SHORT COMMUNICATION

Recapitulation of genome-wide association studies on pulse pressure and mean arterial pressure in the Korean population

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Increased pulse pressure (PP) and decreased mean arterial pressure (MAP) are strong prognostic predictors of adverse cardiovascular events. Recently, the International Consortium for Blood Pressure Genome-Wide Association Studies (ICBP-GWAS) reported eight loci that influenced PP and MAP. The ICBP-GWAS examined 51 cohorts—comprising 122 671 individuals of European ancestry—and identified eight SNPs: five that governed PP and three that controlled MAP. Six of these loci were novel. To replicate these newly identified loci and examine genetic architecture of PP and MAP between European and Asian populations, we conducted a meta-analysis of the eight SNPs combining data from ICBP and general population-based Korean cohorts. Two SNPs (rs13002573 (FIGN) and rs871606 (CHIC2)) for PP and two SNPs (rs1446468 (FIGN) and rs319690 (MAP4)) for MAP were replicated in Koreans. Although our GWAS only found moderate association, we believe that the findings promote us to propose that a similar genetic architecture governs PP and MAP in Asians and Europeans. However, further studies will be needed to confirm the possibility using other Asian population.

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Pulse pressure (PP) is a measure of stiffness in the main arteries, and mean arterial pressure (MAP) is a weighted average of systolic blood pressure (SBP) and diastolic blood pressure (DBP).¹ Increased PP and decreased MAP are strong prognostic predictors of adverse cardiovascular events.² Several genetic loci have been reported to be associated with SBP and DBP in Europeans,^{3–5} Asians^{6–8} and Africans.⁹ However, genetic studies on PP and MAP have been limited to those of European ancestry, including a recent report by the International Consortium for Blood Pressure Genome-Wide Association Studies (ICBP-GWAS).¹⁰

The ICBP-GWAS reported five loci for PP and three loci for MAP. Four (*CHIC2*, *PIK3CG*, *NOV* and *ADAMTS8*) of the PP loci and two (*MAP4* and *ADRB1*) of the MAP loci were novel.¹⁰ The remaining locus (*FIGN*) that was associated with both PP and MAP was recently associated with SBP in a meta-analysis of Asians.⁸

In this study, we conducted an association analysis of the SNPs that were reported by the ICBP-GWAS in 7551 Koreans using data from KARE, an earlier GWAS in Koreans. The subjects and their genotypes in the original study have been reported.⁶ In brief, the 7551 individuals were recruited as population-based cohorts in the Korean Genome and Epidemiology Study (KoGES), residing in KyungGi-Do province, near Seoul, Korea. This study was approved by the Institutional Review Board of the Korea National Institute of

Health, and each participant provided written informed consent for participation.

Blood pressure measurements were taken three times in the supine position. Before the first measurement, the participants rested for 5 min, and three measurements were taken at least 30 s apart. The average of the three measurements was used for this study. PP was defined as SBP – DBP, and MAP was defined as $2/3 \text{ DBP} + 1/3 \text{ SBP}$.

The genotypes were obtained using the Affymetrix Genomewide Human SNP array 5.0. The genotype quality control criteria have been reported in the KARE study.⁶ Of the eight SNPs that were reported by the ICBP-GWAS, one SNP was genotyped in the original KARE data.

To optimize the association analysis in Koreans, the data were imputed using the Chinese-Japanese HapMap data set, allowing us to obtain seven additional imputed SNPs. Ultimately, we analyzed all the eight SNPs. The SNP imputation was performed using the IMPUTE program,¹¹ and the detailed imputation procedure has been published.¹² The International HapMap data from 90 individuals from the JPT and HCB populations were used as a reference panel,¹³ with the reference sample size of 90 individuals having more than 95% imputation accuracy.¹⁴

The effect of genotype was computed by linear regression analysis. We calculated the effect size (β) and standard error (s.e.) of ancestral alleles on body mass index. All analyses assumed an additive genetic

model and were adjusted for sex, age,² body mass index and cohort. Statistical analyses were performed using PLINK, and *P*-values were not adjusted for multiple tests. The coded allele frequency for each ethnic group (CEU, Caucasians; HCB, Chinese; JPT, Japanese; and YRI, Sub-Saharan African) was obtained from the dbSNP database (<http://www.ncbi.nlm.nih.gov/snp>). The estimated sample sizes for 80% study power at $\alpha=0.05$ were based on minor allele frequency, effect size and mean PP or MAP, using QUANTO.¹⁵ We used the inverse-variance meta-analysis method, assuming fixed effects, with Cochran's *Q* test¹⁶ to assess differences in heterogeneity between the ICBP and KARE studies.

In Table 1, the basic characteristics of the ICBP and KARE are described, wherein all blood pressure traits (SBP, DBP, PP and MAP) were lower in KARE versus ICBP subjects.

The coded allele frequencies of the SNPs and the association results are shown in Table 2. Of the five PP-related SNPs, the *P*-values of one SNP was lower than 0.05 and one SNP was lower than 0.10 in KARE. We, however, would like to note that our study is a replication for previously detected loci, for which we generally apply relatively high significance level without adjustment for multiple tests. Given the weak statistical significance in our study, we employed less stringent *P*-value criterion in order to avoid type I error. PP was lower in ICBP individuals with coded alleles of rs13002573 ($\beta = -0.310 \pm 0.55$, $P = 1.8 \times 10^{-8}$), and the same association was observed in KARE ($\beta = -0.380 \pm 0.184$, $P = 0.039$). The coded allele of rs871606 increased PP ($\beta = 0.429 \pm 0.075$, $P = 1.3 \times 10^{-8}$) in ICBP subjects, while a trend association was observed in KARE ($\beta = 0.399 \pm 0.231$, $P = 0.084$).

The *P*-values for one of the three MAP SNP was lower than 0.05 and one SNP was lower than 0.10 in KARE. MAP decreased in ICBP individuals with a coded allele of rs1446468 ($\beta = -0.336 \pm 0.049$, $P = 6.5 \times 10^{-12}$), as was observed in KARE ($\beta = -0.873 \pm 0.199$, $P = 1.2 \times 10^{-5}$). The coded allele of rs319690 increased MAP ($\beta = 0.297 \pm 0.053$, $P = 2.7 \times 10^{-8}$) in the ICBP and KARE ($\beta = 0.383 \pm 0.208$, $P = 0.066$).

The combined effects of ICBP and KARE were tested by the Cochran's *Q* test, and the meta-analysis β , *P*-values and heterogeneity between two populations were described in Table 2. The other SNPs for candidate PP and MAP loci did not pass the *P*-value criterion ($P < 0.10$), but rs17477177 and rs11222084 had low meta-analysis *P*-values, implying that their association would have been significant in larger samples. Based on the estimated sample size for 80% study

Table 1 Basic characteristics of ICBP and KARE subjects

Phenotypes	ICBP	KARE
<i>n</i>	122 627	7551
Cohorts	51	2
	Mean (range)	Mean (range)
Average individual number (range)	2405 (247–22625)	3775 (3470, 4081)
Average %female (range)	54.3 (0–100)	50.4 (47.0, 54.4)
		Mean $\pm$ s.d.
Age (year)	52.6 (31–79)	51.4 $\pm$ 8.8
Body mass index (kg m ⁻²)	26.4 (23.5–28.6)	24.4 $\pm$ 3.1
Systolic blood pressure (mm Hg)	132.6 (119–175.6)	115.7 $\pm$ 17.2
Diastolic blood pressure (mm Hg)	79.7 (70–91.5)	74.2 $\pm$ 11.3
Pulse pressure (mm Hg)	53.5 (42.5–88.4)	41.4 $\pm$ 10.6
Mean arterial pressure (mm Hg)	98.3 (88.8–116.7)	88.0 $\pm$ 12.6

Table 2 Coded allele frequencies in ICBP-GWAS, KARE and dbSNP data and the effect size (β) and significant level (*P*) for ICBP-GWAS, KoGES and the meta-analysis

Coded allele frequency																								
SNP	Geno type ^b	Chr	Nearest gene	Position ^c	Coded allele	dbSNP database					ICBP-GWAS					KARE replication					Meta-analysis			
						ICBP	KARE	CEU	HCB	JPT	YRI	β	s.e.	P-value	β	s.e.	P-value	Sample size ^a	β	P	Q	I		
Pulse pressure																								
rs13002573	I	2	FIGN	164623454	G	0.203	0.495	0.252	0.407	0.401	0.111	-0.310	0.055	1.8 × 10 ⁻⁸	-0.380	0.184	0.039	10868	-0.316	2.1 × 10 ⁻⁹	0.716	0		
rs871606	I	4	CHIC2	54494002	T	0.850	0.787	0.850	0.778	0.767	0.800	0.429	0.075	1.3 × 10 ⁻⁸	0.399	0.231	0.084	14701	0.426	2.3 × 10 ⁻⁹	0.903	0		
rs17477177	I	7	PIK3CG	106199094	T	0.717	0.827	0.717	0.878	0.909	0.925	-0.418	0.057	2.3 × 10 ⁻¹³	-0.302	0.256	0.237	30012	-0.413	1.2 × 10 ⁻¹³	0.659	0		
rs2071518	I	8	NOV	120504993	T	0.167	0.296	0.199	0.163	0.186	0.602	0.312	0.053	3.7 × 10 ⁻⁹	-0.196	0.203	0.335	48869	0.280	4.9 × 10 ⁻⁸	0.016	82.89		
rs11222084	G	11	ADAMTS8	129778440	T	0.375	0.093	0.381	0.000	0.067	0.250	0.337	0.050	1.9 × 10 ⁻¹¹	0.133	0.368	0.718	263013	0.333	1.7 × 10 ⁻¹¹	0.583	0		
Mean arterial pressure																								
rs1446468	I	2	FIGN	164671732	T	0.534	0.544	0.534	0.544	0.466	0.958	-0.336	0.049	6.5 × 10 ⁻¹²	-0.873	0.199	1.2 × 10 ⁻⁵	2072	-0.367	1.3 × 10 ⁻¹⁴	0.009	85.43		
rs319690	I	3	MAP4	47902488	T	0.510	0.667	0.510	0.711	0.750	0.408	0.297	0.053	2.7 × 10 ⁻⁸	0.383	0.208	0.066	12041	0.3022	4.0 × 10 ⁻⁹	0.689	0		
rs2782980	I	10	ADRB1	115771517	T	0.198	0.240	0.265	0.163	0.145	0.442	0.338	0.057	2.5 × 10 ⁻⁹	-0.015	0.284	0.959	>1000000	0.326	5.7 × 10 ⁻⁹	0.265	19.6		

Abbreviations: CEU, Caucasians; Chr, chromosome; HCB, Chinese; I, Cochran's *Q* test heterogeneity between studies; ICBP-GWAS, International Consortium for Blood Pressure Genome-Wide Association Studies; JPT, Japanese; KoGES, Korea Genome and Epidemiology Study; SNP, rsID of single-nucleotide polymorphism; YRI, Sub-Saharan African; *Q*, Cochran's *Q*.

^aSample size for 80% power at $\alpha=0.05$ is based on KARE parameters, including minor allele frequency, effect size and mean value of the markers.

^bGenotype origins marked by I (imputed) and G (genotyped).

^cPositions according to Build 36 and allele coding based on the ancestral allele.

power, our cohort was not enough to exclude false-negative associations in most cases (Table 2).

The limitation of this study was the relatively weak level of significance in the association results in KARE subjects versus the ICBP-GWAS. In addition, our study used seven imputed SNPs of the eight tested SNPs. We do not know whether this weak significance is attributed to our smaller sample size compared with the ICBP-GWAS, the inaccuracy of the imputed genotypes or ethnic differences in PP or MAP. This issue should be examined in other Asian populations.

rs13002573 and rs1446468 lay in the FIGN locus, both of which were significantly associated with blood pressure and hypertension in the Asian study,⁷ suggesting that the FIGN locus regulates blood pressure in humans and is a major risk factor of hypertension. The FIGN encoded a member of ATPases associated with the diverse cellular activities (AAA proteins) group.¹⁷ Although the function of FIGN is largely unknown, the AAA proteins are known as the molecular chaperones that facilitate a variety of functions, including membrane fusion, endosome sorting and meiotic spindle formation.¹⁷ As some molecular chaperones enhance the insulin action,¹⁸ dysfunctional insulin action might lead to the accumulation of inflammatory factors in blood vessel, causing abnormality in blood pressure or diseases such as atherosclerosis.

In summary, two PP loci and two MAP loci were replicated in Koreans, and rs871606 (CHIC2) and rs319690 (MAP4), newly identified loci in the ICBP-GWAS, were validated in an Asian population. Although our GWAS found only moderate association, we believe that the findings promote us to propose that a similar genetic architecture governs PP and MAP in Asians and Europeans. However, further studies will be needed to confirm the possibility using other Asian population.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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