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GENOME-WIDE ASSOCIATION STUDY META-ANALYSIS REVEALS TRANS-ETHNIC REPLICATION OF MEAN ARTERIAL AND PULSE PRESSURE LOCI

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Abstract

We conducted a genome-wide association study meta-analysis of mean arterial pressure and pulse pressure among 26,600 East Asian participants (stage-1) followed by replication study of up to 28,783 participants (stage-2). For novel loci, statistical significance was determined by a $P < 5.0 \times 10^{-8}$ in joint analysis of stage-1 and stage-2 data. For loci reported by the previous mean arterial and pulse pressure genome-wide association study meta-analysis in Europeans, evidence of trans-ethnic replication was determined by consistency in effect direction and a Bonferroni-corrected $P < 1.4 \times 10^{-3}$. No novel loci were identified by the current study. Five independent mean arterial pressure variants demonstrated robust evidence for trans-ethnic replication including rs17249754 at *ATP2B1* ($P = 7.5 \times 10^{-15}$), rs2681492 at *ATP2B1* ($P = 3.4 \times 10^{-7}$), rs11191593 at *NT5C2* (1.1×10^{-6}), rs3824755 at *CYP17A1* ($P = 1.2 \times 10^{-6}$), and rs13149993 at *FGF5* ($P = 2.4 \times 10^{-4}$). Two additional variants showed suggestive evidence of trans-ethnic replication (consistency in effect direction and $P < 0.05$), including rs319690 at *MAP4* ($P = 0.014$) and rs1173771 at *NPR3* ($P = 0.018$). For pulse pressure, robust evidence of replication was identified for 2 independent variants, including rs17249754 at *ATP2B1* ($P = 1.2 \times 10^{-5}$) and rs11191593 at *NT5C2* ($P = 1.1 \times 10^{-3}$), with suggestive evidence of replication among an additional 2 variants including rs3824755 at *CYP17A1* ($P = 6.1 \times 10^{-3}$) and rs2681492 at *ATP2B1* ($P = 9.0 \times 10^{-3}$). Replicated variants demonstrated consistency in effect sizes between East Asian and European samples, with effect size differences ranging from 0.03 to 0.24 mmHg for mean arterial pressure and from 0.03 to 0.21 mmHg for pulse pressure. In conclusion, we present the first evidence of trans-ethnic replication of several mean arterial and pulse pressure loci in an East Asian population.

Keywords

genetics; polymorphism; single nucleotide; blood pressure; hypertension; genome-wide association study; meta-analysis

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CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

INTRODUCTION

Hypertension affects nearly 30% of the world's adult population and has been identified as the leading risk factor for mortality globally¹⁻³. A common complex trait, high blood pressure (BP) is influenced by genomic and environmental factors, as well as their interactions⁴⁻⁷. Recent genome-wide association study (GWAS) meta-analyses have made important strides in advancing hypertension genomic research through the identification of numerous novel loci for systolic blood pressure (SBP) and diastolic blood pressure (DBP)⁴⁻⁷. Mean arterial pressure (MAP), defined as the average pressure in the arteries, and pulse pressure (PP), a measure of large artery stiffness, represent two additional blood pressure components which also predict cardiovascular disease risk and mortality⁸⁻¹¹. Despite their public health relevance and established heritability¹²⁻¹⁴, only one previous GWAS meta-analysis has reported genomic loci influencing these traits¹⁵. Wain and colleagues described several novel MAP and PP loci which they identified exclusively in populations of European descent¹⁵. GWAS meta-analyses in distinct ethnic groups could enable the discovery of additional novel loci for MAP and PP and help to determine whether the previously reported variants are relevant to populations of non-European ancestry.

We carried out the first ever GWAS meta-analysis of MAP and PP in East Asian participants to: 1) identify novel loci influencing MAP and PP; and 2) determine whether loci previously identified in populations of European ancestry could be replicated among a distinct ethnic group. Here we report the results of our two-stage study that included a meta-analysis of MAP and PP GWAS in 26,600 participants and replication study in up to 28,783 participants.

METHODS

Stage-1 GWAS meta-analysis

The Asian Genetic Epidemiology Network (AGEN)-MAP/PP work-group consists of 9 GWAS conducted in East Asian populations. Each AGEN-MAP/PP study collected at least 2 measurements of systolic blood pressure (SBP) and diastolic blood pressure (DBP) in a clinical setting using methods described previously⁶. If participants were taking antihypertension medications, 10 mmHg and 5 mmHg were added to measured SBP and DBP, respectively. Mean MAP and PP were calculated for each participant from SBP and DBP values. Prior to GWAS, each study imputed the HapMap set of approximately 2.4 million single nucleotide polymorphisms (SNPs)¹⁶⁻¹⁸. GWAS of MAP and PP in each study were carried out using linear regression models to adjust for age, age², gender, body mass index, and enrollment site (for multi-site studies). Detailed study-specific information can be found in Table 1, the Supplementary Note, and Table S1.

Inverse-variance weighted fixed effect meta-analyses of MAP and PP results from the 9 GWAS were carried out using METAL¹⁹. SNPs were excluded if they had minor allele frequency (MAF)<0.05, Hardy-Weinberg $P < 1 \times 10^{-6}$, call rate<0.95, imputation quality score<0.5, sample size less than 10,000 or showed evidence of heterogeneity across studies (P for Cochran's Q-test< 1×10^{-6}). Genomic control was applied to each study (Table S1) and the final meta-analyses ($\lambda_{GC}=1.02$ for MAP and $\lambda_{GC}=1.00$ for PP; and Figure S1).

Stage-2 replication studies and joint analyses

Novel SNPs were selected for stage-2 replication genotyping by choosing the most significant SNP from loci which achieved a stage-1 $P < 1.0 \times 10^{-5}$ for MAP or PP. We considered physiological plausibility by also selecting SNPs located within candidate genes²⁰ if they achieved $P < 1.0 \times 10^{-4}$ for either MAP or PP or $P < 1.0 \times 10^{-3}$ for both MAP

and PP. For assessment of trans-ethnic replication, previously identified MAP and PP SNPs¹⁵ which achieved nominal significance ($P < 0.05$) in stage-1 study were selected for evaluation in the *in-silico* replication stage.

In-silico or *de novo* replication genotyping and association analyses were conducted in up to six additional samples of 28,783 participants (Table 1, Supplementary Note). Meta-analysis was again used to combine results across the stage-2 studies and to conduct joint analysis of stage-1 and stage-2 findings. For novel loci, findings were considered significant if they achieved genome-wide significance ($P < 5.0 \times 10^{-8}$) in the joint analysis. For loci previously identified in European populations, a Bonferroni $P < 1.35 \times 10^{-3}$ and consistency in effect direction was considered evidence of replication.

RESULTS

In the stage-1 GWAS meta-analysis of 26,600 participants, genome-wide significance was achieved at 12q21.33 (rs17249754) at the widely reported *ATP2B1* locus for the MAP phenotype ($P = 3.65 \times 10^{-12}$; Figure 1 and Table 2). For PP, novel loci *TCL6* at 14q32.13 (rs2145975; $P = 1.90 \times 10^{-8}$) and *TTC39C* at 18q11.2 (rs11874765; $P = 3.14 \times 10^{-8}$) achieved genome-wide significance in stage-1 study (Figure 1 and Table S2). Six additional novel MAP and PP loci achieved borderline significance ($P < 1.0 \times 10^{-6}$; Figure 1 and Table S2). A full list of stage-1 *P*-values for the associations between each of the 2.4 million SNPs and the MAP and PP phenotypes are publicly available for download at www.agenconsortium.org/publications.php.

A total of 35 independent, novel trait-associated SNPs were selected for stage-2 replication study. None achieved genome-wide significance in joint analysis of stage-1 and stage-2 findings (Table S2). Among 48 SNPs which previously achieved genome-wide significance for MAP or PP traits in European populations¹⁵, 11 independent loci achieved nominal significance in the stage-1 study and were followed-up in stage-2 study (Table S3).

Table 2 provides top trans-ethnic replication results. For the MAP phenotype, rs17249754 at *ATP2B1* achieved genome-wide significance in the joint analysis of stage-1 and stage-2 studies ($P = 7.48 \times 10^{-15}$). Four additional SNPs showed robust evidence of replication for MAP (consistency of effect direction and significance after adjustment for multiple testing), including rs13149993 at *FGF5* ($P = 2.39 \times 10^{-4}$), rs3824755 at *CYP17A1* ($P = 1.21 \times 10^{-6}$), rs11191593 at *NT5C2* (1.13×10^{-6}), and rs2681492 at *ATP2B1* ($P = 3.39 \times 10^{-7}$). Furthermore, two SNPs showed suggestive replication [consistency of effect direction and nominal significance ($P < 0.05$)], including rs319690 at *MAP4* ($P = 0.01$) and rs1173771 at *NPR3* ($P = 0.02$). For the PP phenotype, robust evidence of replication was identified for 2 SNPs including rs11191593 at *NT5C2* ($P = 1.14 \times 10^{-3}$) and rs17249754 at *ATP2B1* ($P = 1.21 \times 10^{-5}$). Suggestive evidence of replication was identified for 2 additional SNPs including rs3824755 at *CYP17A1* ($P = 6.12 \times 10^{-3}$) and rs2681492 at *ATP2B1* ($P = 9.02 \times 10^{-3}$). Effect sizes of replicated MAP and PP loci were very similar between the previous GWAS meta-analysis of Europeans¹⁵ and the current GWAS meta-analysis of East Asians (Figure 2).

DISCUSSION

The current meta-analysis of 26,600 East Asian participants provided robust trans-ethnic replication evidence for 5 independent SNPs at MAP and PP loci previously identified in populations of European ancestry¹⁵, including rs13149993 at *FGF5*, rs3824755 at *CYP17A1*, rs11191593 at *NT5C2*, rs2681492 at *ATP2B1*, and rs17249754 at *ATP2B1*. In addition, two SNPs, rs319690 at *MAP4* and rs1173771 at *NPR3*, showed suggestive evidence of trans-ethnic replication. Further examination of these 7 variants demonstrated

remarkable consistency in per allele effect sizes across populations of East Asian and European ancestry.

Seven SNPs from MAP and PP loci identified in samples of European ancestry showed evidence of trans-ethnic replication in the current study of East Asians. Marker rs17249754 at the *ATP2B1* locus (12q21.33) achieved genome-wide significance for MAP and was robustly associated with PP. Furthermore, rs2681492, a moderately correlated intronic *ATP2B1* SNP ($r^2=0.78$), also showed evidence of trans-ethnic replication for the MAP and PP phenotypes. *ATP2B1* is a widely reported BP-related gene, with marker rs17249754 also identified for the SBP and DBP phenotypes in East Asians^{4-7, 15}. *ATP2B1* is thought to exert its influence on BP regulation through alteration of calcium handling and vasoconstriction in vascular smooth muscle cells²¹. At 3p21.31, the current study provided the first evidence of association for marker rs319690 with a BP-related phenotype among individuals with East Asian ancestry. Marker rs319690 represents an intronic variant of the *MAP4* gene, implicated in heart failure through its interference with beta-adrenergic receptor recycling²². At the *FGF5* locus (4q21.21), marker rs13149993 was associated with both MAP and PP phenotypes in the current study. The *FGF5* rs13149993 variant [or a proxy ($r^2>0.8$)] has been reported previously for its associations with not only MAP but other BP-related phenotypes^{5,7,15}. Furthermore, a variant modestly correlated with rs13149993 at *FGF5*, rs16998073 ($r^2=0.49$), was previously related to SBP and DBP in East Asians^{6,23}. A fibroblast growth factor gene, *FGF5* is expressed in cardiac myocytes and has been shown to promote angiogenesis in the heart²⁴. Near *NPR3* (at 5p13.3), rs1173771 was associated with MAP in the current study. Previously reported for its association with MAP in Caucasians and other BP phenotypes in Caucasians and East Asians^{6,7,15}, *NPR3* encodes the natriuretic peptide receptor C, a peptide known to regulate BP and fluid homeostasis by modifying glomerular filtration rate and sodium urinary excretion²⁵. Finally, moderately correlated SNPs rs3824755 and rs11191593 ($r^2=0.67$) at 10q24.32-10q24.33 were associated with MAP and PP in the current study. Marker rs3824755 is an intronic variant of *CYP17A1*, the gene responsible for the monogenic BP disorder congenital adrenal hyperplasia²⁶, while rs11191593 is an intronic variant of *NT5C2*, a gene involved in DNA synthesis with no known functional role in BP regulation²⁷. Marker rs3824755 (or a proxy) was previously reported to associate with not only MAP and PP¹⁵ but also SBP in the manuscript by Levy and colleagues⁴, while rs11191593 (or a proxy) has been reported previously for numerous BP phenotypes, including SBP and DBP in East Asians^{5-7, 15}.

The current GWAS meta-analysis represents the largest genetic association study of MAP and PP conducted in participants of East Asians ancestry to date. Additional study strengths include the adherence of all studies to a standard analytic protocol and stringent genotyping and imputation quality control procedures at the study and meta-analysis levels. Despite these strengths, the current study failed to identify any novel loci related to MAP and PP traits. Although currently the largest study conducted in East Asians, the stage-1 sample was only one-third the size of that of the prior GWAS meta-analysis of MAP and PP conducted in populations of European ancestry¹⁵. Thus, we still may have lacked the statistical power needed to identify novel variants for MAP and PP. Furthermore, we did not replicate 24 of the 31 loci previously identified in Europeans. Lack of replication could be related to differences in linkage disequilibrium (LD) patterns between Europeans and East Asians. To address this concern, we examined inter-population LD variation at these loci²⁸. Our results showed that LD structure was generally similar between populations at all but five regions (see Figure S2). However, examination of variants in LD with the lead SNP in Europeans did not reveal any further significant associations in East Asians, suggesting that differences in LD may not have been a major factor limiting replication in the current study (data not shown). Lack of replication could also be due to limited statistical power. To assess this issue, we compared effect sizes and MAFs of independent SNPs which achieved genome-

wide significance in Europeans between the two studies (Table S4). Despite differences in the MAF of many of the variants, very strong correlations in effect sizes between populations were observed (Table S4). Furthermore, power calculations demonstrated that we lacked the statistical power to detect associations for the 24 un-replicated loci (Table S5). These data suggest the existence of additional promising MAP and PP loci in East Asian populations that may be identified by future, larger GWAS meta-analyses.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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PERSPECTIVES

The current study of 26,600 East Asian participants from 9 GWAS provides the first evidence of trans-ethnic replication of 7 MAP and PP loci previously identified in populations of European ancestry. In addition, we demonstrate remarkable consistency in allelic effect sizes between populations with vast differences in not only genomic ancestry but also environmental and cultural factors. Our findings add to the accumulating evidence that many genomic associations are reproducible in populations with distinct LD structure, suggesting common genomic mechanisms underlying the development of hypertension and cardiovascular disease across populations.

NOVELTY AND SIGNIFICANCE

What is New?

- The current GWAS meta-analysis of 26,600 East Asians the first evidence of trans-ethnic replication of 7 MAP and PP loci previously identified in populations of European ancestry.
- Per allele effect sizes of replicated variants were consistent between Europeans and East Asians.

What is Relevant?

- The physiologic effects of many common polymorphisms may be generalizable across populations.

Summary

The current meta-analysis of 26,600 East Asian participants from 9 GWAS provided evidence of trans-ethnic replication for 7 MAP and PP variants previously identified in populations of European ancestry¹⁵. These variants demonstrated remarkable consistency in per allele effect sizes across populations of East Asian and European ancestry. We add to the accumulating evidence that many genomic associations are reproducible in populations with distinct linkage disequilibrium structure, suggesting common genomic mechanisms underlying the development of hypertension and cardiovascular disease across populations.

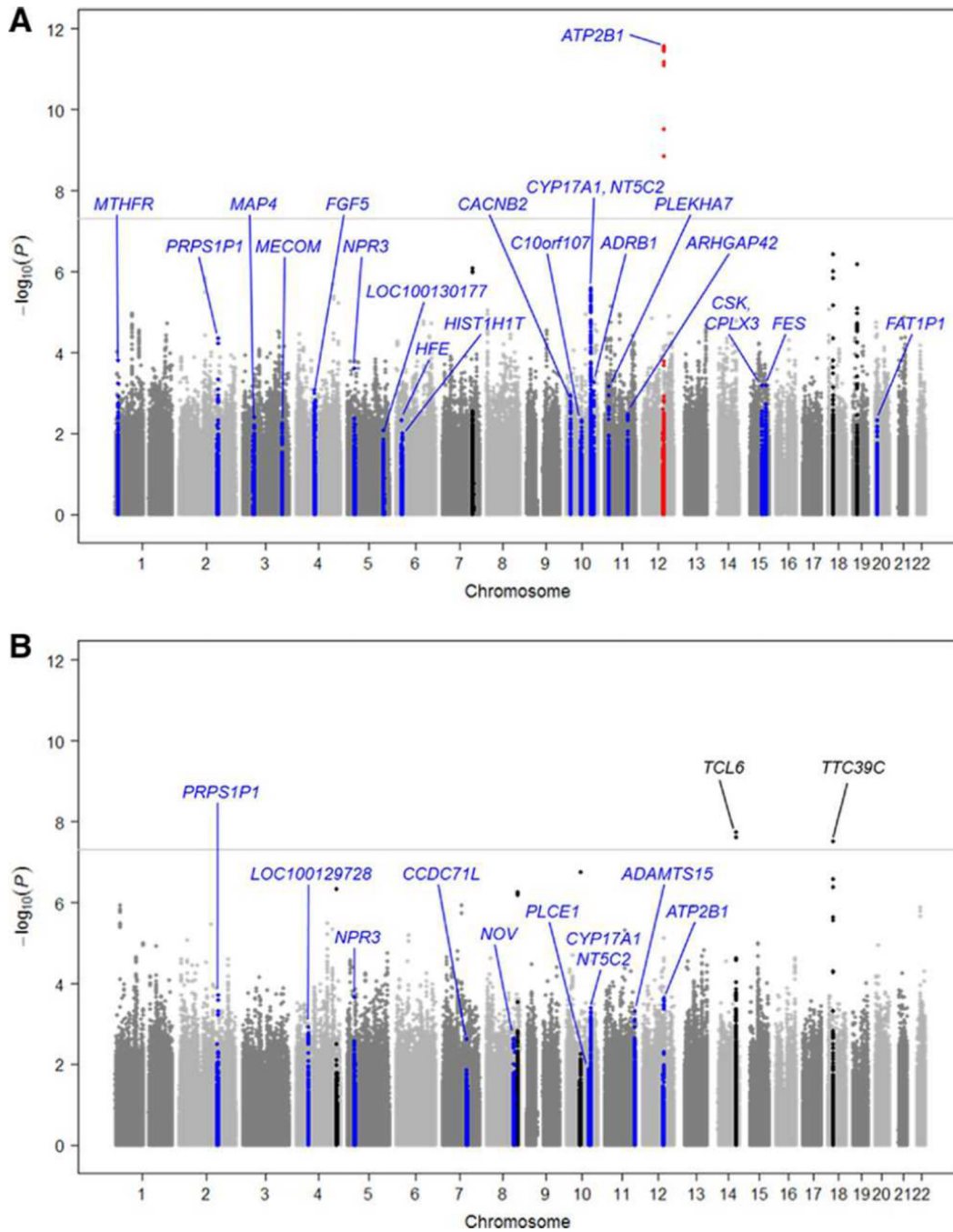


Figure 1. Genome-wide association study (GWAS) meta-analysis results for MAP (a) and PP (b). Loci highlighted in red indicate the 2 Mb regions of SNPs which achieved genome-wide significance in stage-1 and joint analyses of stage-1 and stage-2 studies. Loci highlighted in black indicate the 2 Mb regions of SNPs which achieved borderline significance ($P < 1E-6$) in the stage-1 GWAS meta-analysis. Loci highlighted in blue indicate the 2 Mb regions of SNPs which achieved genome-wide significance in the GWAS meta-analysis of Europeans (unless achieving $P < 1E-6$ in the current study)¹⁵. Loci which achieved genome-wide significance in Europeans¹⁵ or East Asians are labeled (blue if originally identified in Europeans; black if originally identified in the current study).

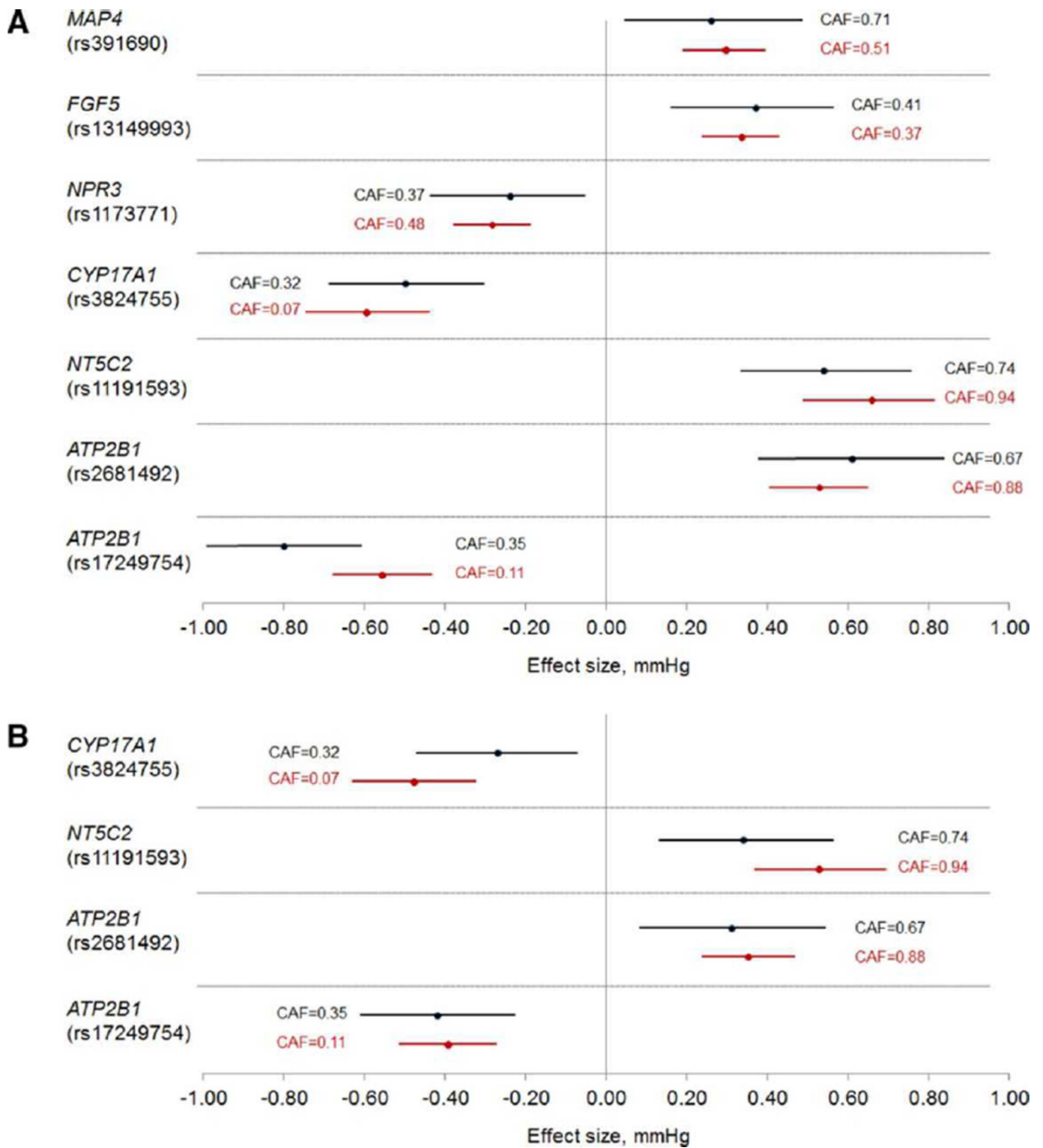


Figure 2. Effect sizes and coded allele frequencies (CAF) for SNPs that showed evidence of trans-ethnic replication for MAP (a) and PP (b) in East Asian participants of the current GWAS meta-analysis. Effect sizes in the current study of East Asians are shown in black while those of the previous GWAS meta-analysis of Europeans¹⁵ are shown in red.

Table 1

Characteristics of AGEN-MAP/PP studies.

Study	N	Ancestry	Blood pressure measurement (device, number of measures)	Age (SD)*	Women†	EMI (SD)‡	SBP (SD)§	DBP (SD)§	MAP (SD)§,¶	PP (SD)§,¶	Hypertension †‡#	Anti-hypertension medication †‡
Stage-1: AGEN-MAP/PP GWAS meta-analysis (n=26,600)												
CAGE	1,547	Japanese	Standard mercury sphygmomanometer, 2–3/digital, 2–3	66.1 (8.0)	42.8	23.5 (3.3)	134.1 (20.3)	76.8 (11.9)	98.4 (14.5)	59.2 (15.6)	56.1	37.9
CLHNS	1,787	Filipino	Standard mercury sphygmomanometer, 3	48.4 (6.1)	100	24.3 (4.4)	120.0 (20.5)	79.8 (12.7)	93.2 (14.5)	40.2 (12.8)	27.3	3.8
GenSalt	1,881	Chinese	Random zero sphygmomanometer, 9	38.7 (9.5)	47.2	23.3 (3.2)	116.9 (14.2)	73.7 (10.3)	88.2 (10.9)	43.2 (9.5)	9.8	0.37
KARE	8,842	Korean	Standard mercury sphygmomanometer, 3	52.2 (8.9)	52.7	24.6 (3.1)	118.7 (19.4)	75.6 (12.0)	90.0 (13.8)	43.1 (11.8)	22.3	10.9
NHAPC	2,817	Chinese	Omnron HEM-705 CP Blood Pressure Monitor, 3	58.6 (6.0)	56.9	24.5 (3.6)	143.0 (24.8)	81.6 (11.7)	102.0 (14.9)	61.5 (18.2)	55.9	28.7
SiMES	2,538	Malay	Random zero sphygmomanometer, 2–3	59.1 (11.1)	50.5	26.4 (5.1)	150.2 (24.8)	81.2 (11.4)	104.2 (10.9)	69.0 (19.1)	69.9	23.0
SP2	2,434	Chinese	Random zero sphygmomanometer, 2–3	48.1 (11.2)	53.5	22.9 (3.7)	130.8 (21.3)	77.6 (11.2)	95.3 (13.6)	53.2 (14.9)	18.0	14.3
Taiwan Type 2 Diabetes Study	1,000	Chinese	Random zero sphygmomanometer, 3	51.2 (17.8)	49.8	23.8 (3.5)	122.6 (19.4)	76.5 (11.0)	91.9 (12.7)	46.1 (14.4)	8.9	6.8
Vanderbilt	3,754	Chinese	Sphygmomanometer, 2–3	57.1 (8.4)	76.0	24.8 (3.5)	128.7 (19.4)	80.5 (10.5)	96.5 (12.6)	48.2 (14.4)	49.0	22.7
Stage-2: Replication study (n=28,783)												
<i>In-silico genotyping studies (n=5,584)</i>												
HEXA	3,703	Korean	Standard mercury sphygmomanometer, 2	53.2 (8.3)	55.4	24.0 (2.9)	121.7 (14.4)	77.1 (9.9)	91.9 (10.7)	44.7 (9.2)	18.7	0
SCES	1,881	Chinese	Random zero sphygmomanometer, 3	58.4 (9.5)	48.7	23.7 (3.5)	140.8 (20.5)	80.6 (9.9)	100.7 (12.1)	60.2 (16.3)	56.1	51.8
<i>De-novo genotyping studies (n=23,199)</i>												
CAGE-Amagasaki	5,331	Japanese	Digital, 2–3	47.8 (12.3)	39.8	23.0 (3.2)	124.3 (17.3)	75.9 (11.0)	92.1 (12.9)	48.4 (8.5)	57.9	23.9
JMGP	11,570	Japanese	Digital cuff-oscillometric device, 2	56.1 (14.0)	50.0	23.0 (3.1)	131.3 (19.6)	78.4 (11.6)	96.0 (13.4)	52.6 (13.1)	41.6	19.2
SMWHS	3,237	Chinese	Sphygmomanometer, 2–3	59.3 (8.8)	56.0	25.3 (3.6)	132.6 (19.6)	82.6 (10.5)	100.7 (13.4)	51.1 (15.0)	53.0	21.3
Suzhou Study	3,061	Chinese	Standard mercury sphygmomanometer, 2	54.2 (10.5)	61.7	24.8 (3.6)	134.2 (19.8)	86.4 (10.2)	70.5 (9.9)	47.8 (14.3)	47.2	27.5

AGEN=Asian Genetic Epidemiology Network; BP=Blood pressure; CAGE=Cardio-metabolic Genome Epidemiology; CLHNS=Cebu Longitudinal Health and Nutrition Survey; DBP=Diastolic blood pressure; GenSalt=Genetic Epidemiology Network of Salt-Sensitivity; GWAS=Genome-wide association study; HTN=Hypertension; JMG=Japanese Millennium Genome Project; KARE=Korean Association Resource; MAP=Mean arterial pressure; N=sample size; NHAPC=Nutrition and Health of Aging Population in China; PP=Pulse pressure; SBP=Systolic blood pressure; SCES=Singapore Chinese Eyes Study; SD=Standard deviation; Vanderbilt=Vanderbilt Genome-Wide Association Studies; SiMES=Singapore Malay Eye Study; SMMWHS=Shanghai Men's and Shanghai Women's Health Studies; SP2=Singapore Prospective Study.

* Age in years;

[†] Data are percentages;

[‡] Measurement in kilograms per square meters;

[§] Measurement in mmHg;

// MAP is calculated as $DBP + (SBP - DBP) / 3$ in each study;

[¶] PP is calculated as $SBP - DBP$ in each study

[#] Hypertension is defined as SBP \geq 140 mmHg and DBP \geq 90 mmHg or taking antihypertension medication.

Table 2
Trans-ethnic replication of MAP and PP loci among East Asian samples of the AGEN consortium.

Locus	Marker	Chromosome	Position (build 36.3)	Nearest Gene	CA/OA	CAF	Stages	N	MAP		PP		Previously reported phenotype		
									Beta*	(SE)	P	Beta*		(SE)	P
3p21.31	rs319690	3	47902488	MAP4 [†]	T/C	0.71	Stage 1	26263	0.28	(0.12)	2.06E-02	0.11	(0.11)	3.42E-01	MAP
							Stage 2	5583	0.20	(0.22)	3.65E-01	0.06	(0.21)	7.65E-01	
4q21.21	rs13149993	4	81377319	FGF5	A/G	0.41	Stages 1+2	31845	0.26	(0.11)	1.36E-02	0.10	(0.10)	3.28E-01	MAP
							Stage 1	25964	0.32	(0.11)	4.57E-03	0.37	(0.11)	5.67E-04	
							Stage 2	5495	0.51	(0.21)	1.35E-02	0.06	(0.20)	7.56E-01	
							Stages 1+2	31459	0.37	(0.10)	2.39E-04	0.30	(0.09)	1.51E-03	
5p13.3	rs1173771 [‡]	5	32850785	NPR3	A/G	0.37	Stage 1	26399	-0.28	(0.11)	1.30E-02	-0.25	(0.11)	1.84E-02	MAP, PP
							Stage 2	5477	-0.08	(0.21)	7.05E-01	0.11	(0.19)	5.62E-01	
10q24.32	rs3824755	10	104585839	CYP17A1 [†]	C/G	0.32	Stages 1+2	31876	-0.24	(0.10)	1.84E-02	-0.17	(0.09)	7.39E-02	
							Stage 1	26130	-0.50	(0.12)	2.42E-05	-0.28	(0.11)	1.46E-02	
10q24.33	rs117249754 [‡]	10	104929205	NT5C2 [†]	T/C	0.74	Stage 2	5571	-0.51	(0.21)	1.65E-02	-0.25	(0.20)	2.12E-01	
							Stages 1+2	31700	-0.50	(0.10)	1.21E-06	-0.27	(0.10)	6.12E-03	
12q21.33	rs2681492	12	88537220	ATP2B1 [†]	T/C	0.67	Stage 1	26044	0.60	(0.13)	2.76E-06	0.38	(0.12)	1.50E-03	MAP, PP
							Stage 2	5577	0.37	(0.23)	1.15E-01	0.21	(0.22)	3.26E-01	
12q21.33	rs17249754 [‡]	12	88584717	ATP2B1	A/G	0.35	Stages 1+2	31621	0.54	(0.11)	1.13E-06	0.34	(0.11)	1.14E-03	
							Stage 1	16915	0.55	(0.15)	1.65E-04	0.19	(0.15)	1.94E-01	
12q21.33	rs17249754 [‡]	12	88584717	ATP2B1	A/G	0.35	Stage 2	5577	0.73	(0.21)	4.47E-04	0.51	(0.19)	8.81E-03	
							Stages 1+2	22492	0.61	(0.12)	3.39E-07	0.31	(0.12)	9.02E-03	
12q21.33	rs17249754 [‡]	12	88584717	ATP2B1	A/G	0.35	Stage 1	25401	-0.82	(0.12)	3.65E-12	-0.40	(0.11)	2.76E-04	MAP, PP
							Stage 2	5504	-0.75	(0.21)	4.55E-04	-0.49	(0.20)	1.37E-02	
12q21.33	rs17249754 [‡]	12	88584717	ATP2B1	A/G	0.35	Stages 1+2	30905	-0.80	(0.10)	7.48E-15	-0.42	(0.10)	1.21E-05	

CA=Coded allele; CAF=CA frequency; MAP=Mean arterial pressure; N=Effective sample size; OA=Other allele; Position=Physical Position (in basepairs); PP=Pulse pressure; SE=Standard error.

* Beta is the effect size in mmHg per coded allele based on an additive genetic model.

[†] Corresponding marker lays within reported gene.

[‡]The variant [or its proxy ($r^2>0.8$)] was previously implicated for SBP or DBP in the genome-wide association study meta-analysis of East Asians conducted by Kato and colleagues.

[§]Significant after Bonferroni correction for 37 statistical tests.

// Although there is evidence of significance for PP, this variant was only identified for MAP in the study by Wain and colleagues. Therefore, this does not represent evidence of trans-ethnic replication. [†]rs1004467, a proxy for rs3824755 in East Asian samples ($r^2=0.95$), achieved genome-wide significance for MAP in the study by Wain and colleagues.

[¶]rs11191548, a proxy for rs1191593 in East Asian samples ($r^2=1.00$), achieved genome-wide significance for PP in the study by Wain and colleagues.