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TGF-β_1 gene-race interactions for resting and exercise blood pressure in the HERITAGE Family Study

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Rivera, Miguel A., Marcos Echegaray, Tuomo Rankinen, Louis Pérusse, Treva Rice, Jacques Gagnon, Arthur S. Leon, James S. Skinner, Jack H. Wilmore, D. C. Rao, and Claude Bouchard. TGF-β_1 gene-race interactions for resting and exercise blood pressure in the HERITAGE family study. *J Appl Physiol* 91: 1808–1813, 2001.—We examined the possible association between a transforming growth factor (TGF)-β_1 gene polymorphism in codon 10 and blood pressure (BP) at rest, in acute response to exercise in the pretrained (sedentary) and trained states, as well as in its training response (Δ) to 20 wk of endurance exercise. Subjects were 257 black and 480 white, healthy sedentary normotensive subjects from the HERITAGE Family Study. The polymorphism was detected by polymerase chain reaction and digestion with the Msp A1 I endonuclease yielding a wild (leucine-10) and a mutant (proline-10) allele. Resting and exercise [50 W plus 60, 80, and 100% maximal oxygen consumption ($\dot{V}O_{2\,max}$)] BP were determined before and after training. Significant ($P < 0.05$) race-genotype interactions were found for systolic (S) BP in both the sedentary and trained states. Among whites but not in blacks, the TGF-β_1 genotypes were significantly ($P < 0.05$) associated with sedentary-state SBP at rest, at 50 W, and at 60 and 100% $\dot{V}O_{2\,max}$ as well as with trained-state SBP at rest and at 80 and 100% $\dot{V}O_{2\,max}$. The leucine-10 homozygotes had significantly ($P < 0.05$) lower SBP than proline-10 homozygotes. ΔBP was not significantly associated with genotype. These results support the hypothesis of an association between the TGF-β_1 marker in codon 10 and SBP at rest and in response to acute exercise in whites but not in blacks.

genetics; polymerase chain reaction; genetic variation; DNA; endurance; transforming growth factor-β_1

IT IS WIDELY ACCEPTED that blood pressure (BP) regulation is influenced by several environmental and genetic factors (6). Genetic epidemiology studies of BP indicate familial aggregation for both resting systolic (S) and diastolic (D) BP (23, 36, 37), with maximal heritability estimates ranging from 30 to 70% (6, 7, 15, 36). Regarding exercise BP, unpublished data from the HERITAGE Family Study reveal maximal heritability estimates of 48–52% (A. S. Leon, P. An, T. Rice, L. Pérusse, J. Gagnon, J. H. Wilmore, J. S. Skinner, D. C. Rao, and C. Bouchard, unpublished observations). However, not much is known about the actual molecular mechanisms underlying the physiological basis of acute BP response to exercise or its chronic adaptation to endurance exercise training. One of the main aims of the HERITAGE Family Study is to study a panel of candidate genes and phenotypes of cardiovascular and metabolic responses to aerobic exercise training (5). The present report considers a candidate gene potentially related to phenotypes of cardiovascular response to exercise: transforming growth factor (TGF)-β_1.

TGF-β_1 is a multifunctional protein that plays an important role in the modulation of cellular growth and differentiation (13) and in the production and degradation of extracellular matrix (ECM) proteins (24) in a wide variety of cell types. It is initially synthesized as a 390-amino acid precursor protein and then is secreted as a latent complex. This latent complex can be activated by extreme pH, heat, or proteolytic enzymes (14). The TGF-β_1 gene is encoded on chromosome l9ql3.1-ql3.3 and displays seven exons (11, 14). TGF-β_1 has attracted attention because of its possible role in cardiovascular pathophysiology (1, 8, 9, 12, 21, 34, 39) and target-organ complications of hypertension (21, 26). Higher concentrations of circulating TGF-β_1 were

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observed in hypertensive compared with normotensive subjects among both blacks and whites (33). Similarly, significant and positive correlations between circulating levels of TGF-β_1 and resting SBP, DBP, and mean arterial pressure were observed in end-stage renal disease patients (21). TGF-β_1 may influence BP by promoting the deposition of ECM proteins on vessel walls, thereby affecting its stiffness and compliance (24). TGF-β_1 may also affect BP because of its ability to *1*) stimulate the synthesis of the vasoconstrictor agent endothelin-1 (ET-1) (19), *2*) increase renin secretion (4), and *3*) inhibit the production of the vasodilator nitric oxide (NO) (29).

Significant associations between various polymorphisms of the TGF-β_1 gene and aspects related to BP regulation have been shown. Among them, a DNA polymorphism in the 5′ promoter region of the TGF-β_1 gene (C-509T) has recently been shown to be associated with plasma concentrations of the TGF-β_1 protein. In addition, a significant association between a TGF-β_1 polymorphism in codon 25 (arginine → proline) and resting SBP of normotensive individuals has also been reported (9). In that study, carriers of the rare proline-25 allele had a resting SBP 5–10 mmHg lower than that of noncarriers. Furthermore, another study found that, among hypertensive subjects, there was a higher percentage of homozygotes for the arginine-25 allele compared with normotensive subjects (21).

Another known polymorphism on the TGF-β_1 gene is found at codon 10 (leucine → proline) on the signal peptide region (9). The heterozygosity index (H = 0.49) of this polymorphism is greater than that of codon 25 (H = 0.15) making it a more informative site. A previous study on this polymorphic site reported a higher frequency of the proline-10 allele in whites than in blacks (33). However, the authors did not look into a possible association between genotypes for that locus and BP. Therefore, the present study examined the hypothesis of an association between the TGF-β_1 gene polymorphism in exon 1, codon 10 (leucine → proline), and BP at rest and in response to acute exercise in the sedentary and trained states, as well as in the training response (Δ) to an endurance-training program in the HERITAGE Family Study cohort.

METHODS

Subjects. Details of the HERITAGE Family Study aims, experimental design, and measurement protocols have been presented in detail in a previous publication (5). The sample for the present study consists of 737 (257 blacks and 480 whites) healthy, sedentary normotensive subjects from 105 black and 99 white nuclear families. Subjects met a series of inclusion criteria, including SBP of <160 mmHg and DBP of ≤99 mmHg. The study protocol had been previously approved by each of the Institutional Review Boards of the HERITAGE Family Study research consortium. Written, informed consent was obtained from each participant. Race-specific values for the physical characteristics are presented in Table 1.

BP and exercise test methodology. BP measures were taken in the morning with the use of the Colin (San Antonio, TX) STBP-780 automated BP unit as described earlier (5). Proper cuff size (child, regular adult, or large adult) was determined by using recent guidelines (17). Subjects were seated in a reclining chair in a semirecumbent position. The laboratory was quiet, with little light and a room temperature between 23 and 26°C. After a rest period of at least 5 min, four BP readings were taken at 2-min intervals. The retained BP was the mean of three valid measurements. Subjects reported to the laboratory on a second day within ±2 h of the time of the first day, and the same procedures were repeated.

Table 1. *Subjects' physical characteristics*

Group	Age, yr	Body Mass, kg	BMI, kg/m^2	Resting SBP, mmHg	Resting DBP, mmHg
Blacks (n = 257)	34.1 ± 11.8	77.8 ± 17.5	28.0 ± 5.9	123 ± 12	73 ± 8
Whites (n = 480)	35.9 ± 14.6	75.6 ± 17.4	25.9 ± 5.0	116 ± 11	66 ± 8

Values are means ± SD. BMI, body mass index; SBP, systolic blood pressure; DPP, diastolic blood pressure.

Subjects completed a total of three exercise tests, each on a different day, both before and after training: a maximal test (Max), a submaximal test (Submax), and a submaximal-to-maximal test (Submax/Max) (32). All exercise tests were conducted on a cycle ergometer (SensorMedics Ergo-Metrics 800S, Yorba Linda, CA). Subjects completed the initial Max by using a graded exercise test protocol, starting at 50 W for 3 min. The rate of work was then increased by 25 W every 2 min thereafter to the point of exhaustion. By using the results of this initial Max, subjects then performed Submax on a second day exercising at 50 W and 60% of their initial maximal oxygen consumption ($\dot{V}O_{2\ max}$). Subjects exercised for ~12 min at each work rate, with a 4-min period of seated rest between work rates. Submax/Max was then performed on a third day, starting with the Submax protocol, i.e., 50 W and 60% of initial $\dot{V}O_{2\ max}$, and progressing to 80% $\dot{V}O_{2\ max}$ for 3-min and maximal level of exertion (100% $\dot{V}O_{2\ max}$).

During the Submax and Submax/Max, BP values were obtained at 50 W and at 60% of initial $\dot{V}O_{2\ max}$, whereas peak BP was obtained at the very end of Max and Submax/Max. The values used in this paper are the mean of the results obtained during and for Submax/Max and Max, before and also after the training program. BP at 80% of initial $\dot{V}O_{2\ max}$ was obtained during Submax/Max. For all exercise tests, oxygen production, carbon dioxide production, expiratory minute ventilation, and the respiratory exchange ratio were determined every 20 s and reported as a rolling average of the three most recent 20-s values by using a SensorMedics 2900 metabolic measurement cart (Yorba Linda, CA). $\dot{V}O_{2\ max}$ was defined as the peak value obtained during the test. Heart rate was determined by electrocardiogram and the Colin STBP-780 instrument, and values were recorded during the last 15 s of each stage of Max and once steady state had been achieved at each of the submaximal work rates during Submax/Max. Further details concerning BP and exercise tests methodology can be obtained from recent publications (32, 38).

Endurance exercise training program. Participants trained under supervision and were required to complete 60 training sessions within 20 wk. Only subjects who completed at least 57 sessions (>95% of target) were defined as compliers and used for investigating the training response. Briefly, subjects exercised following a standardized protocol that required the use of a cycle ergometer (Universal Aerobicycle IV, Cedar Rapids, IA) in the sitting position. The cycle ergometer was

Table 2. *Race-specific allele and genotype frequencies*

	Allele Frequencies*		Genotype Frequencies†		
	Leu 10	Pro 10	Leu 10/Leu 10 (n = 82)	Leu 10/Pro 10 (n = 145)	Pro 10/Pro 10 (n = 39)
Blacks (n = 76)	0.58	0.42	0.32	0.52	0.16
Whites (n = 190)	0.58	0.42	0.31	0.55	0.14
Total (n = 266)	0.58	0.42	0.31	0.54	0.15

Frequencies are for Msp A1 I polymorphism in exon 1 codon 10 of transforming growth factor (TGF)-β, for biologically unrelated, sedentary black and white parents of the HERITAGE Family Study. Leu 10, leucine-10 allele; Pro 10, proline-10 allele. *χ^2 = 0.0, degrees of freedom (df) = 1, P = 1.00; †χ^2 = 0.23, df = 2, P = 0.89.

connected to a computer system (Universal Mednet, Cedar Rapids, IA) that adjusted the power output of the ergometers to maintain constant training heart rates. During the initial 2 wk, subjects trained at a heart rate associated with 55% of each subject's $\dot{V}O_{2\,max}$ for 30 min per session. This was gradually increased to 50 min by the end of *week 14* at a heart rate associated with 75% of $\dot{V}O_{2\,max}$. These levels of intensity and duration were maintained through the remaining 6 wk. Further details concerning the training program can be found in previous publications (32, 38).

Genotype determinations. DNA was extracted from lymphoblastoid cell lines after a standard protocol of digestion by proteinase K and purification with phenol-chloroform. PCR amplification targeted a region [1,874–2,175 base pairs (bp)] in exon 1 covering codon 10, which includes the polymorphic site at *bp 2,005* [T → C (leucine → proline)]. The primers were as follows: 5′-TTC-TCC-CTG-AGG-ACC-TCA-GTC-TTC-3′ (sense) and 5′-TGG-GTT-TCC-ACC-ATT-AGC-ACG-3′ (antisense). A PCR product of 283 bp was generated. The total volume of the PCR was 25 μl of a reaction mixture containing 10 mM Tris·HCl (pH 8.3), 50 mM KCl, 1.5 mM $MgCl_2$, 0.001% gelatin, 200 μM of each dATP, dCTP, dGTP, and dTTP, 0.3 μM of each forward and backward primers, 0.75 unit of *Taq* polymerase (Perkin Elmer Cetus, Norwalk, CT), and 10 ng of DNA. The amplification protocol was *1*) one cycle of denaturation at 95°C for 5 min; *2*) 30 cycles of denaturation at 95°C for 30 s, annealing at 60°C for 30 s, and extension at 72°C for 45 s; and *3*) one final 5-min elongation cycle at 72°C. Preventive contamination measures were taken by the inclusion of PCR reaction mixture without DNA (negative control) in every run of amplification.

The PCR product was digested with 10 units of Msp A1 I. Restriction digest conditions were those recommended by the enzyme manufacturer (New England Biolabs, Mississauga, Ontario, Canada). The resulting fragments were separated by horizontal electrophoresis on 4% agarose gels. Each gel was run for 60 min at 150 mA while refrigerated at 10°C, stained with ethidium bromide, and photographed under ultraviolet transmitted lights. The ΦX174 DNA, digested with *Hae*III, was used as a length marker to estimate the size of the digested DNA fragments. The allele without the mutation (145 bp) was designated as leucine-10, whereas the allele with the point variation (T → C; leucine → proline; 133 bp) site was designated as proline-10.

Statistical analysis. A χ^2 test was used to examine gender differences in allele and genotype frequencies and to determine whether the observed genotype frequencies were in Hardy-Weinberg equilibrium. Associations between phenotypes and genotypes were analyzed using a MIXED procedure in the SAS software package (SAS Institute, Cary, NC) for personal computer (version 6.12) (30). Nonindependence among family members was adjusted for using a "sandwich estimator," which asymptotically yields the same parameter estimates as ordinary least-squares or regression methods, but the standard errors and consequently hypothesis tests are adjusted for the dependencies. The method is general, assuming the same degree of dependency among all members within a family. Possible race-by-genotype interaction effects

Table 3. *Sedentary-state resting and exercise BP by TGF-β_1 Msp A1 I polymorphism (codon 10) genotype in black and white subjects of the HERITAGE Family Study*

	Genotype						
	Blacks			Whites			Race-by-Genotype Interaction
	Leu 10/Leu 10	Leu 10/Pro 10	Pro 10/Pro 10	Leu 10/Leu 10	Leu 10/Pro 10	Pro 10/Pro 10	
				SBP			
Rest	125.5 ± 1.5	126.7 ± 1.5	124.5 ± 1.6	115.1 ± 1.1	115.0 ± 0.8	120.1 ± 1.1*	P = 0.03
50 W	157.0 ± 2.2	155.9 ± 2.0	156.1 ± 3.0	142.7 ± 1.8	145.5 ± 0.8	150.4 ± 2.1*	NS
60% $\dot{V}O_{2max}$	171.8 ± 2.3	168.7 ± 2.0	169.3 ± 3.0	164.2 ± 1.9	166.3 ± 1.8	169.9 ± 2.3†	NS
80% $\dot{V}O_{2max}$	192.5 ± 3.2	186.2 ± 2.6	188.5 ± 3.8	178.6 ± 2.0	181.2 ± 1.9	184.2 ± 2.1	P < 0.04
$\dot{V}O_{2max}$	201.7 ± 3.0	200.2 ± 2.9	205.2 ± 3.3	194.6 ± 2.4	197.4 ± 2.4	201.5 ± 2.8†	NS
				DBP			
Rest	73.7 ± 0.9	74.4 ± 0.9	73.0 ± 1.3	63.8 ± 0.8	66.4 ± 0.6	66.7 ± 0.5*	NS
50 W	80.7 ± 1.1	81.6 ± 0.9	79.4 ± 1.3	71.5 ± 0.9	71.1 ± 0.7	73.2 ± 1.2	NS
60% $\dot{V}O_{2max}$	82.3 ± 1.1	81.9 ± 0.9	79.9 ± 1.5	72.0 ± 1.1	72.2 ± 0.9	73.7 ± 1.5	NS
80% $\dot{V}O_{2max}$	82.7 ± 1.5	84.0 ± 1.2	82.4 ± 2.1	75.2 ± 1.3	75.4 ± 1.0	76.6 ± 1.6	NS
$\dot{V}O_{2max}$	88.3 ± 1.3	88.8 ± 1.4	86.6 ± 2.1	82.3 ± 1.3	82.9 ± 1.3	82.5 ± 1.8	NS

Values are means ± SE. BP, blood pressure; NS, not significant. *Significantly different from whites Leu 10/Leu 10 and Leu 10/Pro 10 (P < 0.05). †Significantly different from whites Leu 10/Leu 10 (P < 0.05).

Table 4. *Trained-state resting and exercise BP by TGF-β_1 Msp A1 I polymorphism (codon 10) genotype in black and white subjects of the HERITAGE Family Study*

	Genotype						
	Blacks			Whites			Race-by-Genotype Interaction
	Leu 10/Leu 10	Leu 10/Pro 10	Pro 10/Pro 10	Leu 10/Leu 10	Leu 10/Pro 10	Pro 10/Pro 10	
				SBP			
Rest	122.8 ± 1.6	121.9 ± 1.1	121.6 ± 2.3	114.1 ± 1.3†	116.1 ± 1.1†	118.3 ± 1.3†	NS
50 W	146.9 ± 2.1	146.1 ± 1.6	145.2 ± 2.9	139.1 ± 1.8	139.6 ± 1.7	142.3 ± 2.1	NS
60% $\dot{V}O_{2max}$	166.9 ± 2.4	166.2 ± 2.1	166.4 ± 3.7	165.2 ± 2.3	166.8 ± 2.0	169.7 ± 2.3	NS
80% $\dot{V}O_{2max}$	189.8 ± 2.7	187.7 ± 2.1	187.3 ± 4.1	184.4 ± 2.3	186.6 ± 2.2	191.9 ± 2.6*	NS
$\dot{V}O_{2max}$	213.7 ± 3.2	207.4 ± 2.6	209.4 ± 3.9	200.0 ± 2.4†	205.4 ± 2.4†	210.5 ± 2.7†	$P = 0.007$
				DBP			
Rest	72.6 ± 1.2	73.8 ± 0.9	72.5 ± 1.7	64.6 ± 0.9	65.9 ± 0.7	66.1 ± 1.0	NS
50 W	72.8 ± 1.2	73.7 ± 1.0	74.3 ± 1.6	68.0 ± 0.9	68.2 ± 0.8	68.8 ± 1.1	NS
60% $\dot{V}O_{2max}$	74.6 ± 1.2	74.2 ± 1.0	73.2 ± 1.8	67.8 ± 1.1	67.4 ± 0.9	67.8 ± 1.4	NS
80% $\dot{V}O_{2max}$	76.5 ± 1.6	77.4 ± 1.2	76.2 ± 2.0	73.1 ± 1.4	72.5 ± 1.1	71.9 ± 1.8	NS
$\dot{V}O_{2max}$	83.8 ± 2.0	84.4 ± 1.3	81.4 ± 2.6	77.0 ± 1.6	78.2 ± 0.8	78.0 ± 2.0	NS

Values are means ± SE. *Significantly different from whites Leu 10/Leu 10 and Leu 10/Pro 10 ($P < 0.05$); †Significantly different from other two genotypes in whites ($P < 0.05$).

were tested by introducing an interaction term in the MIXED model in addition to the genotype and race main effects. If the interaction term was significant, association analyses were performed separately by race. Baseline phenotypes were adjusted for the effects of age, gender, and body mass index (BMI), whereas posttraining values were adjusted for age, gender, and posttraining BMI. ΔBP (ΔBP = pretraining BP − posttraining BP) was adjusted for age, gender, baseline BMI, and baseline value of the phenotype. All phenotypes were regressed on up to a third-degree polynomial in age. In addition to the fully adjusted models, analyses were also performed by adjusting for each covariate separately and by using various combinations of covariates. The results of all of these analyses were globally identical to those of the full model, and, therefore, only the data from the full model are reported.

RESULTS

χ^2 Tests revealed that, in both races, the allele and genotype frequencies were not significantly ($P > 0.05$) different between men and women. Genotypic distributions for blacks and whites were in agreement ($P > 0.05$) with those expected under Hardy-Weinberg equilibrium (Table 2). The allele with the point variation (proline-10) was less frequent. Because no significant genotype-gender interaction effect was detected (not shown) for the variables under study and given that there were similar allelic and genotypic frequency distributions in men and women, the data for both genders were pooled for subsequent analysis. Because significant ($P < 0.05$) race-genotype interactions were found for sedentary-state SBP at rest and 80% $\dot{V}O_{2\,max}$ (Table 3) and at 100% $\dot{V}O_{2\,max}$ in the trained state (Table 4), analyses were performed within each race.

Among whites, the TGF-β_1 genotypes were significantly ($P < 0.05$) associated with sedentary-state SBP at rest as well as at exercise intensities of 50 W and 60 and 100% $\dot{V}O_{2\,max}$ (Table 3). At all these intensities, leucine-10 homozygotes had significantly ($P < 0.05$) lower SBP than proline-10 homozygotes. In contrast, among blacks, no genotypic effect on sedentary-state SBP was evident (Table 3). Significant associations between the TGF-β_1 genotypes and sedentary-state DBP were observed only among whites at rest (Table 3).

In the trained state (Table 4), TGF-β_1 genotypes were significantly ($P < 0.05$) associated with SBP at rest and 80 and 100% $\dot{V}O_{2\,max}$ among whites. Leucine-10 homozygotes had significantly lower SBP than both proline-10 homozygotes and leucine-10/proline-10 heterozygotes. However, among blacks, there was again no evidence of association between the genotypes and trained-state SBP at rest or at any exercise intensity (Table 4). Furthermore, in both races, no association between genotype and DBP was observed in the trained state (Table 4). Finally, neither ΔSBP (Table 5) nor ΔDBP was significantly associated with the TGF-β_1 genotypes.

DISCUSSION

The existence of interactions between racial background and BP phenotypes has been acknowledged for some time (3, 28, 35). However, information on the molecular and genetic basis of these racial differences and how they relate to exercise and exercise training

Table 5. *Δ for SBP by TGF-β_1 Msp A1 I polymorphism (codon 10) genotype in white subjects of the HERITAGE Family Study*

	Genotype			*P* value
	Leu 10/Leu 10	Leu 10/Pro 10	Pro 10/Pro 10	
ΔSBP				
Rest	−0.8 ± 0.6	−0.2 ± 0.4	−0.8 ± 0.8	0.57
50 W	−6.6 ± 0.8	−7.0 ± 0.6	−7.6 ± 1.1	0.75
60% $\dot{V}O_{2max}$	−0.8 ± 0.9	−0.4 ± 0.8	−0.4 ± 1.3	0.95
80% $\dot{V}O_{2max}$	4.2 ± 1.3	4.2 ± 1.1	6.2 ± 1.8	0.63
$\dot{V}O_{2max}$	6.6 ± 1.4	9.8 ± 1.1	11.4 ± 1.9	0.07

Values are means ± SE. Δ, Training response.

has been lacking. The most important finding of this study was the significant TGF-β_1 gene-race interaction for SBP at rest and during exercise. The interaction reported in this study and that recently reported by our laboratory (28) for the angiogenin gene are among the first to provide evidence that the genetic component of racial differences in BP acute response to exercise in the sedentary and trained states can be defined in terms of genes and DNA sequence variation.

Another relevant finding of the present study was the significant association between the TGF-β_1 genotypes and SBP measured at rest and at moderate as well as maximal exercise intensities among whites in the sedentary and trained states. It is noteworthy that whites' homozygotes for the common leucine-10 allele had significantly lower SBP than proline-10 homozygotes at rest and at exercise intensities of 50 W and 60 and 100% $\dot{V}o_{2\,max}$. These results suggest that either the TGF-β_1 gene polymorphism in codon 10 per se or a nearby polymorphism in the same gene or in another gene in linkage disequilibrium with it plays a role in the SBP acute response to submaximal and maximal exercise in sedentary and endurance-trained whites. Although significant associations between genotype and the SBP acute response to exercise were present in whites before and after training, the TGF-β_1 gene marker does not seem to contribute to individual differences in BP responses to endurance training because there were no significant interactions or genotypic effects on ΔSBP or ΔDBP in either race.

Different from the associations found among whites, in the present study, TGF-β_1 genotypes were not associated with SBP of blacks. A previous study of this polymorphism (33) reported that significant differences in allele and genotype frequencies existed between black and white subjects for the codon-10 polymorphism. Nonetheless, that study only used 44 black subjects, and the authors recognized that a larger study was necessary to establish whether racial differences in TGF-β_1 allele and genotype frequencies do exist. In contrast, the present study used a 75% larger sample (76 unrelated black subjects) and found no differences in the allele and genotype frequencies between races. The similarity in genotype frequency between races supports the notion of a true race-TGF-β_1 genotype interaction.

The novelty of our results highlights the importance of the choice of marker. Previous studies have reported significant associations between resting SBP and TGF-β_1 markers in the 5′ region (9) and codon 25 (9, 21) in whites (9, 21) as well as in blacks (21). In whites, the TGF-β_1 5′ region (+72) codon-10 and -25 markers are known to be in strong linkage disequilibrium ($P < 0.001$) (9). However, among the three markers, codon 10 is the most informative with a heterozygosity index of 0.49, whereas the other two are 0.15 or less.

It is known that increased vascular shear stress, which occurs during exercise, provokes the transcription and synthesis of endothelial TGF-β_1 (25). It has been postulated that TGF-β_1 could influence BP regulation by affecting NO, ET-1 and/or renin secretion, which may then modify the physiology of endothelial and vascular smooth muscle cells (10, 21, 22, 31). Early studies indicated that TGF-β_1 increased mRNA levels and secretion of ET-1 in a medium of vascular endothelial cells in vitro (18, 19). ET-1 is a potent vasoconstrictor produced by vascular endothelium (18, 19) and vascular smooth muscle cells (16). Its circulating levels have been shown to be related to hypertension and vascular remodeling (31). Another potential role of TGF-β_1 in modulating vascular tone and reactivity is through the inhibition of NO, a strong vasodilator (26). In addition, TGF-β_1 can affect vascular remodeling by influencing vascular smooth muscle cell growth (1) and by increasing the production of ECM proteins (2, 24). All of the above could link TGF-β_1 to reductions in vascular luminal diameter and distensibility and thus to an increase in peripheral vascular resistance (26), which could potentially explain the TGF-β_1 genotypic effects on SBP during exercise reported herein.

In conclusion, the present study provides support for the hypothesis of an association between a TGF-β_1 marker in codon 10 and SBP in response to acute exercise of moderate and maximal intensities in the sedentary and trained states in whites but not in blacks. The present findings support the notion that differences in resting and exercise BP are partially mediated by genetic mechanisms.

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