table 1. The genomic regions showing promising and suggestive linkages with exercise BP phenotypes are summarized in Tables 2 and 3. Furthermore, the chromosomes with promising linkages are depicted in Figures 1 and 2.

In whites, 1 chromosomal region (10q23-q24, Figure 1) showed promising linkages and another 8 regions (2p24, 2q21, 6q13-q21, 6q23-q27, 14q11.1-q12, 15q24-q25, 16q21, and 22q12-q13) showed suggestive linkages with baseline phenotypes (Table 2). For the training response phenotypes, 1 promising QTL (8q24 for ΔSBP80, Figure 1) and 2 suggestive QTLs (5q31-q33 for ΔDBP50 and 7p12p13 for ΔSBP50) were detected (Table 2). Of the 9 baseline BP QTLs, 6 were for SBP, whereas 3 were specific for DBP. Five of the SBP regions were specific for SBP80 (2p, 2q, 10q, 14q, and 16q), and 1 was specific for SBP50 only (22q). One QTL was detected for baseline DBP50 (6q), and 2 were detected for DBP80 (6q and 15q).

In blacks, 2 regions with promising linkages (11q13-q21 for DBP80 and 18p11.2 for DBP50, Figure 2) and 11 with

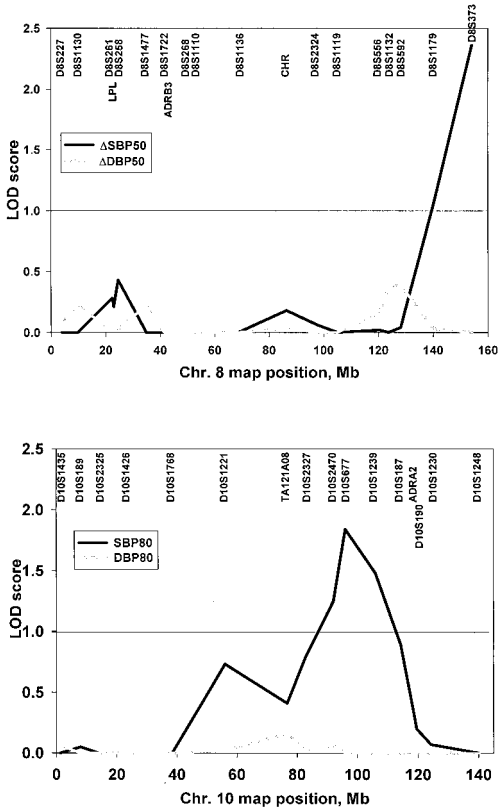

Figure 1. Overview of the multipoint linkage results for chromosomes 8 (SBP50 and DBP50 training responses) and 10 (baseline SBP80 and DBP80) in whites of the HERITAGE Family Study. Chr. indicates chromosome; LPL, lipoprotein lipase, ADRB3, adrenergic receptor-β; CRH, corticotrophin-releasing hormone; and ADRA2, adrenergic receptor-α 2A.

suggestive linkages (2p22-p25 and 11p15.5 for DBP50; 6q21-q23, 7q31-q36, 12p12-p13, 15q26, 16q12-q13, and 17cen-q12 for SBP80; and 8q24, 10q21-q24, and 12p12-p13 for DBP80) were detected for the baseline phenotypes (Table 3). One region at 10q21-q23 showed promising linkage with the DBP80 training response (Table 3, Figure 2). No common QTLs were found for blacks and whites. Adjustment for baseline BMI did not have any major impact on linkages either in blacks or in whites.

Discussion

On the basis of evidence from quantitative genetic studies, it is reasonable to undertake a search for QTLs and, ultimately, the genes affecting Submax BP both in the sedentary state and in response to exercise training. Identifying these QTLs and resolving them in terms of genes and mutations would not only benefit our understanding of basic human exercise physiology but also contribute to our understanding of the genetic basis of BP regulation. This information would very likely also shed light on the molecular mechanisms leading to elevated resting BP levels. The present study is the first attempt to localize such genomic regions, and our results indicate promising evidence for QTLs affecting Submax BP on chromosomes 8q and 10q in whites and on chromosomes 10q, 11q, and 18p in blacks. Moreover, suggestive linkages were detected in several regions in blacks and whites. None of the evidence for any QTL was consistent between the 2 race groups.

The strongest evidence of linkage was detected on chromosome 8, where the most distal marker (D8S373) on the long arm yielded a lod score of 2.36 for SBP50 training response in whites. In blacks, the same marker showed a suggestive linkage with baseline DBP80. The area harbors several potential candidate genes for BP regulation. Perhaps the most interesting one is the CYP11B1/CYP11B2 locus.

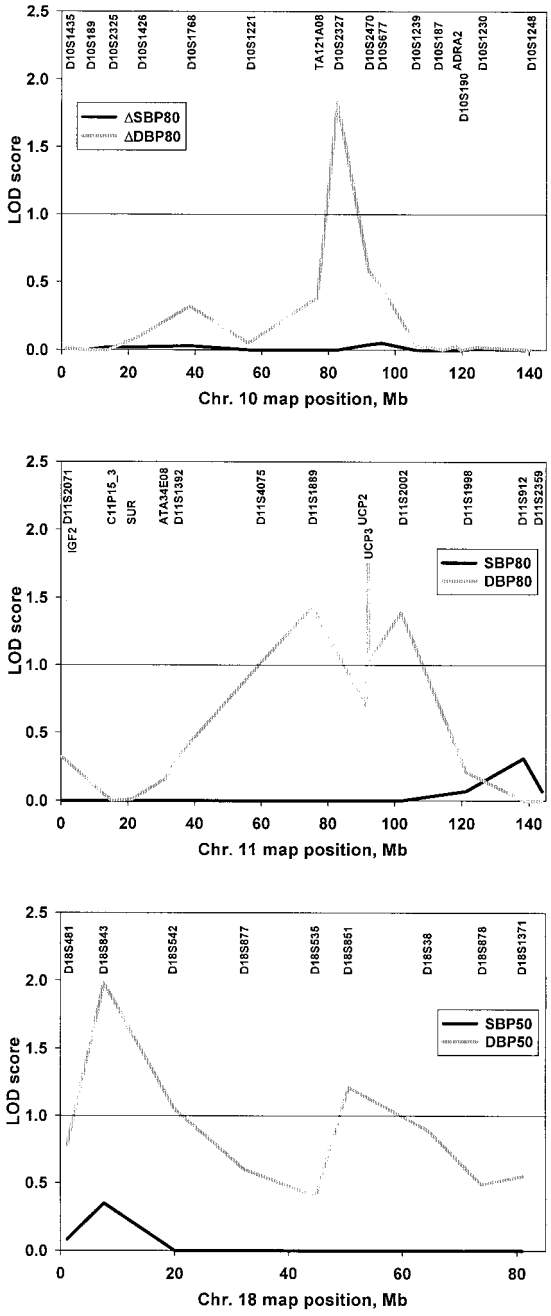

Figure 2. Overview of the multipoint linkage results for chromosomes 10 (SBP80 and DBP80 training responses), 11 (baseline SBP80 and DBP80), and 18 (baseline SBP50 and DBP50) in blacks of the HERITAGE Family Study. IGF2 indicates insulin-like growth factor 2; SHR, sulfonylurea receptor; UCP2, uncoupling protein 2; and UCP3, uncoupling protein 3.

TABLE 3. Promising ($P<0.0023$) and Suggestive ($P<0.01$) Multipoint (SEGPATH) and Corresponding Single-Point (SIBPAL) Linkages With Submax BP Phenotypes in the Sedentary State and in Response to Endurance Training in Blacks

Marker	Chromosome	Map Position, Mb	Trait	SEGPATH Lod	SEGPATH *P*	SIBPAL *P*
D2S1400	2p22-p25	14.900	DBP50	1.49	0.0044	0.007
D6S1040	6q21-q23	128.160	SBP80	1.27	0.0077	0.058
LEP	7q31.3	134.408	SBP80	1.24	0.0084	0.055
D7S2195	7q31-qter	157.995	SBP80	1.47	0.0046	0.007
D7S3070	7q35-q36	162.945	SBP80	1.25	0.0082	0.080
NOS3	7q36	164.257	SBP80	1.18	0.0097	0.857
D8S373	8q21	154.102	DBP80	1.39	0.0057	0.001
D10S2327	10q21-q23	82.723	ΔDBP80	1.83	0.0019	0.002
D10S2470	10q21-q24	92.113	DBP80	1.26	0.0079	0.156
D10S677	10q23-q24	96.068	DBP80	1.27	0.0079	0.001
D11S2071	11p15.5	0.294	DBP50	1.51	0.0042	0.016
IGF2	11p15.5	0.661	DBP50	1.43	0.0051	0.064
D11S1889	11q12-q13	75.347	DBP80	1.43	0.0051	0.007
UCP3	11q13-q21	92.068	DBP80	1.74	0.0023	0.042
D11S2002	11q21-q23	101.962	DBP80	1.39	0.0056	0.0002
GNB3	12p13	8.216	DBP80	1.23	0.0087	0.255
D12S391	12p12-p13	11.989	DBP80	1.21	0.009	0.282
D12S1301	12p12-p13	44.504	SBP80	1.44	0.005	0.043
D15S657	15q26	104.608	SBP80	1.57	0.0035	0.032
D16S3253	16q12-q13	64.632	SBP80	1.28	0.0076	0.010
D17S2196	17p11.2	25.710	SBP80	1.28	0.0076	0.013
D17S1294	17cen-q12	28.318	SBP80	1.63	0.0031	0.005
D18S843	18p11.2	7.602	DBP50	1.98	0.0012	0.007
D18S851	18q21.1	50.612	DBP50	1.21	0.009	0.151

All baseline phenotypes are adjusted for age, gender, and baseline BMI. Training response (Δ) phenotypes are adjusted also for baseline value of the response phenotype.

LEP indicates leptin; NOS3, endothelial NO synthase; and GNB3, guanine nucleotide-binding protein β-3.

CYP11B1 encodes a steroid 11β-hydroxylase enzyme, which catalyzes the terminal step of cortisol biosynthesis. CYP11B2 encodes a related enzyme, aldosterone synthase, which has, in addition to steroid 11β-hydroxylase activity, the 18-hydroxylase and 18-oxidase activities necessary for the final steps of aldosterone synthesis. Mutations in CYP11B1 and CYP11B2 genes lead to a hypertensive form of congenital adrenal hyperplasia[32] and various forms of aldosterone synthase deficiencies characterized by hypotension,[33] respectively. In addition, unequal recombination between these genes causes hypertensive disorder of glucocorticoid-suppressible hyperaldosteronism.[34] To identify the gene(s) contributing to the linkage signals, however, it is necessary to define the QTLs more precisely, first with additional microsatellite markers and linkage analyses, then with linkage disequilibrium tests using single nucleotide polymorphisms, and finally, with resequencing of the strongest positional candidate genes.[35] This approach will be used also for the QTLs reported in the present study.

A single genome-wide scan has a limited power to provide conclusive evidence for QTLs affecting BP phenotypes. Therefore, it is crucial to look for consistent trends across different studies to evaluate the true potential of genomic regions to harbor candidate genes. Unfortunately, there are no other genome-wide scans available for exercise BP phenotypes, but comparison of the present results with the previous resting BP scans reveals some common regions. For example, the D2S1334 marker that was linked with baseline SBP80 in whites in the present study also showed a suggestive linkage with resting SBP in the Genetic Epidemiology Network of Atherosclerosis (GENOA) cohort.[6] Similarly, marker D15S657 was linked with baseline SBP80 in blacks of the HERITAGE Family Study, and the same marker was the nearest one to a resting DBP QTL in a Chinese cohort.[7] In addition, a nearby marker (D15S652) was linked with resting SBP in the GENOA cohort,[6] and another marker (D15S211) further upstream identified a QTL for baseline DBP80 in whites of the HERITAGE Family Study. Marker D14S283, located near the angiogenin locus on the short arm of chromosome 14, showed suggestive linkage with baseline SBP80 in the white cohort of the HERITAGE Family Study and with resting SBP in the Quebec Family Study.[8] Finally, 2

markers at and near the ADRB2 locus showed suggestive evidence of linkage with the DBP50 training response in whites. In the GENOA network cohort, a QTL for resting BP was also detected at 5q,[6] and further positional analyses revealed the ADRB2 locus to be responsible for the signal.[36]

The prevalence of hypertension has been shown to be higher among blacks than whites,[20] and it has been suggested that the mechanisms leading to hypertension in blacks and whites may be different and that some of this variation may have a genetic origin.[37] The majority of the subjects in the HERITAGE Family Study were normotensive, but nevertheless, both resting and exercise BPs at baseline were higher in blacks than in whites.[38] The results of the present study indicate that the chromosomal regions harboring genes that affect exercise BP phenotypes may be different in blacks and whites. In some cases, however, a QTL was detected at the same region but for different phenotypes (ie, D10S677 with DBP80 in blacks and SBP80 in whites) or for the same phenotype but with an adjacent marker (ie, SBP80 with D16S264 in whites and D16S3253 in blacks). Interestingly, in Chinese families, a QTL for resting SBP was detected approximately between these 2 markers in chromosome 16.[7]

In summary, these data from the HERITAGE Family Study provide evidence of several genomic regions that potentially contain genes affecting submaximal exercise BP phenotypes in the sedentary state and in response to endurance training in blacks and whites. The linkage signals were detected in blacks and whites at different genomic regions, which may reflect interactions between QTLs and environmental factors. The exercise BP QTLs overlap, to some extent, those reported previously for resting BP phenotypes. These genomic regions should be explored further to identify the genes and characterize the mutations that contribute to observed interindividual variation in exercise BP phenotypes.

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References

1. Williams RR, Hunt SC, Hasstedt SJ, Hopkins PN, Wu LL, Berry TD, Stults BM, Barlow GK, Schumacher MC, Lifton RP, et al. Are there interactions and relations between genetic and environmental factors predisposing to high blood pressure? *Hypertension*. 1991;18(suppl I):I-29–I-37.
2. Cheng LS, Carmelli D, Hunt SC, Williams RR. Evidence for a major gene influencing 7-year increases in diastolic blood pressure with age. *Am J Hum Genet*. 1995;57:1169–1177.
3. Cheng LS, Livshits G, Carmelli D, Wahrendorf J, Brunner D. Segregation analysis reveals a major gene effect controlling systolic blood pressure and BMI in an Israeli population. *Hum Biol*. 1998;70:59–75.
4. Perusse L, Moll PP, Sing CF. Evidence that a single gene with gender- and age-dependent effects influences systolic blood pressure determination in a population-based sample. *Am J Hum Genet*. 1991;49:94–105.
5. Corvol P, Persu A, Gimenez-Roqueplo AP, Jeunemaitre X. Seven lessons from two candidate genes in human essential hypertension: angiotensinogen and epithelial sodium channel. *Hypertension*. 1999;33:1324–1331.
6. Krushkal J, Ferrell R, Mockrin SC, Turner ST, Sing CF, Boerwinkle E. Genome-wide linkage analyses of systolic blood pressure using highly discordant siblings. *Circulation*. 1999;99:1407–1410.
7. Xu X, Rogus JJ, Terwedow HA, Yang J, Wang Z, Chen C, Niu T, Wang B, Xu H, Weiss S, et al. An extreme-sib-pair genome scan for genes regulating blood pressure. *Am J Hum Genet*. 1999;64:1694–1701.
8. Rice T, Rankinen T, Province MA, Chagnon YC, Perusse L, Borecki IB, Bouchard C, Rao DC. Genome-wide linkage analysis of systolic and diastolic blood pressure: the Quebec Family Study. *Circulation*. 2000;102:1956–1963.
9. Hsueh WC, Mitchell BD, Schneider JL, Wagner MJ, Bell CJ, Nanthakumar E, Shuldiner AR. QTL influencing blood pressure maps to the region of PPH1 on chromosome 2q31–34 in old order Amish. *Circulation*. 2000;101:2810–2816.
10. Sharma P, Fatibene J, Ferraro F, Jia H, Monteith S, Brown C, Clayton D, O'Shaughnessy K, Brown MJ. A genome-wide search for susceptibility loci to human essential hypertension. *Hypertension*. 2000;35:1291–1296.
11. Perola M, Kainulainen K, Pajukanta P, Terwilliger JD, Hiekkalinna T, Ellonen P, Kaprio J, Koskenvuo M, Kontula K, Peltonen L. Genome-wide scan of predisposing loci for increased diastolic blood pressure in Finnish siblings. *J Hypertens*. 2000;18:1579–1585.
12. Levy D, DeStefano AL, Larson MG, O'Donnell CJ, Lifton RP, Gavras H, Cupples LA, Myers RH. Evidence for a gene influencing blood pressure on chromosome 17: genome scan linkage results for longitudinal blood pressure phenotypes in subjects from the Framingham heart study. *Hypertension*. 2000;36:477–483.
13. Pankow JS, Rose KM, Oberman A, Hunt SC, Atwood LD, Djousse L, Province MA, Rao DC. Possible locus on chromosome 18q influencing postural systolic blood pressure changes. *Hypertension*. 2000;36:471–476.
14. Matthews CE, Pate RR, Jackson KL, Ward DS, Macera CA, Kohl HW, Blair SN. Exaggerated blood pressure response to dynamic exercise and risk of future hypertension. *J Clin Epidemiol*. 1998;51:29–35.
15. American College of Sports Medicine. Position stand: physical activity, physical fitness, and hypertension. *Med Sci Sports Exerc*. 1993;25:i–x.
16. Cheng LS, Carmelli D, Hunt SC, Williams RR. Segregation analysis of cardiovascular reactivity to laboratory stressors. *Genet Epidemiol*. 1997;14:35–49.
17. Leon AS, An P, Rice T, Pérusse L, Gagnon J, Wilmore JH, Skinner JS, Rao DC, Bouchard C. Genetic determinants of exercise heart rate and blood pressure in the sedentary state: results from the HERITAGE Family. *Ann Behav Med*. In press.
18. van den Bree MB, Schieken RM, Moskowitz WB, Eaves LJ. Genetic regulation of hemodynamic variables during dynamic exercise: the MCV twin study. *Circulation*. 1996;94:1864–1869.
19. Bouchard C, Leon AS, Rao DC, Skinner JS, Wilmore JH, Gagnon J. The HERITAGE family study: aims, design, and measurement protocol. *Med Sci Sports Exerc*. 1995;27:721–729.
20. The sixth report of the Joint National Committee on prevention, detection, evaluation, and treatment of high blood pressure. *Arch Intern Med*. 1997;157:2413–2446.
21. Skinner JS, Wilmore KM, Krasnoff JB, Jaskolski A, Jaskolska A, Gagnon J, Province MA, Leon AS, Rao DC, Wilmore JH, et al. Adaptation to a standardized training program and changes in fitness in a large, heterogeneous population: the HERITAGE Family Study. *Med Sci Sports Exerc*. 2000;32:157–161.
22. Rice T, Borecki IB, Bouchard C, Rao DC. Commingling analysis of regional fat distribution measures: the Quebec family study. *Int J Obes Relat Metab Disord*. 1992;16:831–844.
23. Chagnon YC, Borecki IB, Perusse L, Roy S, Lacaille M, Chagnon M, Ho-Kim MA, Rice T, Province MA, Rao DC, et al. Genome-wide search for genes related to the fat-free body mass in the Quebec family study. *Metabolism*. 2000;49:203–207.
24. Province MA, Rice T, Borecki IB, Gu C, Rao DC. A multivariate and multilocus variance components approach using structural relationships

to assess quantitative trait linkage via SEGPATH. *Genet Epidemiol*. In press.
25. Province MA, Rao DC. General purpose model and a computer program for combined segregation and path analysis (SEGPATH): automatically creating computer programs from symbolic language model specifications. *Genet Epidemiol*. 1995;12:203–219.
26. Kruglyak L, Lander ES. Complete multipoint sib-pair analysis of qualitative and quantitative traits. *Am J Hum Genet*. 1995;57:439–454.
27. Self GA, Liang KY. Asymptotic properties of maximum likelihood estimators and likelihood ratio tests under nonstandard conditions. *J Am Stat Assoc*. 1987;82:605–610.
28. Rao DC, Province MA. The future of path analysis, segregation analysis, and combined models for genetic dissection of complex traits. *Hum Hered*. 2000;50:34–42.
29. Amos CI, Elston RC, Wilson AF, Bailey-Wilson JE. A more powerful robust sib-pair test of linkage for quantitative traits. *Genet Epidemiol*. 1989;6:435–449.
30. Haseman JK, Elston RC. The investigation of linkage between a quantitative trait and a marker locus. *Behav Genet*. 1972;2:3–19.
31. *S.A.G.E. Statistical Analysis for Genetic Epidemiology* [computer program]. Release 3.1. Cleveland, Ohio: Rammelkamp Center for Education and Research, MetroHealth Campus, Case Western Reserve University; 1998.
32. Curnow KM, Slutsker L, Vitek J, Cole T, Speiser PW, New MI, White PC, Pascoe L. Mutations in the CYP11B1 gene causing congenital adrenal hyperplasia and hypertension cluster in exons 6, 7, and 8. *Proc Natl Acad Sci U S A*. 1993;90:4552–4556.
33. Pascoe L, Curnow KM, Slutsker L, Rosler A, White PC. Mutations in the human CYP11B2 (aldosterone synthase) gene causing corticosterone methyloxidase II deficiency. *Proc Natl Acad Sci U S A*. 1992;89:4996–5000.
34. Lifton RP. Molecular genetics of human blood pressure variation. *Science*. 1996;272:676–680.
35. Boerwinkle E, Hixson JE, Hanis CL. Peeking under the peaks: following up genome-wide linkage analyses. *Circulation*. 2000;102:1877–1878.
36. Bray MS, Krushkal J, Li L, Ferrell R, Kardia S, Sing CF, Turner ST, Boerwinkle E. Positional genomic analysis identifies the B2-adrenergic receptor gene as a susceptibility locus for human hypertension. *Circulation*. 2000;101:2877–2882.
37. O'Donnell CJ, Kannel WB. Is there a racial predisposition to hypertension? *Hypertension*. 1998;32:817–819.
38. Wilmore JH, Stanforth PR, Gagnon J, Rice T, Mandel S, Leon AS, Rao DC, Skinner JS, Bouchard C. Heart rate and blood pressure changes with endurance training: the HERITAGE Family Study. *Med Sci Sports Exerc*. 2001;33:107–116.