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Association of variants in *NEDD4L* with blood pressure response and adverse cardiovascular outcomes in hypertensive patients treated with thiazide diuretics

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Abstract

Objective—Single-nucleotide polymorphisms (SNPs) in *NEDD4L* may influence the ability of the NEDD4L protein to reduce epithelial sodium channel expression. A variant in *NEDD4L*, rs4149601, was associated with antihypertensive response and cardiovascular outcomes during treatment with thiazide diuretics and β-blockers in a Swedish population. We sought to further evaluate associations between *NEDD4L* polymorphisms, blood pressure response and cardiovascular outcomes with thiazide diuretics and β-blockers.

Methods—Four SNPs, rs4149601, rs292449, rs1008899 and rs75982813, were genotyped in 767 patients from the Pharmacogenomic Evaluation of Antihypertensive Responses (PEAR) clinical trial and association was assessed with blood pressure response to hydrochlorothiazide and atenolol. One SNP, rs4149601, was also genotyped in 1345 patients from the International Verapmil SR Trandolapril Study (INVEST), and association was examined with adverse cardiovascular outcomes relative to hydrochlorothiazide treatment.

Results—Significant associations or trends were found between rs4149601, rs292449, rs75982813 and rs1008899 and decreases in blood pressure in whites on hydrochlorothiazide, and a significant association was observed with increasing copies of the GC rs4149601-rs292449 haplotype and greater blood pressure response to hydrochlorothiazide in whites ($P = 0.0006$ and 0.006, SBP and DBP, respectively). Significant associations were also seen with rs4149601 and an

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increased risk for adverse cardiovascular outcomes in whites not treated with hydrochlorothiazide [$P = 0.022$, odds ratio (95% confidence interval) = 10.65 (1.18–96.25)].

Conclusion—*NEDD4L* rs4149601, rs292449 and rs75982813 may be predictors for blood pressure response to hydrochlorothiazide in whites, and *NEDD4L* rs4149601 may be a predictor for adverse cardiovascular outcomes in whites not treated with hydrochlorothiazide.

Keywords

epithelial sodium channel; hypertension; International Verapamil SR Trandolapril Study; neural precursor cell expressed developmentally down-regulated 4 like; Pharmacogenomic Evaluation of Antihypertensive Responses; pharmacogenetics

Introduction

Hypertension is the most common chronic disease in the world, affecting approximately 1 billion people worldwide [1]. It is a major risk factor for acute myocardial infarction (MI), stroke, congestive heart failure and renal failure [2]. Sodium intake is an environmental risk factor shown to play a role in the development of hypertension [3,4]. In addition, genetic factors also influence the development of hypertension, contributing anywhere from 30 to 70% of risk [5,6]. An important cause of monogenic forms of hypertension is due to mutations that alter the expression of the amiloride-sensitive epithelial sodium channel (ENaC) in the distal nephron. ENaC is a membrane protein present in the apical membranes of renal epithelial cells and is responsible for sodium reabsorption in the kidneys [7,8]. An over or underexpression of ENaC has been linked to serious human diseases, such as Liddle's syndrome and pseudohypoaldosteronism type I, respectively [7,8]. The delicate balance of this channel on the epithelial membrane is maintained by the neural precursor cell expressed developmentally down-regulated 4 like (NEDD4L) protein [9,10].

NEDD4L is a ubiquitin ligase consisting of three domains important to ENaC's function: the C2 domain, WW domain and Hect domain [11]. The C2 domain is a calcium-rich lipid-binding domain that is responsible for membrane targeting. The WW domain binds to the PY motif present on ENaC, allowing a close interaction between NEDD4L and ENaC. The C2 domain is not necessary for NEDD4L function, whereas WW and Hect domains are essential to ENaC regulation, targeting ENaC for internalization into the cell and degradation by lysozomes, respectively. The presence of NEDD4L is vital for maintenance of proper sodium reabsorption [10,11].

A G to A polymorphism, rs4149601, located at the last nucleotide of exon 1 in the *NEDD4L* gene creates a cryptic splice site, whereby the A-allele leads to the preferential deletion of the C2 domain [12]. Previous human studies have shown that those with the GG genotype at rs4149601, as compared with the AA genotype, had higher salt sensitivities, lower plasma renin levels and significantly higher DBPs [12,13]. The mechanism underlying these associations is that the A allele results in a deletion of the C2 domain of the gene, allowing for stronger interactions between NEDD4L and ENaC, and increased ENaC downregulation [12].

A recent study conducted by Svensson-Färbom *et al.* [14] in the Nordic Diltiazem Study (NORDIL) found that the G-allele of rs4149601 was associated with significantly greater blood pressure (BP) lowering and improved outcomes in patients on β-blockers and thiazide diuretics. This study further showed no correlation between genotype and outcomes in patients treated with calcium channel blockers (CCBs), a finding that was not surprising given that their mechanism of action does not involve the kidney [14].

We sought to replicate the BP response findings of Svensson-Färbom *et al.* [14] in the Pharmacogenomic Evaluation of Antihypertensive Responses (PEAR) study and determine whether the prior associations were likely due to thiazide or β-blocker therapy. We also aimed to replicate the *NEDD4L* association with cardiovascular outcomes in the International Verapamil SR Trandolapril Study (INVEST).

Materials and Methods

Study design and participants

PEAR—The PEAR study was a prospective, multicenter, randomized, open-label study (clinicaltrials.gov NCT00246519) approved by the Institutional Review Boards at all participating clinical trial study sites, and all patients provided written informed consent. The design for PEAR has been previously described [15]. Briefly, PEAR included 768 patients with mild to moderate hypertension between the ages of 17 and 65 years. Patients were included if they had an average home DBP greater than 85 mmHg and office DBP greater than 90 mmHg at the end of an average 4-week washout period. Participants were excluded if they had DBP greater than 110 mmHg or SBP greater than 180 mmHg, secondary forms of hypertension, treatment with three or more antihypertensive drugs, isolated systolic hypertension, concomitant diseases treated with BP-lowering medications, heart rate less than 55 beats/min, diabetes mellitus, primary renal disease, were pregnant or lactating, had a history of Raynaud syndrome or were treated with drugs associated with BP elevation. After washout, patients were randomized to receive atenolol 50 mg or hydrochlorothiazide (HCTZ) 12.5 mg daily. If BP remained greater than 120/70 mmHg after 3 weeks of treatment, doses were titrated to atenolol 100 mg or HCTZ 25 mg daily, and treatment was continued for an additional 6 weeks. The alternate agent was then added, with similar dose titration for 6–9 weeks of combination treatment. Clinic, home and 24-h ambulatory BPs, along with additional laboratory measures were recorded at baseline, after monotherapy, and after combination therapy [15]. We focused our analyses on the clinic BP phenotype after monotherapy to best replicate the phenotype used in the previous study [14].

INVEST—INVEST (clinicaltrials.gov NCT00133692) was an international, prospective, randomized, open-label, blinded end-point trial in 22 576 patients with hypertension and coronary artery disease, and has been previously described [16]. All patients provided written and informed consent, and the trial was approved by the Institutional Review Board at all participating clinical trial study sites. Patients were randomized to a β-blocker – (atenolol) or a CCB – (verapamil SR) based treatment strategy. HCTZ and trandolapril were available as an add-on treatment in either strategy for BP control or end-organ protection as necessary. The primary outcome was a composite of the first occurrence of all-cause death, nonfatal MI or nonfatal stroke. An independent committee that was blinded to treatment strategy adjudicated events. The main findings from INVEST have been previously published [16]. Overall, BP control and cardiovascular outcomes were similar comparing the two strategies.

The INVEST Genetic Substudy (INVEST-GENES) collected DNA on 5979 patients enrolled in INVEST residing in the United States and Puerto Rico. The genetic substudy was approved by the Institutional Review Boards at the participating study sites and all patients provided written informed consent. A nested case–control study was constructed from INVEST-GENES. Cases (n = 269) were defined as those patients experiencing the primary outcome and were frequency matched to four controls (n = 1076) on the basis of age by decade, sex and race.

Single-nucleotide polymorphism selection, genotyping and quality control

PEAR—Four SNPs in *NEDD4L* were investigated in PEAR. rs4149601 was the main SNP of interest, as it was previously associated with BP response [14]. In addition, rs292449, rs1008899 and rs75982813 were also examined due to their potential impact on NEDD4L function. DNA from patients was genotyped using the TaqMan 7900HT real-time PCR system (Applied Biosystems, Foster City, California, USA). One sample was excluded from genetic analysis due to genotyping quality control procedures (final $n = 767$). Genotyping efficiency and duplicate concordance rates were more than 97 and 100%, respectively, for all four SNPs.

INVEST—Only rs4149601 was genotyped in INVEST due to its prior association with cardiovascular outcomes in patients taking β-blockers and/or diuretics [14]. DNA from patients was genotyped using the TaqMan 7900HT real-time PCR system (Applied Biosystems). Genotyping efficiency and duplicate concordance rates for rs4149601 were 94.3 and 99.1%, respectively.

Statistical analysis

PEAR—Hardy–Weinberg equilibrium (HWE) was measured in each race group using a chi-square test with one degree of freedom. Linear regression was used to model *NEDD4L* SNP and haplotype effects on BP response to HCTZ and atenolol monotherapy. Tests were done under an additive model and a dominant minor allele model except for rs4149601, in which the dominant model was coded as: AA = 0, AG + GG = 1, to be consistent with the previous study [14]. The rs4149601-rs292449 haplotype was coded as zero, one or two copies of the GC haplotype. Differences in SBP and DBP response across genotype and haplotype were evaluated using analysis of variance (ANOVA). All analyses were adjusted for age, sex and baseline BP. Additional analyses of rs292449, rs1008899 and rs75982813 were conducted adjusting for rs4149601, and additional analyses of all significant findings were further adjusted for BMI, smoking and alcohol consumption. Our primary analysis was in whites, investigating monotherapy and combination therapy. SNPs that showed significance in whites was evaluated in African-Americans for replication. All analyses were conducted using the clinic BP phenotype. Pairwise measures of r^2 and D' were assessed using Haploview version 4.2 [17], and haplotypes were constructed using PHASE version 2 [18]. All other statistical analyses were conducted using SAS version 9.2 (SAS Institute Inc., Cary, North Carolina, USA). Due to prior association with rs4149601 and BP response, associations with rs4149601 were considered significant at a P value of less than 0.05 (replication); the other SNPs/haplotypes evaluated were considered significant at a P value of less than 0.0125 ($P < 0.05/4$).

INVEST—HWE was tested in each race/ethnic group using a chi-square test with one degree of freedom. A logistic regression model was used to assess the occurrence of the primary outcome by rs4149601 genotype in patients treated with HCTZ and in patients not HCTZ-treated. Both additive and dominant modes of inheritance were modeled. The AA genotype was coded as the reference in order to be consistent with the previous study [14]. A patient was considered HCTZ-treated if HCTZ was ever prescribed. Analyses were adjusted for age, sex, treatment strategy and history of MI, heart failure or diabetes. Additional tests were performed by treatment strategy, adjusting for HCTZ use. Analyses were conducted by race/ethnic group, with the primary analysis in whites. Positive associations in whites were also tested in the other race/ethnic groups. All statistical analyses were conducted using SAS version 9.2 (SAS Institute Inc.). Due to the prior association between rs4149601 and adverse cardiovascular outcomes, associations were considered significant at a P value of less than 0.05 (replication).

Results

Assessment of blood pressure response to hydrochlorothiazide and atenolol and *NEDD4L* single-nucleotide polymorphisms in PEAR

Baseline characteristics for the PEAR study are summarized in Table 1. Slightly more women than men were included in the study. The majority of patients were white (60.6%); however, there was also a large percentage of African-American individuals (39.4%). On average, patients were obese (BMI = 30.8 kg/m^2) and the average baseline clinic BP of patients was 151/98 mmHg.

The allele frequencies, genotype frequencies and HWE *P* values for the four *NEDD4L* SNPs assessed in PEAR are shown in Supplemental Table 1 (Supplemental Digital Content 1, http://links.lww.com/HJH/A231). Minor alleles were consistent between both race groups in PEAR (whites and African-Americans), with the exception of rs292449. Overall, all SNPs were in HWE after correcting for the number of comparisons made by race (HWE $P > 0.05/4 = 0.0125$).

BP response to HCTZ and atenolol by genotype in each race group is presented in Supplemental Table 2 (Supplemental Digital Content 2, http://links.lww.com/HJH/A231). Among white patients treated with HCTZ, those carrying the G-allele at rs4149601 had significantly greater SBP and DBP reductions than those with the AA genotype (SBP additive $P = 0.0303$ and DBP dominant $P = 0.0372$; Fig. 1). There were no significant associations with BP response and rs4149601 genotype observed in whites treated with atenolol. In addition, the observed association with rs4149601 and BP reduction to HCTZ treatment did not replicate in African-Americans (Supplemental Table 2, Supplemental Digital Content 2, http://links.lww.com/HJH/A231).

Significant associations or trends were also observed with BP response to HCTZ in whites for rs292449, rs1008899 and rs75982813 (Supplemental Table 2, Supplemental Digital Content 2, http://links.lww.com/HJH/A231). These associations or trends remained after adjusting the analysis for rs4149601, suggesting that these are independent signals (Supplemental Table 3, Supplemental Digital Content 3, http://links.lww.com/HJH/A231). In addition, linkage disequilibrium between the four SNPs was relatively low ($D' < 0.3$ and $r^2 < 0.1$), except for between rs1008899 and rs2924499 ($D' = 0.908$, $r^2 = 0.533$, Supplemental Table 4, Supplemental Digital Content 4, http://links.lww.com/HJH/A231). There was no evidence of an association observed with BP response for rs292449, rs1008899 and rs75982813 in whites treated with atenolol. In addition, none of the associations identified in HCTZ-treated whites replicated in African-Americans treated with HCTZ (Supplemental Table 2, Supplemental Digital Content 2, http://links.lww.com/HJH/A231).

As the associations and trends observed in whites with rs292449, rs1008899 and rs75982813 remained after adjustment for rs4149601, we performed a haplotype analysis. A two-SNP haplotype was constructed from rs4149601 and rs292449, as these were the only two SNPs meeting our significance levels and due to the observed linkage disequilibrium in the region (Supplemental Table 4, Supplemental Digital Content 4, http://links.lww.com/HJH/A231). Association was assessed with BP response and the GC haplotype, which represents the alleles associated with the best BP response in single-SNP analysis. Patients with one or two copies of the GC haplotype observed significantly greater BP response than those with zero copies (*P* SBP = 0.0006, *P* DBP = 0.006, Fig. 2).

As the previous study reported associations with BP response and rs4149601 genotype in patients treated with β-blockers and/or diuretics [14], we conducted a similar analysis by

assessing association with combination therapy (both HCTZ and atenolol). In the combined analysis, we did not observe any evidence of association in whites with SBP response and rs4149601 (additive $P = 0.252$, dominant $P = 0.841$; Supplemental Table 5, Supplemental Digital Content 5, http://links.lww.com/HJH/A231) nor with DBP response and rs4149601 (additive $P = 0.869$, dominant $P = 0.346$; Supplemental Table 5, Supplemental Digital Content 5, http://links.lww.com/HJH/A231). In addition, we observed no evidence of association with BP response and rs4149601 in African-Americans with combination therapy.

Given that BP levels may be influenced by a number of factors, including BMI, smoking and alcohol consumption, we performed additional analyses in whites treated with HCTZ of all four single SNPs and the rs4149601-rs292449 GC haplotype, adjusting for these covariates in addition to the covariates that were already in the model (age, sex and baseline BP). The associations and trends observed when the model only included age, sex and baseline BP remained after adjusting for the additional covariates (Supplemental Table 6, Supplemental Digital Content 6, http://links.lww.com/HJH/A231).

Assessment of the occurrence of adverse cardiovascular outcomes, diuretic use and rs4149601 in INVEST

Baseline demographics for the INVEST-GENES case–control are summarized in Table 2. Cases and controls were similar with regard to baseline BMI, SBP, DBP and heart rate. Not surprisingly, cases had a higher baseline incidence of diabetes, heart failure and prior MI when compared with controls.

The allele frequencies, genotype frequencies and HWE P values for rs4149601 in INVEST are shown in Supplemental Table 7 (Supplemental Digital Content 7, http://links.lww.com/HJH/A231). rs4149601 was out of HWE in the Hispanic race/ethnic group (All HWE $P = 0.034$, controls HWE $P = 0.026$, Supplemental Table 7, Supplemental Digital Content 7, http://links.lww.com/HJH/A231), suggesting genotyping error. However, all Hispanic samples run for duplicate concordance matched. In addition, the allele and genotype frequencies observed in our Hispanic cohort fall in between the allele and genotype frequencies for the CEU, MEX and ASW populations in HapMap [19]. This slight deviation in HWE may represent the range of European, African and Native American ancestry observed in Puerto Ricans [20,21].

rs4149601 was examined in INVEST in relation to adverse cardiovascular outcomes (i.e. composite of the first occurrence of all-cause death, nonfatal MI or nonfatal stroke) and diuretic (HCTZ) use (Fig. 3). Among patients treated with HCTZ during INVEST, there was no evidence of a difference in occurrence of the primary outcome on the basis of genotype in whites (P values ranged from 0.361 to 0.943; Fig. 3). In whites not treated with HCTZ (no HCTZ; Fig. 3), the AG genotype was significantly associated with an increased risk for the primary outcome [$P = 0.022$; odds ratio (OR), 10.65; 95% confidence interval (95% CI), (1.18–96.25)]. In addition, when the AG and GG genotype groups were combined, a similar trend was observed ($P = 0.051$; OR, 8.94; 95% CI, 0.99–80.54). We observed no association with rs4149601 and adverse cardiovascular outcomes relative to HCTZ use in Hispanics and in African-Americans (data not shown).

Similar to the analysis from the study by Svensson-Färbom *et al.* [14], we conducted additional analyses by treatment strategy in INVEST (CCB and β-blocker), controlled for HCTZ use. Contrary to the previous study, we observed no association with outcome by genotype in either treatment strategy in INVEST whites, under both additive and dominant models (data not shown).

Discussion

A previous study from the NORDIL trial found that hypertensive patients treated with a thiazide diuretic and/or β-blocker had significantly greater BP lowering and fewer adverse cardiovascular events if they were carriers of the G allele for rs4149601 in *NEDD4L* [14]. As the encoded protein regulates ENaC expression, mechanistically, BP response to HCTZ should be more strongly influenced by genetic variants that alter the presence of ENaC than BP response to β-blockers, as HCTZ's mechanism of action affects sodium and water reabsorption [22]. We confirmed such an association in PEAR, observing significantly greater BP lowering among white rs4149601 G carriers treated with HCTZ. We did not observe a significant association between rs4149601 genotype and antihypertensive response to atenolol or to HCTZ–atenolol combination therapy. This is consistent with the predicted mechanisms of NEDD4L action, which would not be expected to affect response to β-blockers [9–11].

We also investigated association with three other SNPs in *NEDD4L* and BP response to HCTZ and atenolol. We observed significant or trending associations with rs292449, rs75982813 and rs1008899 and BP response to HCTZ, and these results remained after adjustment for rs4149601, suggesting that they may be independent signals. We observed the strongest association with BP lowering in patients carrying one or two copies of the rs4149601-rs292449 GC haplotype. This also suggests that these SNPs represent independent signals. Furthermore, the associations and trends seen with the four single SNPs and the rs4149601-rs292449 GC haplotype remained when we performed additional covariate adjustment, adding BMI, smoking and alcohol consumption into our model.

No association was observed with any of the SNPs and BP response to atenolol. Again, this is consistent with the proposed mechanism of NEDD4L on antihypertensive drug response [9–11]. Furthermore, we did not replicate the associations observed in NEDD4L with BP response to HCTZ in African-Americans. The lack of significance in African-Americans may be a result of lower power in this race group. However, as we did not observe any trends, this is unlikely and suggests that these SNPs may not be the functional variants.

When looking at the composite primary outcome in INVEST, we could not replicate the exact analysis performed by Svensson-Färbom *et al.* [14] by comparing the CCB strategy to the β-blocker strategy because INVEST was designed differently than NORDIL, and a thiazide diuretic was available in both arms. However, when we performed an analysis looking at patients ever treated with HCTZ vs. patients never treated with HCTZ (no HCTZ), we observed a significant increased risk of the primary outcome in G-allele carriers of rs4149601 in whites not treated with HCTZ. These results are similar to what Svensson-Färbom *et al.* [14] saw, in that their diuretic-treated patients with one or two copies of the G-allele had lower risk than those not treated with a diuretic. We did not observe any evidence of association or trends in Hispanics and African-Americans with rs4149601, HCTZ treatment and the primary outcome. This was consistent with what we saw in PEAR, and again suggests that rs4149601 may not be a functional variant, but instead, may tag some unknown functional polymorphism.

Our study is not without limitations. First, in PEAR, we had a much smaller study population than did Svensson-Färbom *et al.* [14]. Our lack of associations in the atenolol arm in whites, and in African-Americans may have been due to reduced power as opposed to a true negative finding. However, there are not even trends for differences in response, so this seems unlikely. In addition, although the treatment strategies in INVEST and NORDIL are similar, there are some differences. In INVEST, HCTZ was a study drug available for add-on in either arm. We accounted for this by performing our analysis as HCTZ treated and

not HCTZ treated, adjusted for treatment strategy. However, it is possible that there are additional variables and differences for which we did not account. Lastly, sodium intake data were not collected in PEAR or INVEST. As salt intake is known to play a major role in HCTZ response and the development of hypertension, this may have been a confounding variable for BP responses.

In summary, our study validated the influence of rs4149601 on BP response to HCTZ, originally reported by Svensson-Färbom *et al.* [14]. However, our data suggest that rs4149601 may not be a predictor for atenolol response, as was previously suggested. In addition, we found other SNPs in the *NEDD4L* gene that are associated with BP response to HCTZ and that a two-SNP haplotype composed of rs4149601 and rs292449 was more strongly associated with BP response to HCTZ than any single SNP. Finally, we saw trends consistent with the prior study, with the effect of rs4149601 genotype, HCTZ treatment and adverse cardiovascular outcomes. Our data suggest that rs4149601, rs292449 and rs75982813 may all be predictors of BP response in whites treated with HCTZ and that the rs4149601 G allele may be a predictor of adverse cardiovascular outcomes in whites whose antihypertensive regimen does not include HCTZ.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

PEAR	Pharmacogenomic Evaluation of Antihypertensive Responses
INVEST	International Verapamil SR Trandolapril Study
MI	myocardial infarction
ENaC	Epithelial sodium channel

NEDD4L	Neural precursor cell expressed developmentally down-regulated 4 like
NORDIL	Nordic Diltiazem Study
BP	blood pressure
HCTZ	hydrochlorothiazide
CCB	calcium channel blocker
INVEST-GENES	INVEST Genetic Substudy
HWE	Hardy–Weinberg Equilibrium
OR	odds ratio
CI	confidence Interval

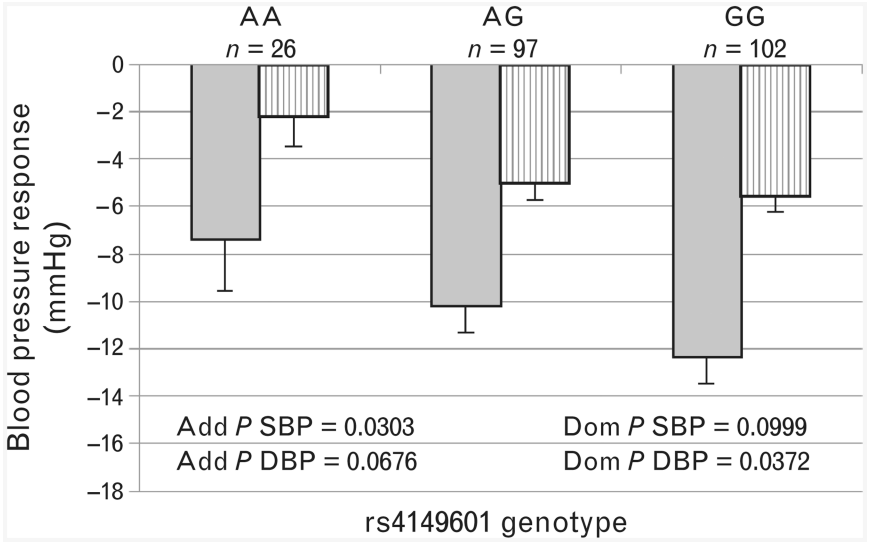

Figure 1.

Blood pressure response by rs4149601 genotype in white patients treated with hydrochlorothiazide in PEAR. Solid gray bars indicate ΔSBP, and gray and white lined bars indicate ΔDBP. Values are shown as means ± standard error. Add: additive, Dom: dominant.

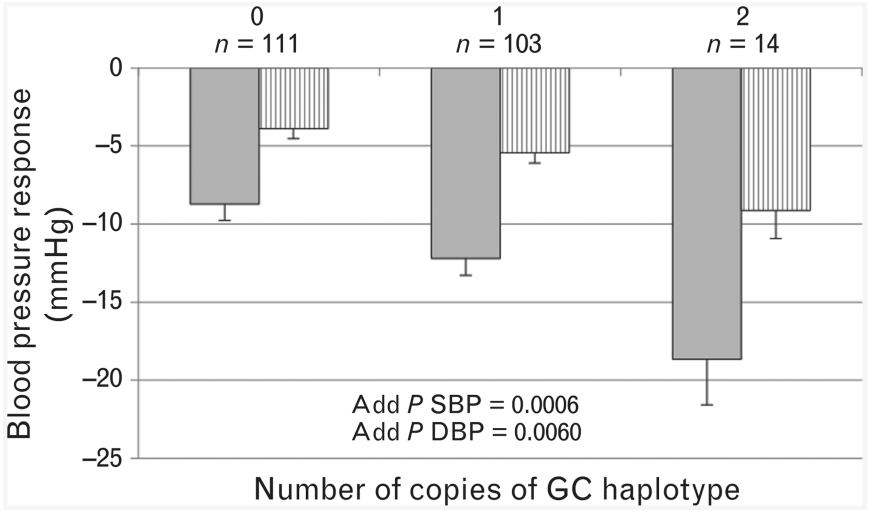

Figure 2.

Blood pressure response by copy of rs4149601-rs292449 GC haplotype in white patients treated with hydrochlorothiazide in PEAR. Solid gray bars indicate ΔSBP, and gray and white lined bars indicate ΔDBP. Values are shown as means ± standard error. Add: additive.

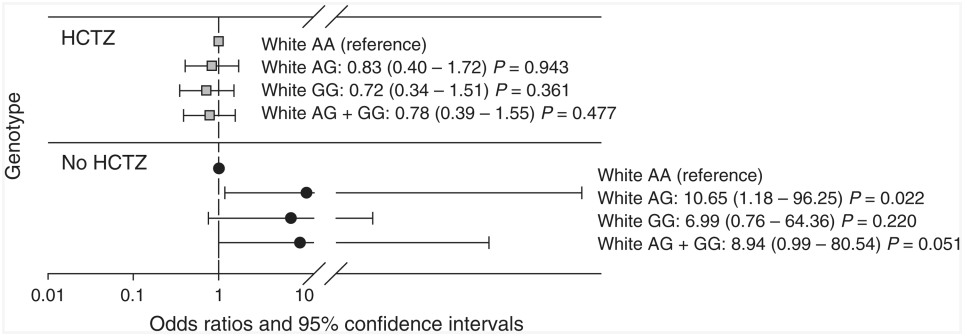

Figure 3.

Effect of rs4149601 and hydrochlorothiazide treatment on the risk of the primary outcome in INVEST. The gray square point estimates correspond to HCTZ-treated individuals, and the black circle point estimates correspond to individuals not treated with HCTZ (No HCTZ).

Table 1
Baseline demographics and characteristics in PEAR

Characteristics	Patients (*n* = 767)
Age, mean (SD) (years)	48.8 (9.2)
Male	363 (47.3)
Race	
White	465 (60.6)
African-American	302(39.4)
Duration of hypertension, mean (SD) (years)	6.6 (7.2)
Smoking status	
Current smoker	111 (14.5)
Ex-smoker	180 (23.4)
BMI, mean (SD) (kg/m^2)	30.8 (5.5)
Baseline clinic blood pressure	
SBP, mean (SD) (mmHg)	151.4 (12.6)
DBP, mean (SD) (mmHg)	98.4 (6.1)

Values are presented as number (percentage) unless otherwise noted.

Table 2
Baseline demographics and characteristics in INVEST

Characteristics	Cases (*n* = 269)	Controls (*n* =1076)
Age, mean (SD) (years)	70.9 ± 10.6	70.3 ± 9.4
Male	134 (49.8)	536 (49.8)
Race/ethnicity		
White	159 (59.1)	636 (59.1)
Hispanic	76 (28.3)	304 (28.3)
African-American	34 (12.6)	136 (12.6)
BMI, mean (SD) (kg/m^2)	27.4 ± 4.7	28.9 ± 5.5
SBP, mean (SD) (mmHg)	150.4 ± 18.5	148.7 ± 18.0
DBP, mean (SD) (mmHg)	83.5 ± 11.3	84.1 ±10.2
Heart rate, mean (SD) (beats/min)	75.8 ± 8.6	74.3 ± 9.7
Medical history:		
Diabetes	99 (36.8)	72 (6.7)
Heart failure (class I–III)	28 (10.4)	41 (3.8)
Myocardial infarction	102 (37.9)	288 (26.8)

Values are presented as number (percentage) unless otherwise noted.