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G protein β3 polymorphism and hemodynamic and body composition phenotypes in the HERITAGE Family Study

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Rankinen, Tuomo, Treva Rice, Arthur S. Leon, James S. Skinner, Jack H. Wilmore, D. C. Rao, and Claude Bouchard. G protein β3 polymorphism and hemodynamic and body composition phenotypes in the HERITAGE Family Study. *Physiol Genomics* 8: 151–157, 2002. First published January 22, 2002; 10.1152/physiolgenomics.00102.2001.—A C825T polymorphism of the G protein β3 (*GNB3*) gene has been reported to be associated with hypertension and obesity. We analyzed the associations between the *GNB3* C825T polymorphism and hemodynamic and body composition phenotypes in the sedentary state and their responses to endurance training in mainly normotensive white (n = 473) and black (n = 255) men and women. Blood pressure (BP) and heart rate (HR) were measured at rest and during submaximal exercise at constant power output (50 W), and stroke volume and cardiac output were obtained during exercise. Body composition was assessed with underwater weighing. Baseline systolic BP (SBP) at 50 W was slightly higher in the white CC homozygotes (P = 0.036), whereas in blacks the CC genotype was associated with a lower resting HR (P = 0.012). In blacks, the CC homozygotes showed a greater training-induced reduction in HR at 50 W (P = 0.013) and a similar trend was observed also in whites (P = 0.053). Black women carrying the CC genotype showed significantly greater reductions in resting SBP and diastolic BP (DBP) than the TT homozygotes, whereas in black men the changes in resting BP were similar across the genotypes ($P < 0.05$ for sex-by-*GNB3* interactions). The *GNB3* genotype was not associated with baseline body composition in blacks or whites. In blacks, the TT genotype was associated with a greater training-induced decrease in fat mass (P = 0.012) and percent body fat (P = 0.006). These data suggest that DNA sequence variation in the *GNB3* locus is not a major modifier of endurance training-induced changes in hemodynamic and body composition phenotypes in healthy but previously sedentary subjects. The *GNB3* genotype may play a minor role in HR and body fatness regulation in blacks and in responsiveness of resting BP to endurance training in black women.

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blood pressure; heart rate; body fatness; exercise training; genotype

WHILE INVESTIGATING THE ROLE of Na^+/H^+ exchanger in hypertension, it was noticed that some hypertensive subjects exhibit enhanced postreceptor signal transfer activity (35). Further studies narrowed down the increased signaling activity to G_i proteins and, subsequently, a C825T transition in exon 10 of the G protein β3 gene (*GNB3*) was identified (36). The 825T allele is associated with a splice variant, in which 123 nucleotides are deleted in exon 9 resulting in an isoform of *GNB3* that is 41 amino acids shorter. The short isoform is biologically active and is associated with enhanced G protein activation.

Siffert and coworkers (36) reported an increased frequency of the T allele in hypertensives, and this finding was later confirmed in other cohorts from Germany (6, 20), Australia (7), and the Caribbean and West Africa (14). Furthermore, the *GNB3* 825T allele has been reported to be associated with elevated diastolic blood pressure (DBP) and aldosterone-to-renin ratio and decreased renin and prorenin levels in whites (31), as well as with several intermediate hypertension phenotypes, such as enhanced renal perfusion rate, increased risk of left ventricular hypertrophy, and impaired diastolic filling (21, 29, 45). Moreover, two studies have reported an association between the *GNB3* 825T allele and enhanced coronary vasoconstriction (4, 25). However, no associations with hypertension were found in the Projet d'Etude des Genes de l'hypertension Artérielle Sévere a modérée Essentielle (PEGASE) and Etude Cas-Témoins de l'Infarctus du Myocarde (ECTIM) studies (11), as well as in Japanese hypertensives (22).

Observations that Na^+/H^+ exchanger activity (intermediate phenotype for the short isoform of *GNB3*) is higher in obese subjects and that pertussis toxin-sensitive G proteins are involved in adipogenesis prompted Siffert and coworkers (33, 34) to investigate the associations between the *GNB3* genotype and body

mass index (BMI). They found that carriers of the T allele had significantly greater BMI levels in several cohorts of young men from various ethnic groups, as well as in hypertensive subjects (33, 34). The *GNB3* genotype was also reported to be associated with body fat distribution in Nunavut Inuits (19), and the *GNB3* TT genotype was associated with greater postpregnancy weight retention, especially among physically inactive women (17). On the other hand, the *GNB3* genotype was not associated with overweight or obesity in Australian and Japanese subjects (8, 27).

Regular physical activity and exercise training play an important role in the prevention and treatment of high blood pressure (18) and in body weight control (16). However, there are marked interindividual differences in responsiveness to exercise training, and genetic factors have been shown to contribute to this variability (1, 2, 10). The purpose of this study was to analyze the associations between the *GNB3* C825T polymorphism, and resting and submaximal exercise hemodynamic phenotypes and body composition, measured in the sedentary state, and their responses to 20 wk of endurance training in a cohort of 728 sedentary but normotensive subjects from the Health, Risk Factors, Exercise Training and Genetics (HERITAGE) Family Study.

SUBJECTS AND METHODS

Subjects. The study cohort consists of 473 white subjects (230 males and 243 females) from 99 nuclear families and 255 black subjects (88 males and 167 females) from 114 family units. The study design and inclusion criteria have been described previously (9). To be eligible, the individuals were required to be in good health, i.e., 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, defined as not having engaged in regular physical activity over the previous 6 mo. Individuals with resting systolic blood pressure (SBP) greater than 159 mmHg and/or DBP more than 99 mmHg were excluded. Other exclusion criteria are fully described in a previous publication (9). The prevalences of overweight and obesity were 31.2% and 32.4% in blacks and 30.8% and 19.3% in whites, 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.

Exercise training program. The exercise intensity of the 20-wk training program was customized for each participant based on the heart rate (HR)-$\dot{V}O_2$ relationship measured at baseline (38). During the first 2 wk, the subjects trained at a HR corresponding to 55% of the baseline $\dot{V}O_{2\,max}$ for 30 min per session. Duration and intensity of the training sessions were gradually increased to 50 min and 75% of the HR associated with baseline $\dot{V}O_{2\,max}$, which were then sustained for the last 6 wk. Training frequency was three times per week, and all training was performed on cycle ergometers in the laboratory. HR was monitored during all training sessions by a computerized cycle ergometer system (Universal FitNet System), which adjusted ergometer resistance to maintain the target HR. Trained exercise specialists supervised all exercise sessions.

Hemodynamic phenotypes. Both resting and exercise blood pressures (BP) were measured using automated units (model STBP-780; Colin, San Antonio, TX), and the recordings were confirmed by technicians wearing headphones (43). Resting BP was measured on two separate days before 11:00 AM in the postabsorptive state. Subjects were asked not to use any caffeine-containing or tobacco products within 2 h prior to measurements. Measurements were done in a quiet room at neutral ambient temperature (24–25°C) with the lights dimmed. Subjects rested for 5 min prior to the initial measurement in a reclining chair with legs slightly elevated and back support reclined at about 45° from the ground. Following the rest period, at least four BP readings were taken at 2-min intervals between measurements. The first recording was automatically discarded, and three valid measurements were kept. Resting SBP and DBP were defined as the mean of all valid readings taken on both days, i.e., a maximum of six.

Submaximal exercise BP was measured during two cycle ergometer tests, both before and after training in relative steady state after 8–12 min at a constant power output (50 W). BP was recorded twice during each test, and the mean of four readings was used for analyses. HR was recorded by electrocardiography, and values were obtained once steady state had been achieved. Cardiac output (Q) was determined twice at 50 W using the Collier CO_2 rebreathing technique (13), as described by Wilmore et al. (40). A mean of the two measurements was used for the analyses. Stroke volume (SV) was calculated by dividing cardiac output by heart rate (Q/HR).

Body composition. Stature was measured to the nearest 0.1 cm with the subject standing erect on a flat surface, with heels, buttocks, and back pressed against the stadiometer, and the head positioned in the Frankfort horizontal plane. Body mass was recorded to the nearest 100 g using a balance scale with subjects clothed only in a light-weight bathing suit. BMI was calculated by dividing body mass (kg) by stature squared (m^2). Body density was assessed by underwater weighing (5). Pulmonary residual volume was measured using the oxygen dilution technique (44) in the Indiana, Minnesota, and Texas clinical centers and by the helium dilution method (24, 26) in the Quebec clinical center. Body density was converted to percent body fat (%Fat) using the equations of Siri (37) for white men, Lohman (23) for white women, Schutte et al. (32) for black men, and Ortiz et al. (28) for black women. Reproducibility of the body density, fat mass (FM), and pulmonary residual volume assessments were very high with intraclass correlations for repeated measures ranging between 0.97 and 1.00 without significant differences between the four clinical centers (41).

Genotype determinations. Genomic DNA was prepared from permanent lymphoblastoid cells by the proteinase K and phenol/chloroform technique. DNA was dialyzed four times against 10 mmol/l Tris-1 mmol/l EDTA (pH 8.0) buffer for 6 h at 4°C and ethanol precipitated.

The C825T polymorphism of the *GNB3* gene was typed with the polymerase chain reaction (PCR) using previously reported primers (36), followed by digestion with *Bsa*JI. The PCR was performed in standard buffer (Qiagen, Valencia, CA), and each 15-μl PCR reaction contained 100 ng genomic DNA, 0.2 μmol/l each primer, 200 μmol/l each dNTPs, and 0.5 U *Taq* polymerase (Qiagen). The reactions were incubated at 94°C for 5 min, 60°C for 45 s, and 72°C for 1 min, followed by 35 cycles of 94°C for 1 min, annealing at 60°C for 45 s, and extension at 72°C for 1 min, then finally one cycle of 72°C for 10 min, using a thermal cycler (model 9600; Perkin-Elmer, Norwalk, CT). The PCR product was digested with 2 U of *Bsa*JI (New England BioLabs, Mississauga, Ontario, Canada) at 60°C for 3 h. The resulting fragments

were separated on 2.5% agarose gel and visualized under ultraviolet light after ethidium bromide staining.

Statistical analyses. A chi-square test was used to confirm that the observed genotype frequencies were in a Hardy-Weinberg equilibrium. Associations between the *GNB3* C825T marker and hemodynamic and body composition phenotypes were analyzed using a MIXED procedure in the SAS software package. Non-independence 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. Baseline BP phenotypes were adjusted for age, sex, and BMI, and BP training response phenotypes were adjusted for age, sex, baseline BMI, and baseline value of the BP phenotype. Baseline body composition phenotypes were adjusted for age and sex [fat-free mass (FFM) also for height], whereas training responses were adjusted for age, sex, and baseline value of the response phenotype. Sex-specific associations between the genotype and hemodynamic phenotypes were tested by adding a sex-by-genotype interaction term into the MIXED model. We also tested whether the allele and genotype frequencies differ between the lowest and highest quartiles of the phenotypes using a chi-square test. However, since these results were identical to those from the MIXED model, only the MIXED model results are reported.

RESULTS

Baseline characteristics of the subjects are summarized in Table 1. Training-induced changes in resting and submaximal exercise hemodynamic phenotypes and in body composition have been described in detail elsewhere (39, 42, 43). The frequency of the T allele was 0.76 and 0.27 in blacks and whites, respectively. The genotype frequencies were in Hardy-Weinberg equilibrium both in blacks and whites.

Hemodynamic phenotypes. The *GNB3* genotype was not associated with resting BP phenotypes in whites (Table 2). Resting HR training response showed a significant association with the *GNB3*, but the association was due to a smaller response in the heterozygotes, whereas the CC and TT homozygotes showed similar responses. The C allele homozygotes had about 7 and 3 mmHg higher baseline SBP at 50 W (SBP50) than the T allele homozygotes and the heterozygotes, respectively. Other baseline phenotypes were not associated with the *GNB3* genotype. Submaximal exercise BP training responses did not differ across the genotypes. However, the TT homozygotes showed a smaller SV at 50 W (SV50) ($P = 0.012$) training response than the heterozygotes and C allele homozygotes. The HR at 50 W (HR50) training responses tended also to be smaller in the TT homozygotes ($P = 0.053$). There was no evidence of genotype-by-sex interactions for any of the phenotypes in whites.

In blacks, the CC homozygotes had about 5 beats/min lower resting HR than the heterozygotes and the T-allele homozygotes (Table 3). Other resting and submaximal exercise phenotypes in the sedentary state were similar across the *GNB3* genotypes. The CC homozygotes showed a significantly ($P = 0.013$) greater training-induced reduction in HR50 than the TT genotype, with heterozygotes showing an interim response. There were significant genotype-by-sex interaction effects on resting SBP and DBP training responses (Fig. 1). No associations were found in men, but in women the CC homozygotes showed greater reductions in SBP ($P = 0.0058$) and DBP ($P = 0.032$) than the other genotypes.

Body composition. In whites, baseline FM, %Fat, and FFM did not differ among the *GNB3* genotypes (Table

Table 1. *Baseline characteristics of the subjects*

Phenotype	Blacks		Whites	
	Men	Women	Men	Women
Age, yr	32.7(12.3)	33.1(11.2)	35.9(14.9)	34.9(14.0)
rSBP, mmHg	125.5(10.0)	122.4(13.0)	120.3(10.7)	112.8(10.0)
rDBP, mmHg	72.8(8.0)	72.7(8.8)	68.2(9.2)	63.9(7.2)
rHR, beats/min	63.0(8.5)	69.2(8.3)	62.0(8.4)	67.0(8.6)
SBP50, mmHg	154.8(17.2)	155.9(21.7)	146.1(18.0)	142.9(20.9)
DBP50, mmHg	80.2(10.5)	79.4(11.6)	72.2(11.5)	70.3(11.0)
HR50, beats/min	109.6(11.4)	134.7(16.2)	106.5(11.6)	128.2(15.2)
SV50, ml/beat	110.7(14.7)	86.7(14.4)	109.0(17.6)	85.7(14.2)
Q50, l/min	12.0(1.4)	11.5(1.4)	11.5(1.6)	10.8(1.4)
BMI, kg/m^2	27.4(5.6)	28.3(6.5)	26.6(4.9)	25.1(5.0)
FM, kg	20.9(11.8)	28.1(12.8)	20.0(10.8)	21.0(10.8)
% Fat	23.0(8.4)	36.1(8.8)	22.7(9.0)	30.0(9.8)
FFM, kg	64.2(9.1)	46.3(6.3)	63.5(7.9)	45.5(5.2)
GNB3 genotype, *n* (%)				
CC	5(5.9)	8(4.9)	119(52.2)	128(52.2)
CT	35(41.2)	60(36.8)	93(40.8)	100(40.8)
TT	45(52.9)	95(58.3)	16(7.0)	17(7.0)
C allele	45(26.5)	76(23.3)	331(72.6)	356(72.7)
T allele	125(73.5)	250(76.7)	125(27.4)	134(27.3)

Values are means, and standard deviations are in parentheses; however, values in parentheses for "*GNB3* genotype" are in percent. SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; "r," resting; "50," measurement at constant power output of 50 W; SV, stroke volume; Q, cardiac output; BMI, body mass index; %Fat, percent body fat; FM, fat mass; and FFM, fat-free mass.

Table 2. *Resting and submaximal exercise (50 W) hemodynamic phenotypes in the sedentary state and in response to a 20-wk endurance training program according to the GNB3 C825T genotype in whites*

	GNB3 C825T Genotype			
	CC (n = 247)	CT (n = 193)	TT (n = 33)	P Value
rSBP, mmHg				
Baseline	117.2(1.0)	115.8(1.2)	116.4(1.8)	0.428
Response	+1.1(0.6)	+0.7(0.7)	−0.1(1.2)	0.562
rDBP, mmHg				
Baseline	65.0(0.7)	64.4(0.8)	65.9(1.4)	0.502
Response	+0.3(0.5)	+0.5(0.5)	−0.8(0.8)	0.274
rHR, beats/min				
Baseline	64.0(1.0)	64.4(1.0)	63.6(1.7)	0.812
Response	−3.1(0.6)	−1.9(0.7)	−3.8(1.2)	0.013
SBP50, mmHg				
Baseline	147.5(1.3)	144.4(2.0)	140.8(2.7)	0.036
Response	−4.7(1.3)	−5.4(1.3)	−1.8(2.3)	0.174
DBP50, mmHg				
Baseline	70.4(0.9)	70.7(1.0)	70.5(1.5)	0.961
Response	−2.9(0.5)	−3.5(0.6)	−2.1(1.6)	0.569
HR50, beats/min				
Baseline	117.4(1.8)	116.4(2.1)	113.3(2.4)	0.156
Response	−11.8(0.8)	−10.5(0.8)	−8.9(1.2)	0.053
SV50, ml/beat				
Baseline	98.8(2.1)	99.9(2.1)	104.7(3.0)	0.089
Response	+6.0(1.2)	+3.2(1.3)	+2.2(2.2)	0.012
Q50, l/min				
Baseline	11.3(0.1)	11.3(0.2)	11.5(0.3)	0.755
Response	−0.4(0.1)	−0.5(0.1)	−0.4(0.2)	0.378

Values are least-squares means, and SE are in parentheses; n = no. of subjects. Baseline phenotypes are adjusted for age, sex, and BMI (SBP50, DBP50, HR50), or body surface area (SV50, Q50). Training response phenotypes are adjusted for age, sex, baseline value of the phenotype, and baseline BMI (SBP50, DBP50, HR50) or body surface area (SV50, Q50).

4). Training-induced changes in all body composition phenotypes were also similar across the genotypes. In blacks, the baseline body composition phenotypes were not associated with the *GNB3* genotype. However, the FM and %Fat training responses differed significantly (P = 0.012 and 0.006, respectively) among the three genotypes. The CC homozygotes had a slight increase in FM and no change in %Fat, whereas the heterozygotes and TT homozygotes showed mean decreases of 1.0 and 1.2 kg in FM and 1.0 and 1.1% unit in %Fat, respectively. Changes in FFM were similar among all three genotypes. There was no evidence for sex-by-genotype interactions on body composition phenotypes.

DISCUSSION

Previous studies have reported significant associations between the *GNB3* C825T polymorphism and hypertension, as well as hemodynamic phenotypes, such as renal perfusion, left ventricular hypertrophy, left ventricular diastolic filling, and coronary vasoconstriction. In the present study, the *GNB3* genotype was not associated with resting BP among the mainly normotensive sedentary HERITAGE subjects. In blacks, the CC homozygotes showed lower resting HR than the TT homozygotes, whereas in whites the CC genotype was associated with higher submaximal exercise SBP. The novel feature of the present study is the investigation of endurance training-induced changes in hemodynamic and body composition phenotypes and their associations with the *GNB3* genotype. Training-induced increases in submaximal exercise stroke volume in whites and decreases in HR50 both in blacks and whites were greater in the CC homozygotes. However, it should be noted that the greater training responses in the white CC homozygotes reflected to some extent their lower SV50 and higher HR50 at baseline. In blacks the initial HR50 values did not differ across the *GNB3* genotypes. There are no previous studies on the associations between the *GNB3* C825T genotype and submaximal exercise hemodynamic phenotypes. However, Schafers et al. (30) reported an elevated resting stroke volume and a greater fall in resting stroke volume in response to acute administration of propranolol, a β-adrenoceptor antagonist, in healthy young men carrying the GNB3 825T allele compared with the CC homozygotes.

Although the *GNB3* polymorphism was not associated with resting BP training response in either ethnic group, there was a significant sex-by-generation interaction effect on training-induced changes in resting BP in blacks. Among women, the C allele was associated with greater decreases in SBP and DBP than the T

Table 3. *Resting and submaximal exercise (50 W) hemodynamic phenotypes in the sedentary state and in response to a 20-wk endurance training program according to the GNB3 C825T genotype in blacks*

	GNB3 C825T Genotype			
	CC (n = 13)	CT (n = 97)	TT (n = 145)	P Value
rSBP, mmHg				
Baseline	125.2(3.2)	126.2(1.4)	125.8(1.5)	0.945
Response	−4.0(2.0)	−2.2(1.3)	−1.2(1.3)	0.276
rDBP, mmHg				
Baseline	71.2(1.9)	72.7(1.2)	74.1(1.2)	0.161
Response	−1.3(1.8)	−1.3(1.0)	−1.1(0.9)	0.975
rHR, beats/min				
Baseline	61.6(1.6)	67.0(1.2)	67.2(1.0)	0.012
Response	−1.6(1.3)	−3.0(0.8)	−1.8(0.9)	0.403
SBP50, mmHg				
Baseline	157.8(6.5)	157.2(2.4)	157.7(2.1)	0.974
Response	−13.4(2.8)	−12.0(1.4)	−12.1(1.3)	0.857
DBP50, mmHg				
Baseline	78.0(2.2)	78.0(1.4)	79.0(1.3)	0.309
Response	−9.5(1.5)	−7.7(1.0)	−7.6(1.0)	0.489
HR50, beats/min				
Baseline	120.9(4.2)	120.2(2.2)	120.0(2.1)	0.968
Response	−14.5(1.1)	−12.4(0.9)	−11.5(0.8)	0.013
SV50, ml/beat				
Baseline	99.2(4.2)	98.1(1.8)	98.7(2.2)	0.945
Response	+7.9(2.7)	+7.9(1.4)	+5.4(1.5)	0.183
Q50, l/min				
Baseline	11.7(0.4)	11.5(0.2)	11.6(0.2)	0.749
Response	−0.3(0.3)	−0.1(0.1)	−0.3(0.2)	0.397

Values are least-squares means, and SE are in parentheses; n = no. of subjects. Baseline phenotypes are adjusted for age, sex, and BMI (SBP50, DBP50, HR50) or body surface area (SV50, Q50). Training response phenotypes are adjusted for age, sex, baseline value of the phenotype, and baseline BMI (SBP50, DBP50, HR50) or body surface area (SV50, Q50).

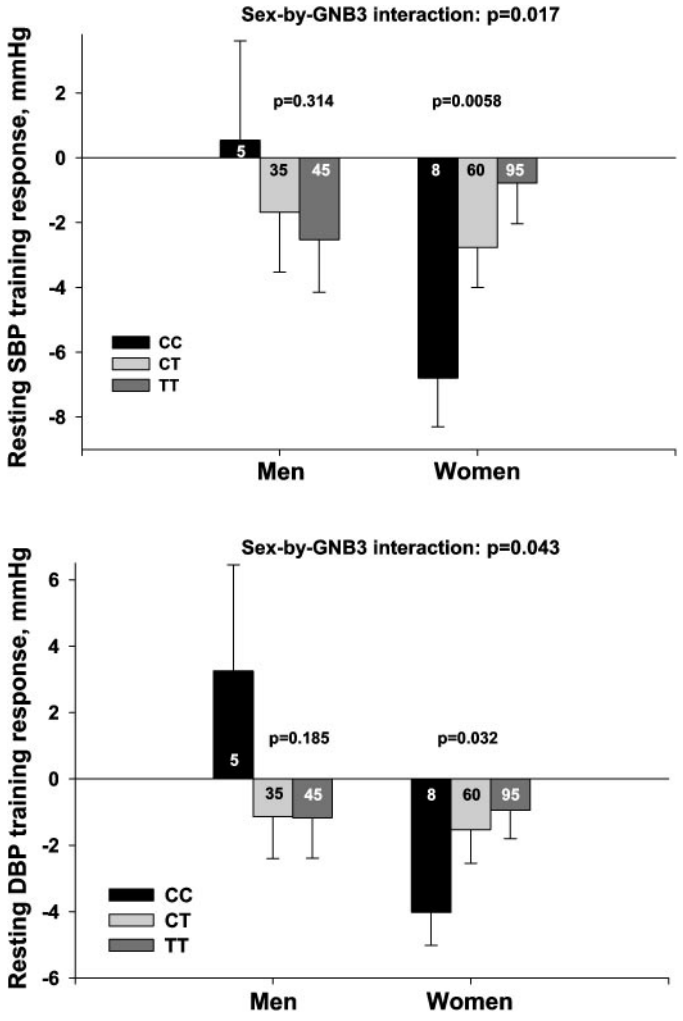

Fig. 1. Sex-by-*GNB3* interaction effect on training-induced changes in resting systolic (SBP) and diastolic (DBP) blood pressure in black men and women. The number of subjects is shown in each bar.

allele, whereas in men the training responses did not differ between the genotypes. This kind of sexual dimorphism has been previously reported for genes encoding components of the renin-angiotensin system (3, 12, 15). These differences may indicate that some underlying sex-specific hormonal or other physiological factors modify the genotype-phenotype associations. This would not be surprising in light of the well-documented sex differences in several hemodynamic phenotypes and the putative cardioprotective effect of estrogens. However, similar interaction effects were not observed in whites. This is most likely due to the significantly lower baseline BP levels in whites and therefore nonsignificant training-induced changes in resting BP. This observation remains to be verified in other suitable cohorts of black men and women.

Obesity is a major risk factor for hypertension, and since pertussis toxin-sensitive G proteins are involved in adipogenesis, Siffert and coworkers (33) investigated the associations between the *GNB3* genotype and BMI. Despite marked differences in the frequency of the T allele between ethnic groups, they found that the T allele was associated with greater BMI in 18- to 30-yr-old males from Germany, China, and South Africa. However, there were only a few clinically obese (BMI $>$ 30 kg/m^2) subjects in these cohorts. Two other studies found no differences in the *GNB3* allele and genotype frequencies between normal weight controls and obese cases (8, 27). In the present study, none of the adiposity phenotypes was associated the *GNB3* polymorphism, and the *GNB3* allele frequencies did not differ between normal weight (BMI $<$ 25 kg/m^2) and obese (BMI $>$ 30 kg/m^2) subjects (data not shown). However, in blacks the CC genotype tended to be associated with greater FM and %Fat at baseline and the T allele was associated with greater training-induced reduction in both phenotypes.

In the interpretation of the association between the *GNB3* genotype and FM and %Fat training responses in blacks, it should be noted that the CC homozygotes showed a tendency for higher values at baseline. As well, the *GNB3* main effect for FM and %Fat training responses became statistically significant only after the baseline values were included in the models. This pattern suggests that the effect of initial fatness level on body fat changes varies among the *GNB3* genotypes. As expected, baseline FM and %Fat were inversely correlated with respective changes both in blacks and whites. However, in blacks the inverse correlations were observed only in the TT and CT genotypes, whereas in the CC homozygotes the correlations were nonsignificant and tended to be positive rather than negative. Thus the most likely interpretation for the

Table 4. *Body composition in the sedentary state and in response to a 20-wk endurance training program according to the GNB3 C825T genotype in subjects of the HERITAGE Family Study*

	GNB3 C825T genotype			
	CC	CT	TT	*P* Value
Whites				
n	244	193	33	
FM, kg				
Baseline	20.8(1.0)	22.3(1.2)	21.2(1.4)	0.216
Response	−1.0(0.2)	−0.8(0.2)	−1.0(0.3)	0.784
FFM, kg				
Baseline	53.8(0.4)	54.7(0.5)	55.4(0.9)	0.092
Response	+0.7(0.1)	+0.6(0.1)	+0.5(0.2)	0.598
%Fat				
Baseline	27.0(0.9)	28.1(0.9)	26.6(1.3)	0.217
Response	−1.2(0.2)	−1.0(0.2)	−1.3(0.3)	0.538
Blacks				
n	11	97	142	
FM, kg				
Baseline	32.1(3.8)	23.6(2.0)	24.9(2.2)	0.097
Response	+0.8(0.5)	−1.0(0.3)	−1.2(0.2)	0.012
FFM, kg				
Baseline	57.3(1.7)	55.4(1.1)	56.6(1.1)	0.242
Response	+1.1(0.4)	+0.5(0.4)	+0.4(0.4)	0.482
%Fat				
Baseline	33.5(2.4)	28.4(1.3)	28.6(1.4)	0.151
Response	+0.0(0.3)	−1.0(0.2)	−1.1(0.2)	0.006

Values are least-squares means, and SE are in parentheses; *n* = no. of subjects.

significant association is that despite a greater body fat level in the sedentary state, the black CC homozygotes were resistant to a training-induced reduction in FM. In fact, the difference in FM and %Fat between the CC homozygotes and the T allele carriers reached statistical significance after the training program ($P = 0.020$ and 0.010, respectively). Also, it should be noted that the nonresponsiveness among the CC homozygotes was not due to differences in compliance to the training program, because all the training sessions were supervised and all the subjects included in the present analyses completed the same training program. Furthermore, changes in other indicators of training responsiveness were similar across the genotypes (e.g., $\dot{V}O_{2\,max}$), or even greater in the CC homozygotes (e.g., HR50). Interestingly, the CC homozygotes showed lower resting HR and greater training-induced reduction in submaximal exercise HR, indicating that their tendency to accumulate more body fat did not disturb their more favorable HR profile. Thus our data do not support the view that the *GNB3* C825T genotype is a major determinant of body composition in the sedentary state or its response to endurance training.

In conclusion, these data from the HERITAGE Family Study suggest that DNA sequence variation in the *GNB3* locus is not a major modifier of endurance training-induced changes in hemodynamic and body composition phenotypes in healthy, but previously sedentary subjects. The *GNB3* genotype may play a minor role in HR regulation in blacks and in responsiveness of resting BP to endurance training in black women. These findings remain to be confirmed in future studies.

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