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## Heritability of Blood Pressure Responses to Cold Pressor Test in a Chinese Population

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### Abstract

**BACKGROUND**—Genetic determinants of blood pressure (BP) responses to the cold pressor test (CPT), a phenotype associated with risk of hypertension and cardiovascular disease has not been well studied.

**METHODS**—We examined the heritability of BP response to CPT in 1,994 subjects from 627 families in rural north China. BP was measured prior to and at 0, 1, 2, and 4 minutes after the participants immersed their hand in ice water for 1 minute. Heritabilities of baseline BP and responses at 0 minutes, maximum response, and area-under-the-curve during CPT were computed using a variance components method. Additionally, bivariate heritabilities were calculated to test the existence of shared genetic determinants between baseline BP and responses to CPT.

**RESULTS**—Heritabilities of baseline BP and responses to CPT were estimated from 14% to 35%, which all significantly differed from 0 ( $p \leq 0.002$ ). Genetic correlations (standard error) due to the same genes between baseline BP and responses to CPT ranged from  $-0.07$  (0.14) to 0.21 (0.15), which were not significantly different from 0. Genetic correlations between reactivity and recovery were 0.67 (0.10) and 0.59 (0.10) for systolic and diastolic BP, respectively, which were significantly different from 0.

**CONCLUSIONS**—We concluded: 1) baseline BP and BP responses to CPT had strong genetic determinants; 2) baseline BP and BP response to CPT did not share the same genetic components; and 3) BP reactivity and recovery shared the same genetic components. These findings may lead to a better understanding of the genetic mechanism of BP responses to CPT.

### Keywords

blood pressure; heritability; cold pressor test; genetics; hypertension

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Disclosures  
None

## Introduction

It is well documented that genes, environment, and gene-environment interactions determine an individual's blood pressure (BP) level and risk of hypertension<sup>1</sup>. Genetic epidemiology studies reported that the heritability of BP, the proportion of variance explained by genetic factors, ranged from 20% to 50% in human populations<sup>2</sup>. These studies also indicated that genetic influences on BP varied by race, age, and environmental factors<sup>2-5</sup>.

The cold pressor test (CPT), which measures the response of BP to the stimulus of external cold, has long been a standard test for characterization of sympathetic function and has been documented to predict the subsequent risk of hypertension in normotensive persons<sup>6-9</sup>. Twin and pedigree studies reported that BP reactivity to CPT was significantly influenced by genetic effects<sup>10-14</sup>. For example, significant heritabilities were found for systolic BP (SBP) responses (0.12-0.37) but not for diastolic BP (DBP) among 419 individuals distributed across four large European American families<sup>13</sup>. A recent study reported a significant genetic influence on BP reactivity and recovery during CPT among 835 participants from 18 extended Amish families<sup>14</sup>. It was also found that both shared and unshared genetic factors influence BP reactivity and recovery. Shared genetic factors contribute to the total correlation of the two phenotypes, and this genetic correlation can be inferred by bivariate analysis. The heritability of BP responses to CPT and the genetic correlation between BP reactivity and recovery has not been reported in Asian populations.

In the Genetic Epidemiology Network of Salt Sensitivity (GenSalt) study, we conducted CPT among 1,994 subjects from 627 families living in rural north China. In this analysis, we report the heritabilities of BP responses to CPT as well as the genetic correlations between baseline, reactivity, and recovery BP phenotypes.

## Methods

### Study Participants

The GenSalt study participants were recruited from 6 sites in rural areas of north China. These sites were selected based on homogeneity of the population with respect to ethnicity, lifestyle and nutritional risk factors<sup>15</sup>. A community-based BP screening was conducted among persons aged 18-60 years in the study villages to identify potential probands and their families for the study. Those with mean systolic BP between 130-160 mm Hg and/or diastolic BP between 85-100 mm Hg and no use of antihypertensive medications and their siblings, offspring, parents, and spouses were recruited for the CPT study. The detailed eligibility criteria for the probands and siblings/offspring/parents/spouses are presented elsewhere<sup>15</sup>. In general, individuals who had stage-2 hypertension, secondary hypertension, use of antihypertensive medications, history of clinical cardiovascular disease, diabetes, or chronic kidney disease, pregnancy, or heavy alcohol use were excluded from the GenSalt study. Overall, 2,000 subjects took part in the CPT and 1,994 participants from 627 families completed the entire test and were included in this analysis. Family relationships were verified using genome-wide microsatellite data.

Institutional Review Boards at all participating institutes approved the GenSalt study. Written informed consent was obtained from each participant.

### Data Collection

A standardized questionnaire was administered by a trained staff member to collect information on demographic characteristics, personal and family medical history, and lifestyle risk factors. BP measurements were obtained at each clinical visit by trained and certified observers according to a common protocol adapted from procedures recommended

by the American Heart Association<sup>16</sup>. Participants were advised to avoid alcohol, cigarette smoking, coffee/tea, and exercise for at least 30 minutes prior to their BP measurement. After the participant had remained sitting for 20 minutes and before the ice water immersion, 3 BP measurements were obtained using a standard mercury sphygmomanometer. The mean of these three BP measurements was considered the baseline BP. Then, the participant immersed their left hand in the ice water bath (3°C to 5°C) to just above the wrist for 1 minute. BP measurements at 0, 1, 2, and 4 minutes were obtained using a standard mercury sphygmomanometer after the left hand had been removed from the ice water bath. The CPT was well-tolerated in all subjects and no side effects were reported.

### Statistical Analyses

Heritability was analyzed for baseline BP and BP responses to CPT, including the maximum BP response, BP response at time 0, and area-under-curve (AUC) above baseline BP. Response at time 0 is the difference between BP at time 0 and baseline BP; and maximum response is the largest BP difference between BP at any of the 4 CPT tested time-points and baseline BP. In addition, the AUC of BP response to CPT was further divided into BP reactivity (from baseline to time 0) and recovery (from time 0 to time 4).

Pearson's correlations between BP responses and age, sex, generation, field center, baseline BP, BMI, water temperature, room temperature and arm circumference are  $-0.133\sim 0.146$ . The BP responses were adjusted for the effects of age, sex, generation, and field center groups. BP responses were regressed on the covariates in a stepwise manner, and only those with significant p-values (less than 0.05) were retained. Next, the squared residual from the first regression was regressed on the same covariates in a stepwise manner to control for heteroscedasticity. The final adjusted phenotype was computed as the residual from the first regression, divided by the square root of the predicted score from the second regression. A final standardization step was taken to ensure a mean of zero and a standard deviation of one.

Heritability analysis was performed using a maximum likelihood variance components method that was implemented in the program SOLAR<sup>17</sup>. For a phenotype variable  $y$ , its variance ( $\sigma_y^2$ ) is decomposed into the part from the additive genetic effect ( $\sigma_g^2$ ) and the remaining part from the unexplained effect ( $\sigma_e^2$ ), i.e.  $\sigma_y^2 = \sigma_g^2 + \sigma_e^2$ . The heritability ( $h^2$ ) of phenotype  $y$  is computed by the ratio of variance attributable to additive genetic effects ( $\sigma_g^2$ ) versus the total phenotypic variance ( $\sigma_y^2$ ),  $h^2 = \sigma_g^2 / \sigma_y^2$ . The hypothesis test of no heritability ( $H_0: h^2 = 0$ ) versus having heritability ( $H_1: h^2 \neq 0$ ) is conducted by likelihood ratio test.

We also performed a bivariate analysis to estimate the correlations of genetic components using SOLAR<sup>17</sup>. For a pair of traits,  $y_1$  and  $y_2$ , with heritabilities  $h_1^2$  and  $h_2^2$  respectively, their correlation ( $\rho$ ) can be decomposed into genetic correlation ( $\rho_g$ ) and environment correlation ( $\rho_e$ ) according to the following mathematical formula:

$\rho_p = \rho_g \sqrt{h_1^2 h_2^2} + \rho_e \sqrt{(1 - h_1^2)(1 - h_2^2)}$ . We tested the null hypothesis  $\rho_g = 0$  versus  $H_1: \rho_g \neq 0$  to infer correlated or shared genetic effects (reject  $H_0$ ), and tested the null hypothesis of  $\rho_g = 1$  (or  $-1$ ) versus  $H_1: \rho_g \neq 1$  (and  $-1$ ) to infer independent or non-shared genetic effects (reject  $H_0$ ). We also tested  $H_0: \rho_e = 0$  versus  $H_1: \rho_e \neq 0$  for correlated or shared environment effects.

BMI, water temperature, room temperature and arm circumference were used as covariates in the heritability and bivariate analysis by SOLAR<sup>17</sup>.

## Results

The 1,994 participants who completed CPT consisted of 638 probands, 921 siblings, 61 spouses, 182 parents and 192 offspring from 627 two and three generation families. The characteristics of study participants are summarized in table 1. As expected, the probands had the highest mean baseline levels of body mass index (BMI), SBP and DBP among all groups.

The mean SBP and DBP responses to CPT are presented in figure 1. Both mean SBP and DBP achieved maximum levels at time 0 after ice water immersion for one minute among all groups. Thereafter, mean BP levels gradually recovered back to the baseline level 4 minutes after cold stimulus. Ninety-one point five percent of probands, 95.6% of parents, 90.2% of siblings, 100% of spouses and 96.4% of offspring achieved maximum SBP at time 0 while 80.4% of probands, 80.8% of parents, 81.4% of siblings, 83.6% of spouses and 82.8% of offspring achieved maximum DBP at time 0. Table 2 shows the maximum BP responses, BP responses at time 0 and AUC of BP responses for both SBP and DBP. The parents had the largest SBP responses but smallest DBP responses while offspring had the smallest SBP responses but largest DBP responses. This pattern was similarly observed for absolute BP responses as well as reactivity AUC. On the other hand, probands had the largest and offspring had the smallest recovery AUC of SBP while spouses had the largest and parents had the smallest recovery AUC of DBP.

Table 3 presents the heritabilities (standard error, SE) of baseline BP and BP responses to CPT. All heritability estimates are significantly different from zero (all  $p \leq 0.002$ ). The heritabilities of baseline BP were 0.20 for SBP and 0.35 for DBP. The heritabilities of SBP responses to CPT varied from 0.28 to 0.30 while the heritabilities of DBP responses to CPT varied from 0.25 to 0.28. The heritability of SBP recovery AUC was 0.14 and DBP recovery AUC was 0.20. The overall AUC was 0.16 for SBP and 0.21 for DBP.

Table 4 shows that genetic correlations ( $\rho_G$ ) between baseline SBP and SBP responses to CPT (maximum response, response at time 0, and reactivity, recovery and overall AUC) varied from 0.16 to 0.21, which were not significantly different from 0 but differed from 1. On the other hand, the genetic correlation between SBP reactivity and recovery AUC was 0.67, which significantly differed from both 0 and 1. The environmental correlation was not significant between baseline SBP and maximum SBP response and SBP response at time 0, but significant between baseline SBP and SBP recovery AUC and overall AUC. Both genetic and environmental correlations between SBP recovery and reactivity AUC significantly differed from 0. A similar pattern of genetic correlations was observed between baseline DBP and DBP responses to CPT. Environmental correlation, however, was significant between baseline DBP and all DBP responses to CPT.

## Discussion

This study contributes to our understanding on the genetic mechanisms of BP responses to CPT in several ways. To our knowledge, this is the largest family study and the first one in an Asian population to examine the genetic contribution to BP responses to CPT, which adds to findings from other populations<sup>13, 14</sup>. Our study also comprehensively examined the heritabilities of absolute BP responses, AUC of BP responses, as well as AUC of BP reactivity and recovery. Furthermore, genetic correlations among baseline BP and BP responses to CPT were investigated.

Additional strengths of our study include that all study participants were living in north rural China with homogeneous lifestyles for many generations and were all of Han Chinese ethnicity. A stringent quality control process was implemented during data collection. We

controlled for potential confounding effects due to age, sex, generation, field center, BMI, water temperature, room temperature and arm circumference in our analysis.

Our study documents a genetic influence on baseline BP with heritability of 20%-35% which is consistent with prior reports in Western populations<sup>3, 4, 13, 14, 18-20</sup>. Our study further indicates that both SBP and DBP responses to CPT are significantly inheritable. A few twin studies similarly suggested a genetic basis for both SBP and DBP responses to CPT.<sup>11, 12, 21</sup> In addition, two previous family studies in Caucasians reported a significant heritability of BP responses to CPT, although one of them did not show significant heritability for DBP<sup>13</sup>.

The CPT method in our study differs from one conducted in Amish families<sup>14</sup>. In the present study, subjects immersed their hand in ice water for 1 minute and BP measurements were taken after the cold stimulation. In contrast, in the Amish families, subjects immersed their hand in ice water for 2.5 minutes and BP measurements were taken both during and after the stimulation. Due to these methodological differences, the highest BP responses occurred at different times and altered the estimation of BP reactivity and recovery. In spite of this variation, both studies concluded that BP response is inheritable, and that both shared and unshared genetic components underlie BP reactivity and recovery during CPT.

Our bivariate analysis of genetic correlation indicates independent genetic effects between baseline BP and BP responses to CPT. This is consistent with previous twin studies that showed no evidence for common genetic effects on baseline BP and BP responses to CPT<sup>11, 12, 21</sup>, and is also consistent with a previous family study that showed no genetic correlation between baseline BP and BP responses to CPT<sup>13</sup>. Our findings of an independent genetic effect may suggest different physiologic pathways involved in the regulation of baseline BP and BP response to CPT.

Our study showed that BP recovery had a strong positive genetic correlation with BP reactivity during CPT. This finding suggests that the same genes might influence both BP recovery and reactivity. Nevertheless, our findings also suggest that BP recovery and reactivity are not the result of complete pleiotropy and unique genes are responsible for BP recovery and reactivity, given the fact that the genetic correlation significantly differs from 1 ( $p \leq 0.005$ ). The shared but incomplete pleiotropic effects were also consistently found in a recent family study conducted by Roy-Gagnon et al<sup>14</sup>.

In summary, our findings of genetic influences on baseline BP and BP responses to CPT in Chinese participants are in strong agreement with previous family and twin studies in Western populations. Our results contribute new evidence that different genetic factors are responsible for the regulation of baseline BP and BP responses to CPT, and both different and common genetic factors controlled BP reactivity and recovery during CPT. These findings could be used to guide the search for specific genes underlying baseline BP and BP responses to CPT. Not only can the finding of genetically correlated traits increase the power of linkage mapping, but also differentiate pleiotropic effects from coincidence linkage<sup>22</sup>.

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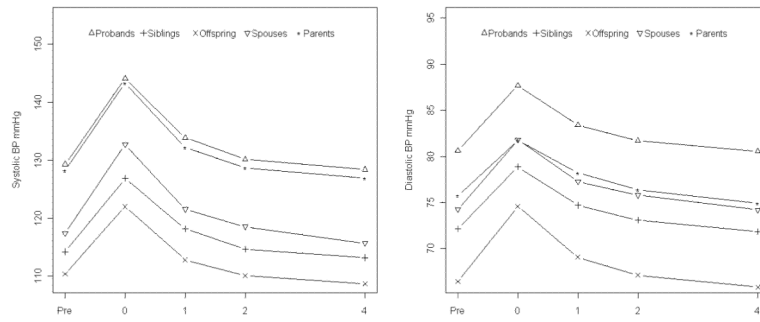
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**Figure 1.**

Mean systolic blood pressure (left panel) and mean diastolic blood pressure (right panel) during the cold pressor test among probands, siblings, offspring, spouses, and parents. Pre, 0, 1, 2 and 4 on the x-axis indicate cold pressor test time points: prior to ice water immersion, immediately after end of ice water immersion, and 1, 2 and 4 minutes after end of ice water immersion.



Table 1

## Characteristics of 1,994 Study Participants

	Probands	Siblings	Offspring	Spouses	Parents
No. of subjects	638	921	192	61	182
Age, years	40.7 ± 8.2	39.5 ± 7.7	23.5 ± 6.7	48.7 ± 6.5	55.5 ± 3.7
Male, %	61.1	50.6	46.4	32.8	44.8
BMI, kg/m <sup>2</sup>	24.2 ± 3.3	23.1 ± 2.9	21.5 ± 3.3	23.7 ± 3.7	23.6 ± 3.5
SBP, mm Hg	129.3 ± 12.1	114.3 ± 12.7	110.6 ± 12.3	117.0 ± 17.1	128.3 ± 21.4
DBP, mm Hg	80.6 ± 9.7	72.2 ± 9.8	66.6 ± 9.4	74.2 ± 11.2	75.6 ± 12.0

Data presented are mean ± standard deviation values, unless otherwise stated.

Table 2

## Mean Blood Pressure Response to Cold Pressor Test

	Probands	Siblings	Offspring	Spouses	Parents
Maximum BP Response					
SBP	15.1 ± 10.3	13.1 ± 9.5	11.8 ± 8.2	15.0 ± 11.3	15.5 ± 12.1
DBP	7.8 ± 5.9	7.5 ± 6.1	8.8 ± 6.7	8.1 ± 6.3	6.9 ± 5.2
BP Response at time 0					
SBP	14.8 ± 10.6	12.6 ± 10.1	11.6 ± 8.3	15.0 ± 11.3	15.3 ± 12.2
DBP	7.1 ± 6.5	6.7 ± 6.8	8.0 ± 7.3	7.4 ± 6.7	6.1 ± 5.7
Reactivity area-under-curve					
SBP	7.4 ± 5.3	6.3 ± 5.0	5.8 ± 4.2	7.5 ± 5.6	7.7 ± 6.1
DBP	3.5 ± 3.3	3.4 ± 3.4	4.0 ± 3.6	3.7 ± 3.4	3.1 ± 2.9
Recovery area-under-curve					
SBP	12.4 ± 19.0	9.5 ± 18.1	5.6 ± 16.3	10.6 ± 22.0	11.3 ± 21.2
DBP	7.8 ± 13.7	7.0 ± 14.2	7.0 ± 14.8	8.1 ± 15.3	6.2 ± 14.3
Total area-under-curve					
SBP	19.7 ± 22.7	15.8 ± 21.7	11.4 ± 19.1	18.1 ± 26.7	18.9 ± 25.9
DBP	11.3 ± 15.9	10.3 ± 16.6	11.0 ± 17.2	11.8 ± 17.6	9.3 ± 16.4

Data presented are mean ± standard deviation values.

**Table 3**  
**Heritability of Blood Pressure at Baseline and Blood Pressure Response to Cold Pressor Test**

	SBP		DBP	
	$h^2 \pm SE$	p-value	$h^2 \pm SE$	p-value
Baseline BP	$0.20 \pm 0.05$	<0.0001	$0.35 \pm 0.05$	<0.0001
Maximum BP response	$0.29 \pm 0.05$	<0.0001	$0.28 \pm 0.05$	<0.0001
BP response at time 0	$0.28 \pm 0.05$	<0.0001	$0.25 \pm 0.05$	<0.0001
Reactivity AUC	$0.30 \pm 0.05$	<0.0001	$0.26 \pm 0.05$	<0.0001
Recovery AUC	$0.14 \pm 0.05$	0.002	$0.20 \pm 0.05$	<0.0001
Overall AUC	$0.16 \pm 0.05$	0.0002	$0.21 \pm 0.05$	<0.0001

Response at time 0 is the difference between BP at time 0 and baseline BP while maximum response is the largest BP difference between BP at any of the 4 CPT tested time-points and baseline BP.  $h^2$  = heritability; SE = standard error.

**Table 4**  
**Genetic ( $\rho_G$ ) and Environmental ( $\rho_E$ ) Correlation Between Baseline Blood Pressure and Blood Pressure Response to the Cold Pressor Test**

Pairs of traits	$\rho_G$ (SE)	P value		
		H0: $\rho_G = 0$	H0: $\rho_E = 0$	
Systolic blood pressure				
Baseline-maximum response	0.21 (0.15)	0.14	-0.02 (0.05)	0.61
Baseline-response at time 0	0.18 (0.15)	0.21	-0.005 (0.05)	0.91
Baseline-reactivity AUC	0.18 (0.15)	0.21	-0.005 (0.05)	0.91
Baseline-recovery AUC	0.16 (0.21)	0.46	-0.13 (0.04)	0.004
Baseline-overall AUC	0.16 (0.19)	0.41	-0.11 (0.04)	0.02
Recovery AUC-reactivity AUC	0.67 (0.10)	0.0007	0.66 (0.03)	<0.0001
Diastolic blood pressure				
Baseline-maximum response	0.10 (0.12)	0.42	-0.19 (0.05)	0.0003
Baseline-response at time 0	0.08 (0.12)	0.53	-0.14 (0.05)	0.005
Baseline-reactivity AUC	0.08 (0.12)	0.48	-0.15 (0.05)	0.004
Baseline-recovery AUC	-0.07 (0.14)	0.63	-0.22 (0.05)	<0.0001
Baseline-overall AUC	-0.03 (0.13)	0.83	-0.22 (0.05)	<0.0001
Recovery AUC-reactivity AUC	0.59 (0.10)	0.0006	0.67 (0.03)	<0.0001

$\rho$  is the Pearson correlation between pairs of traits, and it is split into two components, genetic correlation ( $\rho_G$ ) and environment correlation ( $\rho_E$ ). For H0:  $\rho_G = 1$  (or  $-1$ ), the p-value is  $\leq 0.005$  and results are not shown here.