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## Genomic Association Analysis of Common Variants Influencing Antihypertensive Response to Hydrochlorothiazide

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### Abstract

To identify novel genes influencing blood pressure response to thiazide diuretic therapy for hypertension, we conducted genome-wide association meta-analyses of  $\approx 1.1$  million single nucleotide polymorphisms in a combined sample of 424 European Americans with primary hypertension treated with hydrochlorothiazide from the Pharmacogenomic Evaluation of Antihypertensive Responses Study (N=228) and the Genetic Epidemiology of Responses to Antihypertensive Study (N=196). Polymorphisms associated with blood pressure response at  $p < 10^{-5}$  were tested for replication of the associations in independent samples of hydrochlorothiazide-treated European hypertensives. The rs16960228 polymorphism in protein

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kinase C, alpha replicated for same-direction association with diastolic blood pressure response in the Nordic Diltiazem Study (N=420) and the Genetics of Drug Responsiveness in Essential Hypertension Study (N=206), and the combined four-study meta-analysis  $p$ -value achieved genome-wide significance ( $p=3.3 \times 10^{-8}$ ). Systolic/diastolic blood pressure responses were consistently greater in carriers of the rs16960228 A allele than in GG homozygotes (4/4 mmHg greater) across study samples. The rs2273359 polymorphism in the *GNAS-EDN3* region also replicated for same-direction association with systolic blood pressure response in the Nordic Diltiazem Study, and the combined three-study meta-analysis  $p$ -value approached genome-wide significance ( $p=5.5 \times 10^{-8}$ ). The findings document clinically-important effects of genetic variation at novel loci on blood pressure response to a thiazide diuretic, which may be a basis for individualization of antihypertensive drug therapy and identification of new drug targets.

## Keywords

Hypertension; high blood pressure; antihypertensive therapy/diuretics; hydrochlorothiazide; genomics; pharmacogenomics; protein kinase C

## Introduction

The purpose of this study was to scan the human genome for single nucleotide polymorphisms (SNPs) that predict blood pressure (BP) response to the most commonly prescribed thiazide diuretic, hydrochlorothiazide (HCT), in European Americans with primary hypertension. Although previous studies of genes hypothesized to regulate BP reported polymorphisms associated with BP response to diuretic therapy,<sup>1, 2</sup> none of the reported associations has been replicated across multiple independent studies.<sup>3</sup> In contrast to the approach of candidate gene studies, the genome-wide association (GWA) approach employed in the present study requires no a priori selection of candidate genes and has the potential to identify genes not previously implicated to influence BP or drug response.<sup>4</sup> Recent GWA analyses in persons of European descent document the success of this approach in identifying novel genetic variants influencing BP level, hypertension, and adverse cardiovascular disease outcomes.<sup>5</sup>

Our first objective was to conduct a GWA analysis for BP response to HCT in European American (i.e., White) participants in the Pharmacogenomic Evaluation of Antihypertensive Responses (PEAR) Study,<sup>6</sup> in whom office, home, ambulatory daytime and night time BP responses were measured and a weighted average BP response was calculated. While all four methods measure the same BP response signal (but with different errors), calculation of the weighted average BP response minimizes measurement error and, thereby, maximizes the signal-to-noise ratio and power to identify genetic predictors of BP response.<sup>7</sup> Our second objective was to further increase statistical power to discover novel SNPs influencing BP response to HCT by conducting a meta-analysis of the combined GWA analysis results from the PEAR Study participants and participants in our previous Genetic Epidemiology of Responses to Antihypertensives (GERA) Study.<sup>8</sup> Our third objective was to validate the SNPs most strongly implicated in the meta-analysis by testing for replication of the associations with BP response to HCT in independent samples of European hypertensives from the Nordic Diltiazem (NORDIL) Study,<sup>9</sup> the Genetics of Drug Responsiveness in Essential Hypertension Study (GENRES),<sup>10</sup> and a study conducted in Milan, Italy.

## Methods

### Study participants

The PEAR study (<http://clinicaltrials.gov/ct2/show/NCT00246519>) was approved by the Institutional Review Board at each site; all participants gave written informed consent; and all study procedures were in accordance with institutional guidelines and the Declaration of Helsinki and the U.S. Code of the Federal Regulations for Protection of Human Subjects.<sup>6</sup> The methods and procedures for recruitment, the initial consent and screening visit, physical examination, blood pressure measurement, and collection of blood and urine samples have been previously described (please see <http://hyper.aha.journals.org>, Supplementary Methods).<sup>11</sup> For the GWA analyses in PEAR participants (described below), a composite weighted average of the office, home, ambulatory daytime and nighttime BP responses was calculated based on the row sums of the inverse of the inter-method covariance matrices.<sup>7</sup> For the other study samples, the most precise measure of BP response available was analyzed, i.e., the office BP response for the GERA and NORDIL Study participants and the 24-hour ambulatory BP response for the GENRES and Milan (Italian) Study participants.

### Statistical analyses

In preliminary GWA analyses in HCT-treated European American PEAR Study participants, each SNP was tested for association with the BP response phenotypes using an additive model that included pretreatment blood pressure level, sex, and age as adjustment variables.<sup>12</sup> Although principal components (PC) analysis detected no population substructure, the first and second PCs were forced into all models. The SNP association results from both PEAR and GERA Study samples were combined in a meta-analysis, assuming fixed effects and using inverse-variance weighting as implemented in the METAL software program.<sup>13</sup> SNPs with meta-analysis  $p$ -values  $< 5 \times 10^{-8}$  were deemed genome-wide significant.<sup>14</sup> From SNPs with meta-analysis  $p$ -values  $< 1 \times 10^{-5}$ , we selected 1-2 SNPs with the smallest  $p$ -values at each locus to test for replication in the HCT-treated NORDIL Study participants. Replication in NORDIL Study participants was defined as a Bonferroni-corrected one-sided  $p < 0.05$ , since only SNPs with the same direction of effect as in PEAR and GERA Study participants were of interest. SNPs that replicated in NORDIL Study participants were further tested for replication in HCT-treated participants from the GENRES and the Milan (Italian) Study.

Additional validation of the SNP associations that replicated among HCT-treated European hypertensives was pursued in two ways. First, we assessed whether variation across the entire region of the genes identified (in hypertensives of European descent) may be associated with BP response to HCT among African Americans. Second, because known predictors of BP response to diuretics are inversely related to BP response to beta blockers and other inhibitors of the renin-angiotensin system,<sup>15</sup> we assessed whether the SNPs associated with BP response to HCT had opposite direction associations with BP response to a beta blocker in the PEAR Study European Americans randomized to atenolol.<sup>11</sup> Finally, we tested the *PRKCA* SNP most strongly and consistently associated with BP response to HCT (i.e., rs16960228) for association with lymphocyte mRNA expression (please see <http://hyper.aha.journals.org>, Supplementary Methods).

## Results

### Sample descriptions

The HCT-treated European Americans from the PEAR and GERA Studies did not differ significantly in the percentage of women or office systolic BP or diastolic BP responses (Table 1). Mean BMI was significantly less and mean age and pretreatment office BP were

significantly greater in the PEAR than GERA Study participants. In the PEAR Study participants, inter-individual variation of the weighted average of office, home, ambulatory daytime and nighttime BP response was less than for the office BP response, as expected.<sup>7</sup>

### Genome-wide association analyses of BP response to hydrochlorothiazide

No SNP reached the genome-wide significance level (i.e.,  $p < 5 \times 10^{-8}$ ) for association with systolic BP or diastolic BP response in the GWA analysis of the composite weighted average BP responses in PEAR Study HCT-treated European Americans (N=228), or in the separate GWA analysis of office BP responses in GERA Study HCT-treated European Americans (N=196), (please see <http://hyper.aha.journals.org>, Figure S1 and Table S1). However, in the meta-analysis of 1,092,841 SNP associations measured in both the PEAR and GERA Study participants (N=424), one SNP association achieved genome-wide significance for diastolic BP response and two SNP associations achieved genome-wide significance for systolic BP response (Figure 1). The SNP that achieved genome-wide significance for association with diastolic BP response was on chromosome 14q31.3 (rs2776546,  $p=4.9 \times 10^{-8}$ ), and the two SNP that achieved genome-wide significance for association with systolic BP response were on chromosome 9q22.33 (rs238,  $p=2.9 \times 10^{-8}$ ) and on chromosome 20p13 (rs4815273,  $p=4.5 \times 10^{-8}$ ). Each of these loci included from three to as many as 15 SNPs associated with the BP response at the  $p < 10^{-5}$  level of significance (please see <http://hyper.aha.journals.org>, Table S2).

The meta-analysis  $p$ -values for SNPs in genes previously reported to be associated with BP response to HCT<sup>1,2</sup> (e.g., adducin 1 and WNK lysine deficient protein kinase 1) did not achieve the  $p < 10^{-5}$  level of significance (please see <http://hyper.aha.journals.org>, Table S3) and were not considered in the replication analyses described below.

### Replication of SNP associations with BP responses to HCT in independent samples

We selected representative SNPs from each of the loci with meta-analysis  $p$ -values  $< 1 \times 10^{-5}$  (Table 2). The selected SNPs were tested for replication of the associations with the office BP responses to HCT in an independent sample of HCT-treated hypertensive Europeans from the NORDIL Study (N=420) (please see <http://hyper.aha.journals.org>, Supplementary Methods and Supplementary Table S4). Of the 10 SNPs tested for association with diastolic BP response, two SNPs in the chromosome 17q24.3 locus, rs4791040 and rs16960228, replicated for same-direction associations with office diastolic BP response (Table 2). The nominal 1-sided  $p$ -values for rs4791040 ( $p=6.3 \times 10^{-3}$ ) and for rs16960228 ( $p=6.0 \times 10^{-3}$ ) remained statistically significant after Bonferroni correction for the six diastolic BP response loci tested ( $p=0.04$ , for both). When the SNP association results from the three independent samples were combined, the three-study meta-analysis  $p$ -values approached genome-wide significance (for rs4791040,  $p=6.2 \times 10^{-8}$ ; for rs16960228,  $p=6.0 \times 10^{-8}$ ).

Although neither of the two chromosome 20p13 SNPs replicated for association with systolic BP response in the NORDIL Study participants, a chromosome 20q13.32 SNP, rs2273359, was nominally associated ( $p=2.5 \times 10^{-2}$ ) and the three-study meta-analysis  $p$ -value for its association with systolic BP response closely approached genome-wide significance ( $p=5.5 \times 10^{-8}$ ) (Table 2).

The chromosome 17q24.3 and chromosome 20p13 SNPs that replicated in NORDIL Study participants were further tested for replication in the GENRES and Milan (Italian) Study participants. The chromosome 17q24.3 SNP rs16960228 replicated for same-direction association with 24-hour ambulatory diastolic BP response to HCT in GENRES Study participants (N=206) (1-sided  $p=0.04$ ) but not with office diastolic BP response in the Milan

(Italian) Study participants (N=195) (1-sided  $p=0.58$ ). The combined four-study meta-analysis  $p$ -value for rs16960228 achieved genome-wide significance ( $p=3.3 \times 10^{-8}$ ). The variant A allele carriers from each of the five studies demonstrated consistently greater BP responses to HCT than the GG homozygotes (Figure 2). Based on the weighted average BP response phenotypes measured in PEAR Study participants, the estimated difference in systolic/diastolic BP response was 4/4 mmHg greater among the rs16960228 variant A allele carriers.

Although the chromosome 20q13 SNP rs2273359 was not measured or imputed in the GENRES or Milan (Italian) Study participants (and, therefore, could not be tested for replication in these additional independent samples), among the PEAR, GERA, and NORDIL Study participants, the variant G allele carriers from each of the three studies demonstrated consistently greater BP responses to HCT than the CC homozygotes (no GG homozygotes were observed) (Figure 3). Based upon the weighted average BP response phenotypes measured in PEAR Study participants, the estimated difference in systolic/diastolic BP response was 7/5 mmHg greater among the rs2273359 variant G allele carriers (Figure 3).

### Further validation of SNP associations with BP responses to antihypertensive drug therapy

**Regional associations in African Americans with HCT response**—The chromosome 17q24.3 SNP rs16960228 are located in the gene encoding protein kinase C, alpha (*PRKCA*), a plausible candidate to influence BP (see Discussion). SNPs in the nearby chromosome 17q24.2 region of *PRKCA* were significantly associated with diastolic BP response to HCT in PEAR African Americans (N=148) (e.g., rs6504428;  $p=8.8 \times 10^{-5}$ ) (please see <http://hyper.aha.journals.org>, Supplementary Figure S2). The chromosome 20q13.32 SNP rs2273359 is in the gene encoding TH1-like (*TH1L*) between *GNAS* and *EDN3*, a region associated with BP level and hypertension in GWA meta-analyses of large samples of European descent.<sup>5</sup> SNPs in the chromosome 20q13.32 region between *TH1L* and *GNAS1* were also associated with systolic BP response to HCT in PEAR African Americans (e.g., rs234613,  $p=0.02$ ) (please see <http://hyper.aha.journals.org>, Supplementary Figure S4). There were differences between races in the linkage disequilibrium between these and other SNPs across the *PRKCA* gene and the *GNAS-TH1L* regions (please see <http://hyper.aha.journals.org>, Supplementary Figures S4 and S5).

**Opposite direction association with BP response to atenolol**—In a parallel, independent sample of PEAR Study European Americans randomized to atenolol (N=233),<sup>6</sup> the chromosome *PRKCA* SNP rs16960228 was associated with diastolic BP response to the beta blocker with the direction of association opposite to that observed with BP response to HCT (1-sided  $p=0.01$ ). The chromosome 20q13 SNP rs2273359, however, was not significantly associated with systolic BP response to atenolol in the PEAR European American study participants ( $p=0.95$ ).

**Gene expression analysis of PRKCA**—Gene expression of *PRKCA* was measured using RNA isolated from whole blood collected prior to HCT treatment (baseline) from 36 European American PEAR Study participants selected based on rs16960228 genotype (please see <http://hyper.aha.journals.org>, Supplementary Methods). Carriers of the rs16960228 variant A allele (N=12) had significantly greater mean relative *PRKCA* expression level than the GG homozygotes (N=24) ( $p=0.03$ ) (Figure 4).



## Discussion

We sought to identify common genetic variants in Whites of European descent that are predictive of BP response to HCT, the most commonly-prescribed diuretic for the treatment of hypertension.<sup>16</sup> Our results provide substantial evidence that chromosome 17q24 variation within *PRKCA* influences inter-individual variation in BP response to HCT. We found statistically significant and directionally consistent associations of rs16960228 with diastolic BP response to HCT in four independent samples of White hypertensives of European descent, with a directionally consistent albeit not statistically significant association in a fifth European sample. The association of rs16960228 with diastolic BP response to HCT achieved genome-wide significance in a meta-analysis combining results from the first four samples. The contribution of *PRKCA* variation to differences in BP response to HCT was further validated by finding that other SNPs within *PRKCA* were associated with diastolic BP response to HCT in hypertensive African Americans. Among European American hypertensives, the association of rs16960228 with diastolic BP response to atenolol was directionally opposite to its association with diastolic BP response to HCT, as is the case for known predictors of BP response to these two drug classes.<sup>15</sup> Finally, the rs16960228 variant A allele that predicted greater BP response to HCT was also found to be associated with greater pretreatment *PRKCA* expression.

Our results also provide evidence that chromosome 20q13.32 variation in a region between *GNAS* and *EDN3*, which previous GWA meta-analyses of large samples of European descent have associated with BP level and hypertension,<sup>5</sup> may also influence BP response to HCT. We found statistically significant and directionally consistent associations of rs2273359 within *THIL* with systolic BP response to HCT in the three independent samples of White hypertensives of European descent in which this SNP was available for analyses, and the three-study meta-analysis *p*-value closely approached genome-wide significance. The possible role for variation in this region in influencing BP response was bolstered by finding that other chromosome 20q13.32 SNPs between *THIL* and *GNAS* were associated with systolic BP response to HCT in African American hypertensives.

The target of HCT and other thiazide-like diuretics is the sodium-chloride cotransporter in the distal convoluted tubule.<sup>17</sup> Variants in the regulators of renal sodium transport, or in the vasoactive systems opposing BP decline in response to sodium and volume loss, are obvious candidates to influence BP response to HCT.<sup>15</sup> From this perspective, variations in both of the identified gene regions appear to be plausible candidates to influence BP response to HCT. *PRKCA* expression has been reported in brain, endothelium, heart and cardiac myocytes, smooth muscle, kidney, and adrenal cortex.<sup>18-20</sup> The *PRKCA* protein is involved in calcium signaling, vascular smooth muscle contraction, vascular endothelial growth factor signaling, and aldosterone-regulated sodium reabsorption pathways.<sup>21</sup> *THIL* is downstream of *GNAS*, the stimulatory G-protein alpha subunit (Gs-), a key component of the signal transduction pathway linking receptor-ligand interactions with the activation of adenylyl cyclase and a variety of cellular responses including calcium signaling and vascular smooth muscle contraction.<sup>21</sup>

Replication across multiple, appropriately-designed, well-powered, independent samples has become the gold standard for reliability of pharmacogenetic associations.<sup>4</sup> By this standard, the present GWA meta-analysis of BP response to HCT is unique among genetic studies of antihypertensive drug responses. The only two previously reported GWA analyses for BP response to antihypertensive drugs did not have available samples to test for replication across independent studies.<sup>22, 23</sup> None of the several prior report associations of polymorphisms in hypothesized candidate genes<sup>1, 24</sup> has been consistently replicated across

independent studies,<sup>3</sup> and none of the hypothesized candidate genes is within the regions identified in subsequent GWA analyses.<sup>22, 23</sup>

The present study has several limitations. First, even though the sample size for the combined PEAR and GERA Study GWA meta-analysis was twofold greater than the previous GWA analysis of BP response to HCT,<sup>22</sup> power was not adequate to detect variants with small effects on BP response comparable to those found for BP level and hypertension.<sup>5, 7</sup> Second, even though the identified chromosome 17q24 and 20q13.32 regions harbor genes that are biologically plausible candidates, the SNPs we analyzed are intronic in *PRKCA* and *THIL* and unlikely to be functional. Presumably, they are in linkage disequilibrium with functional variants that influence gene expression or protein structure but have not been identified.

## Perspective

Large inter-individual differences in BP response reported since the earliest trials involving thiazide diuretics<sup>25</sup> have been attributed to variation in activity of the BP regulatory systems targeted by antihypertensive drugs.<sup>26</sup> Measurements of genetic variation hold the promise of individualization of antihypertensive drug therapy based on matching the pathophysiologic disturbance elevating BP to the pharmacological action of the drug prescribed. Results of the present study support GWA analysis as an effective method to identify common genetic variants that may be a basis for individualization of antihypertensive drug therapy and identification of new drug targets.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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## Novelty and Significance

### What Is New?

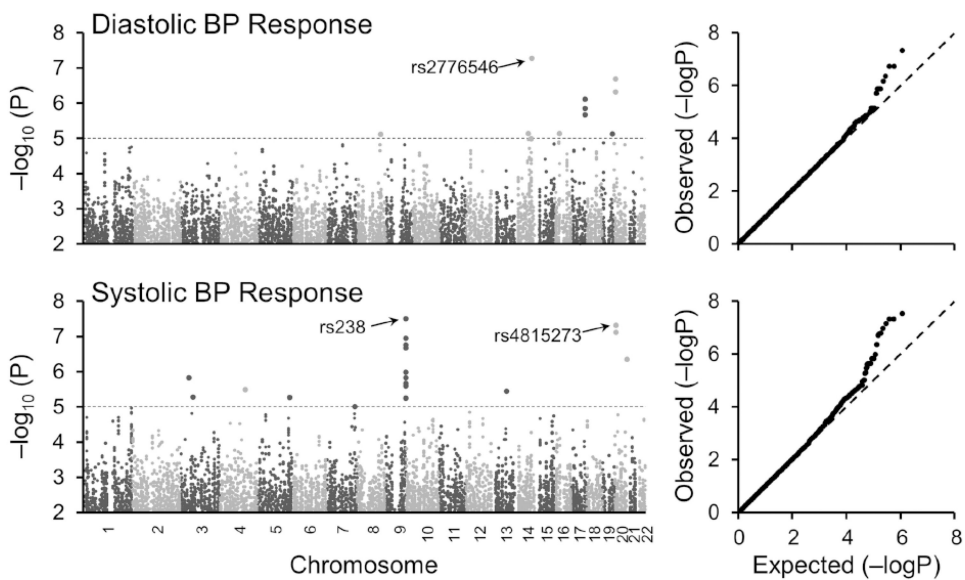
Meta-analysis of two GWA analyses of BP response to the most commonly prescribed antihypertensive drug hydrochlorothiazide in European American hypertensives with replication of single nucleotide polymorphism associations in independent samples of European hypertensives.

### What Is Relevant?

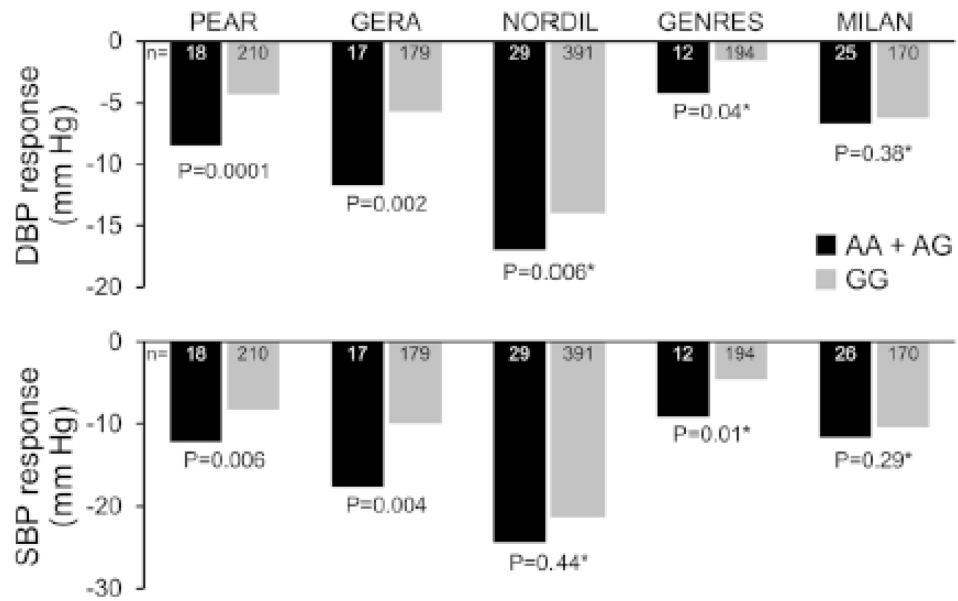
Common variants in protein kinase C, alpha (PRKCA) and in the stimulatory G-protein alpha subunit (GNAS) region have clinically relevant effects on BP response to hydrochlorothiazide in hypertensives of European descent that may be a basis for individualization of antihypertensive drug therapy and identification of new drug targets

### Summary

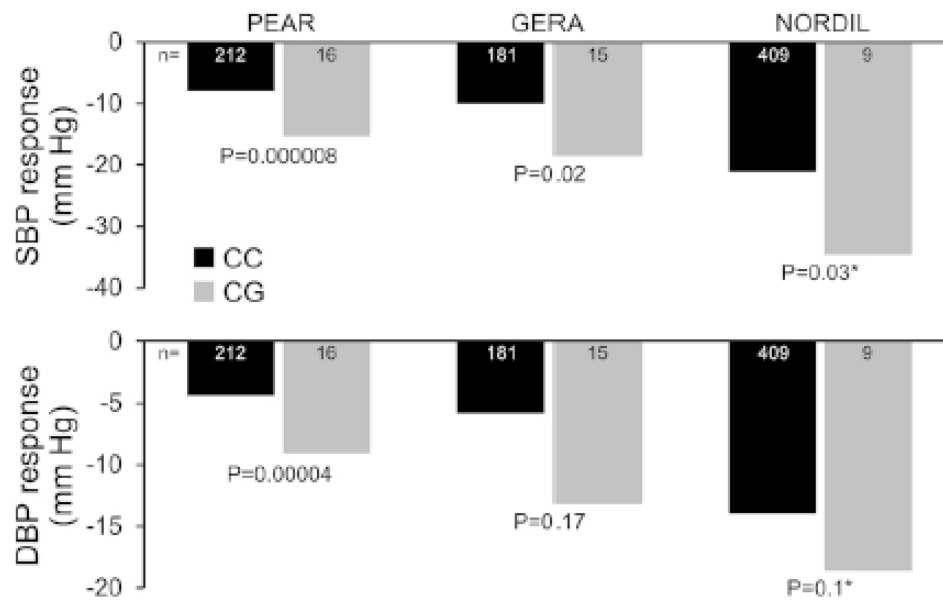
Meta-analysis of two GWA analyses of BP response to hydrochlorothiazide in European American hypertensives succeeded in identifying common genetic variants that have clinically relevant effects on BP response that replicate in European hypertensives treated with a thiazide diuretic.



**Figure 1.** Manhattan plots and quantile-quantile plots from meta-analysis of genome-wide association analysis results for blood pressure response to hydrochlorothiazide in European American PEAR and GERA study participants.

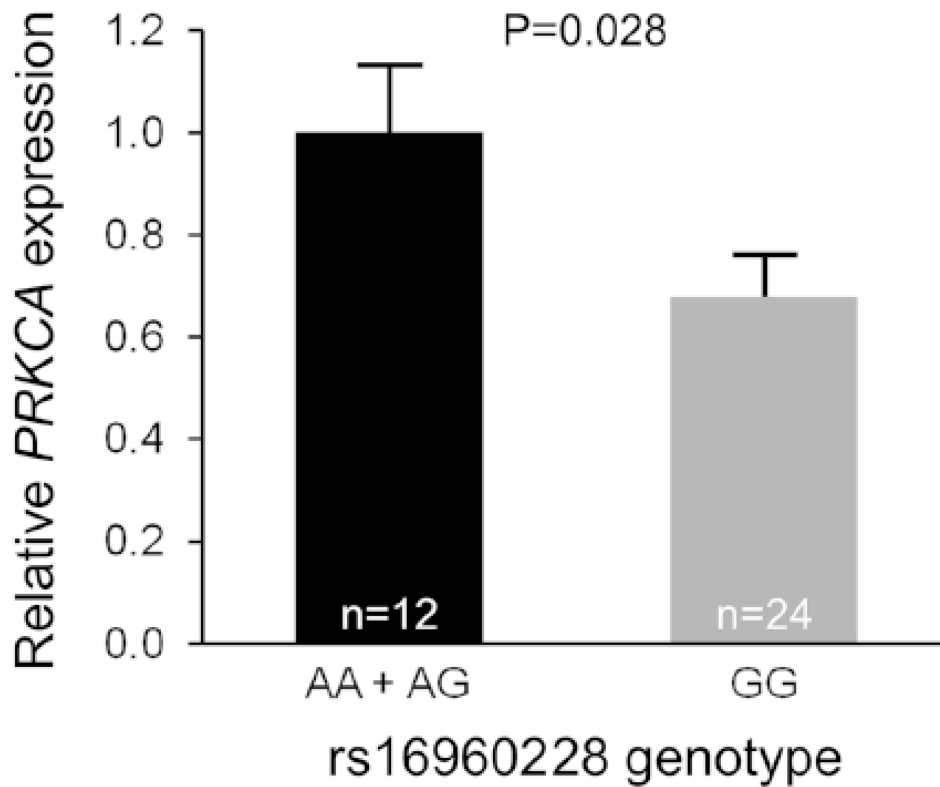


**Figure 2.** Plot of blood pressure response to hydrochlorothiazide by chromosome 17 rs16960228 genotype of participants from five independent studies. Panel A: diastolic blood pressure response; Panel B: systolic blood pressure response. The blood pressure responses are adjusted for pretreatment blood pressure levels, age, and sex and  $p$ -values are for contrast of adjusted means between genotype groups.



**Figure 3.** Plot of blood pressure response to hydrochlorothiazide by chromosome 20 rs2273359 genotype of participants from three independent studies. Panel A: systolic blood pressure response; Panel B: diastolic blood pressure response. The blood pressure responses are adjusted for pretreatment blood pressure levels, age, and sex and *p*-values are for contrast of adjusted means between genotype groups.





**Figure 4.** Plot of relative gene expression of *PRKCA* by rs16960228 genotype in whole blood collected from European American PEAR Study participants at baseline prior to HCT treatment. Expression data were normalized to beta-2 microglobulin; error bars indicate standard error of mean.

**Table 1**  
**Description of hydrochlorothiazide-treated European Americans from the PEAR and GERA studies**

Descriptive characteristic	PEAR study participants N=228	GERA study participants N=196	<i>p</i> -value
Women, N (%)	91 (40)	84 (43)	0.54
Age, years	50.4 ±9.4	48.5 ±7.3	0.02
BMI, kg·m <sup>-2</sup>	30.3 ±4.9	31.3 ±5.57	0.04
Pretreatment office systolic BP, mmHg	151.8 ±12.4	142.7 ±12.6	<0.0001
Pretreatment office diastolic BP, mmHg	98.1 ±5.8	95.6 ±5.7	<0.0001
Office systolic BP response, mmHg	-11.0 ±12.8	-10.9 ±13.0	0.97
Office diastolic BP response, mmHg	-5.01±7.17	-6.26 ±8.83	0.11
Composite average systolic BP response, mmHg	-8.5 ± 7.02	NA	NA
Composite average diastolic BP response, mmHg	-4.68 ± 4.79	NA	NA

PEAR, Pharmacogenomic Evaluation of Antihypertensive Responses; GERA, Genetic Epidemiology of Responses to Antihypertensives; BMI, body mass index; BP, blood pressure; NA, not available. BP response was defined as final minus baseline value (negative sign indicates BP decline in response to drug and was adjusted for pretreatment BP level, age, gender. In PEAR study participants, the composite average BP response is a weighted average of the office, home, ambulatory daytime and nighttime BP responses.

**Table 2**  
**Single nucleotide polymorphisms associated with blood pressure response to hydrochlorothiazide in meta-analyses of genome-wide association analyses of European American samples and replication analysis of European sample**

BP Response	SNP	Chr	Alleles	Meta-analysis of PEAR+GERA study GWA analyses		Replication analysis in NORDIL study participants		PEAR+GERA+NORDIL study meta-analysis	
				Allele Freq	p-value	Allele Freq	p-value*	Allele Freq	p-value
Diastolic	rs2432742	8	A G	0.86	7.03E-06	0.82	6.16E-01	-1.57	5.22E-04
	rs221903	14	T C	0.37	6.98E-06	0.37	4.33E-01	1.15	2.40E-04
	rs2776546	14	A C	0.87	4.9E-08	0.84	9.80E-02	-2.22	7.07E-07
	rs9933692	16	A G	0.22	6.93E-06	0.19	6.79E-01	-1.36	2.95E-04
	rs4074471	16	T G	0.78	6.92E-06	0.81	6.80E-01	1.36	2.94E-04
	rs4791040	17	T C	0.96	1.36E-06	0.96	6.25E-03	4.17	6.19E-08
	rs16960228	17	A G	0.04	1.37E-06	0.04	5.96E-03	-4.16	6.03E-08
	rs7247267	19	T G	0.25	7.05E-06	0.21	4.79E-01	1.40	1.43E-03
	rs4815273	20	T C	0.46	1.96E-07	0.45	7.36E-01	-1.20	7.36E-05
	rs6083538	20	T C	0.45	4.6E-07	0.45	7.35E-01	-1.18	1.28E-04
	rs2306667	3	T C	0.83	4.88E-06	0.77	3.35E-01	2.63	6.05E-05
	rs17010902	4	A G	0.07	3.12E-06	0.06	8.11E-01	-4.34	8.02E-04
	rs4376293	5	T C	0.49	5.01E-06	0.41	7.14E-01	-1.77	2.08E-04
	rs11763492	7	A G	0.22	9.35E-06	0.24	9.69E-01	-1.59	4.51E-03
	rs13223171	7	T C	0.22	9.44E-06	0.24	9.67E-01	-1.59	4.29E-03
	rs689979	9	T C	0.45	2.02E-06	0.44	6.79E-01	1.84	1.36E-04
	rs238	9	A G	0.46	2.90E-08	0.45	1.10E-01	2.22	9.61E-6
	rs4815273	20	T C	0.46	4.50E-08	0.45	3.45E-01	-2.34	5.65E-07
	rs6083538	20	T C	0.45	6.84E-08	0.44	3.38E-01	-2.34	7.95E-07
rs2273359	20	C G	0.04	4.15E-07	0.02	2.47E-02	8.15	5.54E-08	

PEAR, Pharmacogenomic Evaluation of Antihypertensive Responses; GERA, Genetic Epidemiology of Responses to Antihypertensives; NORDIL, Nordic Diltiazem Study; BP, blood pressure; alleles: coded allele shown to the left of the non-coded allele as in the example of A/G SNP in which AA=0, AG=1 and GG=2, where G is the coded and A the non-coded allele; allele freq, frequency of the coded allele;  $\beta$ , model regression coefficient, mmHg per coded allele; \*, 1-sided p-value for same direction association as in meta-analysis of PEAR+GERA study participants.