Genetic Predisposition to Higher Blood Pressure Increases Risk of Incident Hypertension and Cardiovascular Diseases in Chinese

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Abstract—Although multiple genetic markers associated with blood pressure have been identified by genome-wide association studies, their aggregate effect on risk of incident hypertension and cardiovascular disease is uncertain, particularly among East Asian who may have different genetic and environmental exposures from Europeans. We aimed to examine the association between genetic predisposition to higher blood pressure and risk of incident hypertension and cardiovascular disease in 26 262 individuals in 2 Chinese population-based prospective cohorts. A genetic risk score was calculated based on 22 established variants for blood pressure in East Asian. We found the genetic risk score was significantly and independently associated with linear increases in blood pressure and risk of incident hypertension and cardiovascular disease (P range from 4.57×10^{-3} to 3.10×10^{-6}). In analyses adjusted for traditional risk factors including blood pressure, individuals carrying most blood pressure–related risk alleles (top quintile of genetic score distribution) had 40% (95% confidence interval, 18–66) and 26% (6–45) increased risk for incident hypertension and cardiovascular disease, respectively, when compared with individuals in the bottom quintile. The genetic risk score also significantly improved discrimination for incident hypertension and cardiovascular disease and led to modest improvements in risk reclassification for cardiovascular disease (all the $P<0.05$). Our data indicate that genetic predisposition to higher blood pressure is an independent risk factor for blood pressure increase and incident hypertension and cardiovascular disease and provides modest incremental information to cardiovascular disease risk prediction. The potential clinical use of this panel of blood pressure–associated polymorphisms remains to be determined. **(*Hypertension*. 2015;66:786-792. DOI: 10.1161/HYPERTENSIONAHA.115.05961.)** ● **Online Data Supplement**

Key Words: blood pressure ■ cardiovascular diseases ■ genetic markers ■ hypertension ■ incidence

Hypertension is a common disorder and a leading cardiovascular risk factor that is determined by multiple environmental and inherited factors.[1,2] Genome-wide association studies (GWAS) have identified multiple single nucleotide polymorphisms (SNPs) associated with blood pressure (BP).[3–9] Genetic risk scores (GRSs) based on those genetic variants identified in European populations were reported to be associated with incident hypertension and cardiovascular events.[10,11] Recently, GWAS in East Asian and Chinese not only replicated previously reported BP loci in European populations but also identified several East Asian–specific variants for BP,[4,12] which suggested that both shared and population-specific BP susceptibility were commonly present. Moreover, besides genetic heterogeneity, there are marked differences between Chinese and Europeans in environmental exposure factors, including weight, diet, physical activity, obesity, alcohol drinking, and

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tobacco use, which affect the variability of BP.[13] Therefore, it is necessary to evaluate the predictive abilities of these genetic markers for cardiovascular diseases (CVD) in non-European population.

In the present study, we genotyped 22 genetic variants that have been associated with BP in East Asian and investigated whether the variants in aggregate would contribute to BP increase and incident hypertension and CVD in 26 262 individuals in 2 prospective cohorts.

Methods

Study Population

Study samples were recruited from the International Collaborative Study of Cardiovascular Disease in Asia (InterASIA in China)[14] and China Cardiovascular Health Study (CCHS) project. InterASIA used a 4-stage stratified sampling method to select a nationally representative sample of the general population aged 35 to 74 years in China. A total of 15 838 individuals completed the survey and examination in 2000 and 2001, and the follow-up in 2008 was conducted. CCHS has been a population-based investigation of risk factors for CVDs in China since 2006 and 2007, and the follow-up of individuals from Shandong province of China in CCHS project was conducted in 2013 and 2014. For this study, the analyses were limited to participants for whom complete data were available for both follow-up data and the GRSs. These restrictions resulted in 26 262 individuals (11 272 from InterASIA and 14 990 from CCHS) after exclusion of prevalent CVD cases at baseline. Because individuals from CCHS did not have follow-up data of BP, only individuals from InterASIA were eligible to examine BP. Of them, 3062 had hypertension at baseline, and 486 had missing data on BP mainly because of death at follow-up. This left 7724 participants were eligible for the present analysis of BP increase and incident hypertension.

Three BP measurements were obtained from each participant by trained and certified observers according to a standard protocol recommended by the American Heart Association. BP was measured with the participant in the sitting position after 5 minutes of rest. In addition, participants were advised to avoid alcohol, cigarette smoking, coffee/tea, and exercise for at least 30 minutes before their BP measurements. For individuals who were taking antihypertensive medication, BP was imputed by adding 10 and 5 mm Hg for systolic BP (SBP) and diastolic BP (DBP), respectively. Hypertension was defined by the presence of SBP≥140 mm Hg or DBP≥90 mm Hg or self-reported of taking a medication for the treatment of hypertension. Normotensive controls were defined as individuals not taking any antihypertensives and having an SBP<140 mm Hg and a DBP<90 mm Hg.

Each study obtained approval from the institutional review boards of local research institutions. All participants gave written informed consent.

Follow-Up

The end point of cardiovascular events was defined as myocardial infarction, angina, coronary revascularization, stroke, and death attributable to coronary artery disease (CAD) and stroke. The follow-up examination included tracking study participants or their proxies to a current address, performing in-depth interviews to ascertain disease status and vital information and obtaining hospital records and death certificates. If a study participant reported a hospitalization or emergency department overnight stay because of a study outcome during the in-person interview, the participant's hospital records, including medical history, physical examination findings, laboratory test results, and discharge diagnosis, were abstracted by trained staff using a standard form. All deaths reported during the in-person interview were verified by obtaining death certificates from the local public health department or police department. An end point assessment committee, consisting of cardiologists, neurologists, and a clinical epidemiologist at the Chinese Academy of Medical Sciences in Beijing, China, reviewed all hospital records and death certificates and determined the final diagnosis of event or underlying cause of death. Two committee members independently verified the diagnosis, and discrepancies were adjudicated by discussion involving additional committee members.

SNPs Selection, Genotyping, and GRS

We selected SNPs from GWAS of BP published in East Asian. Ten SNPs have been associated with SBP or DBP with GWAS significance in East Asian,[4] and we also identified and replicated 19 BP loci in Chinese population.[12] We pruned these SNPs and identified 22 uncorrelated (r^2<0.5) SNPs. Of these SNPs, 2 (rs10745332 and rs17030613) were in *MOV10* but showed weak linkage disequilibrium (r^2=0.19 HapMap CHB+CEU). We genotyped them using iPLEX Sequenom MassARRAY platform (Sequenom). We assessed the cumulative effect of 22 SNPs by using a BP GRS. Each SNP was weighted by the average effect size (β-coefficient) for SBP and DBP obtained from the reported GWAS (Table S1 in the online-only Data Supplement). The GRS was calculated by multiplying each β-coefficient by the number of corresponding risk alleles (0/1/2) and then summing the products. Missing genotype data for each SNP were imputed using the average risk allele frequency. However, if >3 SNP genotypes were missing for a given individual, the GRS was set as missing for that individual.

Statistical Analysis

We tested associations between SNPs and BP change and incident hypertension and CVD adjusted for traditional risk factors: sex, age, and body mass index. We defined BP change as a difference between follow-up and baseline values. We also assessed the proportion of BP-raising alleles with positive associations with hypertension and CVD (β>0), and we tested whether this proportion differed from 0.5 (proportion of SNPs with a β>0 by chance) using an exact binomial test. Association of GRS with BP increase was analyzed using linear regression. Associations of the GRS with incident hypertension and CVD outcomes were analyzed using logistic regression and Cox proportional hazards regression, respectively, in models adjusting for different traditional risk factors. To evaluate the improvement in risk discrimination by using the genetic information, we compared *C*-indices[15] for the different models with and without the GRS. We further assessed the use of GRS for CVD risk prediction by estimating the net reclassification improvement (NRI), continuous NRI, and the integrated discrimination index.[16] For the reclassification tables, cut points of 5%, 10%, and 20% were used. Clinical NRI was calculated for the subjects who were classified as the intermediate-risk group (5%–20%) in model without GRS.[17] The model calibration was assessed with the Hosmer–Lemeshow goodness-of-fit test.[18] Results from the 2 populations were combined with inverse-variance–weighted random-effects meta-analyses. The statistical package R (version 3.0.2) was used for all analyses.

Results

Complete follow-up and the genetic information data were available for 26 262 participants who had not had prevalent CVD at baseline. Baseline characteristics of the participants are shown in Table 1. The participants were all of self-reported Chinese Han ancestry. The individuals in CCHS were older, more likely to be women, and had higher BP than those in InterASIA.

Single Variants and Incident Hypertension and CVD

For both incident hypertension and CVD, 20 of 22 (91%) SNPs displayed a positive association in a direction consistent with their effect on BP, a proportion much higher than the 50% expected by chance (P=6.06×10^{-5}; Table 2). Six of the 22 SNPs were significantly associated with BP change or incident

Table 1. Baseline Characteristics of the Participants

Characteristics	InterASIA	CCHS
Male/female(% male)	5412/5860 (48.01)	6324/8666 (42.19)
Age, y (SD)	48.56 (9.70)	52.60 (7.85)
Body mass index, kg/m^2 (SD)	23.88 (3.66)	24.51 (3.61)
SBP, mm Hg (SD)	124.25 (19.62)	135.53 (23.77)
DBP, mm Hg (SD)	79.23 (11.24)	83.52 (13.19)
Hypertension (%)	27.16	45.76
Total cholesterol, mmol/L	4.82 (0.97)	4.63 (0.96)
HDL, mmol/L	1.30 (0.37)	1.38 (0.42)
Triglycerides, mmol/L	1.54 (1.13)	1.64 (1.24)
Alcohol consumers, %	25.04	17.95
Cigarette smoking, %	38.37	25.50
Family history of cardiovascular disease, %	13.39	6.90

Hypertension is defined as SBP≥140 mm Hg and DBP≥90 mm Hg or taking antihypertensive medication. CCHS indicates China Cardiovascular Health Study; DBP, diastolic blood pressure; HDL, high-density lipoprotein; InterASIA, International Collaborative Study of Cardiovascular Disease in Asia; and SBP , systolic blood pressure.

hypertension at nominal significance (P<0.05), whereas *FGF5* displayed significant association with incident hypertension at a Bonferroni-corrected threshold (P=7.12×10^{-5}<0.05/22). For incident CVD, 5 loci (*CASZ1*, *SLC4A7*, *GUCY1A3*, *ALDH2*, and *JAG1*) showed nominal significance (P<0.05).

GRS and BP Increase and Incident Hypertension

During the mean follow-up period of 7.9 years, 2559 individuals developed incident hypertension. Figure 1A showed the distribution of GRS by incident hypertension. There was significant difference of GRS between individuals with hypertension and without hypertension (P=1.55×10^{-9}). The GRS was independently associated with linear increases in BP over time and risk of incident hypertension (Table 3). An increase of 1 SD of the GRS was associated with an increase of 0.12 mm Hg/y (P=1.01×10^{-6}) in SBP and 0.07 mm Hg/y (P=2.45×10^{-6}) in DBP and a 19% increase in the odds of incident hypertension (P=2.52×10^{-11}) after adjustment for age, sex, and body mass index. The cumulative incident hypertension was 29.4%, 31.6%, 32.4%, 36.2%, and 36.8% from the lowest to highest quintile of GRS. Individuals in the second, third, fourth, and fifth quintiles of risk score had about 22%, 28%, 40%, and 62% increased risk for incident hypertension, respectively, compared with those in the lowest quintile (P=1.09×10^{-9} for trend; Figure 2A), in models adjusting for non-BP risk factors. After further adjustment for baseline SBP and DBP, the magnitude of the association of incident hypertension was attenuated only slightly and remained statistically

Table 2. Association of Single SNP With Blood Pressure Change, Incident Hypertension, and Cardiovascular Disease

SNP	Nearby Gene	CHR	Position	Risk/No-Risk Allele	ΔSBP Per y		ΔDBP Per y		Hypertension		CVD	
					β (SE)	*P* Value	β (SE)	*P* Value	β (SE)	*P* Value	β (SE)	*P* Value
rs880315	*CASZ1*	1	10719453	C/T	0.05 (0.04)	0.19	0.04 (0.02)	0.09	0.04 (0.04)	0.30	0.11 (0.05)	0.02
rs17030613	*MOV10*	1	112971190	C/A	0.10 (0.03)	2.77×10^{-3}	0.05 (0.02)	0.02	0.10 (0.04)	6.54×10^{-3}	0.05 (0.07)	0.50
rs10745332	*MOV10*	1	112990576	A/G	0.11 (0.05)	0.01	0.03 (0.03)	0.25	0.13 (0.05)	7.79×10^{-3}	−0.03 (0.06)	0.61
rs16849225	*FIGN*	2	164615066	C/T	0.06 (0.04)	0.08	0.04 (0.02)	0.10	0.06 (0.04)	0.11	0.01 (0.04)	0.81
rs820430	*SLC4A7*	3	27523904	A/G	0.02 (0.04)	0.57	0.01 (0.02)	0.66	0.05 (0.04)	0.17	0.09 (0.05)	0.04
rs9815354	*ULK4*	3	41887655	A/G	0.02 (0.05)	0.61	0.04 (0.03)	0.13	0.06 (0.05)	0.17	0.01 (0.06)	0.89
rs9810888	*CACNA1D*	3	53610635	G/T	0.06 (0.04)	0.11	0.02 (0.02)	0.37	0.09 (0.04)	0.01	0.08 (0.04)	0.05
rs1902859	*FGF5*	4	81376727	C/T	0.05 (0.04)	0.15	0.06 (0.02)	0.01	0.14 (0.04)	7.12×10^{-5}	0.03 (0.04)	0.48
rs6825911	*ENPEP*	4	111601087	C/T	−0.02 (0.03)	0.64	−0.03 (0.02)	0.24	−0.02 (0.04)	0.65	0.03 (0.07)	0.67
rs13143871	*GUCY1A3*	4	156838654	T/C	0.01 (0.04)	0.81	0.004 (0.03)	0.88	0.08 (0.04)	0.09	0.12 (0.06)	0.04
rs1173766	*NPR3*	5	32840285	C/T	0.03 (0.04)	0.34	0.01 (0.02)	0.83	0.05 (0.04)	0.17	0.04 (0.07)	0.60
rs1799945	*HFE*	6	26199158	G/C	0.11 (0.09)	0.25	0.02 (0.06)	0.78	0.09 (0.09)	0.32	0.03 (0.11)	0.79
rs9266359	*HLA-B*	6	31440718	C/T	0.04 (0.04)	0.32	0.01 (0.02)	0.75	0.01 (0.04)	0.82	0.02 (0.04)	0.60
rs2021783	*CYP21A2*	6	32152829	C/T	0.05 (0.04)	0.28	0.04 (0.03)	0.20	0.04 (0.04)	0.31	0.08 (0.05)	0.14
rs4409766	*CYP17A1*	10	104606653	T/C	0.05 (0.04)	0.18	0.03 (0.03)	0.25	0.07 (0.04)	0.06	0.07 (0.05)	0.15
rs4757391	*SOX6*	11	16259515	C/T	0.07 (0.04)	0.09	0.05 (0.03)	0.08	0.07 (0.04)	0.07	0.01 (0.05)	0.82
rs17249754	*ATP2B1*	12	88584717	G/A	0.03 (0.04)	0.46	0.01 (0.02)	0.57	0.01 (0.04)	0.86	0.04 (0.05)	0.34
rs11066280	*ALDH2*	12	111302166	T/A	0.01 (0.04)	0.76	0.06 (0.03)	0.03	−0.003 (0.04)	0.95	0.14 (0.06)	0.02
rs1991391	*TBX3-TBX5*	12	113837049	G/A	0.04 (0.05)	0.43	0.04 (0.03)	0.23	0.07 (0.05)	0.18	0.04 (0.06)	0.52
rs35444	*TBX3*	12	114036820	A/G	0.11 (0.04)	0.01	0.07 (0.03)	5.82×10^{-3}	0.06 (0.04)	0.17	−0.02 (0.05)	0.66
rs11067763	*MED13L*	12	114682724	A/G	0.05 (0.04)	0.17	0.03 (0.02)	0.16	0.03 (0.04)	0.49	0.06 (0.04)	0.15
rs1887320	*JAG1*	20	10913998	A/G	0.02 (0.04)	0.68	0.03 (0.02)	0.24	0.04 (0.04)	0.33	0.10 (0.04)	0.02

SNP IDs and chromosomal positions are based on National Center for Biotechnology Information Build 36 of the genome. Effect size estimates (β) correspond to mm Hg per risk allele for SBP and DBP and log(odds) per risk allele for hypertension and CVD. CHR indicates chromosome; CVD, cardiovascular disease; DBP, diastolic blood pressure; SBP, systolic blood pressure; and SNP, single nucleotide polymorphism.

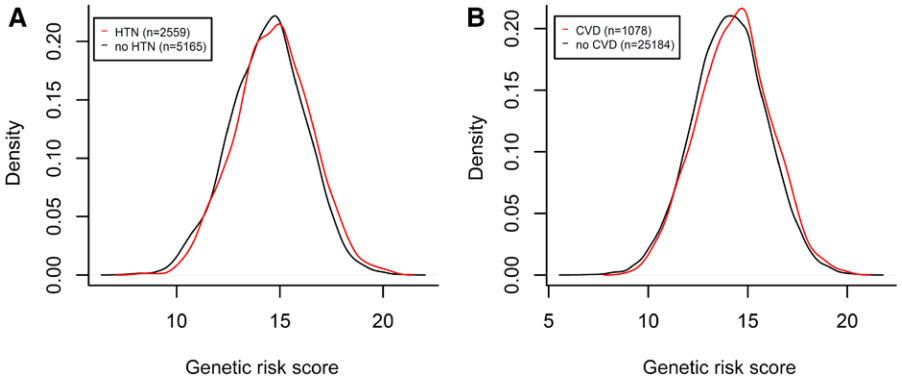

Figure 1. Distribution of genetic risk score by incident hypertension (HTN; **A**) and cardiovascular diseases (CVDs; **B**) event status. The *y*-axis is the proportion of the group (either with or without incident hypertension/CVD) with a given genetic risk score.

significant (P=3.82×10^{-5}). Adding GRS to the different models including traditional risk factors improved risk discrimination of incident hypertension (C-index change=0.3%–0.5%; all P<0.05; Table 4).

GRS and Incident CVD

During the mean follow-up time of 6.9 years, we observed 378 CADs, 749 strokes, and 1078 composite CVD in 26 262 individuals. As anticipated, mean of GRS was significantly higher in individuals with CVD than in those with non-CVD (P=6.50×10^{-7}; Figure 1B). Increased hazard of 13% to 19% for CAD, stroke, and CVD was observed for 1 SD of the GRS (all P<0.05), in models adjusting for non-BP risk factors. Hazard ratios comparing the highest quintiles of GRS with the lowest quintiles after adjustment for age, sex, and body mass index were 1.47 (1.16–1.78), 1.50 (1.27–1.73), and 1.43 (1.24–1.62) for incident CAD, stroke, and CVD, respectively (Table 3; Figure 2B). The hazard ratios for incident CVD were somewhat reduced and remained statistically significant, when baseline SBP and antihypertensive treatment were further included into the models.

C-index analysis showed improvement in risk discrimination of incident CVD. Adding GRS to the different models resulted in a change of 0.2% in the C-index (all P<0.05; Table 4). Integrated discrimination index (0.08%–0.1%; P<0.05) indicated statistically significant improvement in prediction, when genetic information was added to the models 1 and 2. Integrated discrimination index were no longer significant after further adjustment for SBP and antihypertensive treatment (Table S2). However, the GRS significantly improved the reclassification in all models (NRI=1.73%–2.53%; continuous NRI=6.27%–11.08%; all P<0.05). We also observed a significant improvement in reclassification of individuals at the intermediate risk (clinical NRI=3.23%; P=1.00×10^{-5}; Table S3). Overall, 25 CVD cases (4%) and 262 noncases (5%) at the intermediate risk (5%–20% risk category) were correctly reclassified. The calibration of the models with (P=0.24) and without the GRS (P=0.12) was good.

Discussion

In a sample of 26 262 participants, we found that a panel of 22 BP variants established in East Asian was strongly associated with risk for incident hypertension and CVD beyond baseline BP levels and other established risk factors. But the genetic score only brings a modest improvement in the prediction of incident CVD. The potential clinical use of this panel of SNPs remains to be determined.

Previous studies in European populations have investigated the association of GRSs, based on BP genetic variants identified in Europeans, with incident hypertension[10] and CVD.[11] However, the results might not be generalized to populations with genetic backgrounds different from that of European populations. For example, at least 6 common variants identified in Europeans were monomorphic or had low minor allele frequency (<0.05) in the Chinese population,[12] suggesting genetic heterogeneity between different ethnic populations. Kato et al[4] published the first large-scale GWAS meta-analysis for BP in East Asians. We further performed a large-scale GWAS studies in Chinese involving a total of 80 962 individuals, and we not only found 14 previous reported loci could be generalized to Chinese population but also identified 4 novel loci and a Chinese specific variant for BP. Of note, even for the BP variants confirmed in Chinese, the effect sizes of variants still differed between Chinese and European populations. Considering that both shared and population-specific BP susceptibility were commonly present, we integrated the established genetic variants for BP to date in East Asian and evaluated the predictive abilities of the genetic information for risk of both hypertension and CVD in Chinese population.

We assessed the individual and joint effects of BP-related SNPs on increases in BP and risk of incident hypertension and CVD. Except rs6825911 in *ENPEP*, all the other 21 SNPs were associated with mild increases in SBP (range, 0.01–0.11 mm Hg per allele) or DBP (range, 0.004–0.07 mm Hg per allele) in each year. Almost all of these SNPs were also observed to increase the risk of both hypertension and CVD. The overall evidence from all SNPs examined indicates a directionality-consistent association with incident hypertension and CVD for the great majority of BP-raising alleles. Although each SNP exerts a modest effect, a combination of SNPs, in aggregate, can have a substantial influence on hypertension and CVD. Consistent with single variants finding, the variants in aggregate were significantly associated with linear increases in BP and risk of incident hypertension. These associations were largely independent of BP level measured at baseline. By accumulation, individuals in the top compared with bottom quintiles of GRS differed by an increase of 2.61

Table 3. Association of the GRS With BP Change, Incident Hypertension, and CVD

Trait Analysis	Continuous GRS (Per SD)	*P* Value	Quintiles of GRS				
			Q2 vs Q1	Q3 vs Q1	Q4 vs Q1	Q5 vs Q1	*P* for Trend
BP							
β (95% CI)*							
ΔSBP/y	0.12 (0.07 to 0.17)	1.01×10^{-6}	0.17 (0.02 to 0.33)	0.22 (0.07 to 0.38)	0.31 (0.16 to 0.46)	0.33 (0.18 to 0.49)	4.66×10^{-6}
ΔDBP/y	0.07 (0.04 to 0.11)	2.45×10^{-6}	0.07 (−0.03 to 0.16)	0.09 (−0.01 to 0.19)	0.14 (0.05 to 0.24)	0.22 (0.12 to 0.32)	3.10×10^{-6}
HTN							
OR (95% CI)*	1.19 (1.13 to 1.25)	2.52×10^{-11}	1.22 (1.04 to 1.43)	1.28 (1.09 to 1.51)	1.40 (1.19 to 1.64)	1.62 (1.38 to 1.90)	1.09×10^{-9}
OR (95% CI)†	1.18 (1.13 to 1.25)	3.84×10^{-11}	1.22 (1.04 to 1.43)	1.27 (1.08 to 1.50)	1.40 (1.19 to 1.64)	1.61 (1.38 to 1.89)	1.71×10^{-9}
OR (95% CI)‡	1.14 (1.08 to 1.20)	2.86×10^{-6}	1.15 (0.97 to 1.37)	1.21 (1.02 to 1.44)	1.30 (1.10 to 1.55)	1.40 (1.18 to 1.66)	3.82×10^{-5}
CVD							
HR (95% CI)*	1.16 (1.10 to 1.22)	1.34×10^{-6}	1.16 (0.95 to 1.36)	1.18 (0.97 to 1.38)	1.42 (1.23 to 1.62)	1.43 (1.24 to 1.62)	2.50×10^{-5}
HR (95% CI)§	1.16 (1.10 to 1.22)	2.01×10^{-6}	1.15 (0.95 to 1.36)	1.18 (0.98 to 1.38)	1.43 (1.24 to 1.63)	1.42 (1.23 to 1.61)	2.95×10^{-5}
HR (95% CI)‖	1.11 (1.05 to 1.17)	9.32×10^{-4}	1.11 (0.90 to 1.31)	1.15 (0.95 to 1.35)	1.32 (1.13 to 1.52)	1.26 (1.06 to 1.45)	4.57×10^{-3}
CAD							
HR (95% CI)*	1.13 (1.04 to 1.23)	9.83×10^{-3}	1.23 (0.90 to 1.55)	1.45 (1.14 to 1.76)	1.36 (1.04 to 1.68)	1.47 (1.16 to 1.78)	1.62×10^{-2}
HR (95% CI)§	1.13 (1.04 to 1.23)	1.09×10^{-2}	1.23 (0.90 to 1.55)	1.45 (1.14 to 1.77)	1.36 (1.04 to 1.68)	1.46 (1.15 to 1.78)	1.73×10^{-2}
HR (95% CI)‖	1.09 (1.00 to 1.19)	6.42×10^{-2}	1.20 (0.87 to 1.52)	1.41 (1.10 to 1.72)	1.28 (0.96 to 1.60)	1.33 (1.02 to 1.65)	8.38×10^{-2}
Stroke							
HR (95% CI)*	1.19 (1.11 to 1.26)	3.14×10^{-6}	1.20 (0.96 to 1.45)	1.13 (0.89 to 1.38)	1.56 (1.32 to 1.79)	1.50 (1.27 to 1.73)	4.61×10^{-5}
HR (95% CI)§	1.18 (1.11 to 1.25)	5.05×10^{-6}	1.20 (0.95 to 1.44)	1.14 (0.89 to 1.38)	1.57 (1.34 to 1.80)	1.48 (1.25 to 1.72)	5.53×10^{-5}
HR (95% CI)‖	1.12 (1.05 to 1.19)	1.80×10^{-3}	1.14 (0.89 to 1.38)	1.11 (0.86 to 1.35)	1.43 (1.20 to 1.66)	1.28 (1.05 to 1.52)	6.63×10^{-3}

BMI indicates body mass index; BP, blood pressure; CI, confidence interval; CAD, coronary artery disease; CVD, cardiovascular disease; DBP, diastolic blood pressure; GRS, genetic risk score; HR, hazard ratio; OR, odds ratio; and SBP, systolic blood pressure.

*The covariates were sex, age, and BMI.

†The covariates were sex, age, BMI, smoking and drinking status, pulse rate, and education.

‡The covariates were sex, age, BMI, smoking and drinking status, pulse rate, education, SBP, and DBP.

§The covariates were sex, age, BMI, smoking and drinking status, diabetes mellitus, total cholesterol, high-density lipoprotein cholesterol, and family history of CVD.

‖The covariates were sex, age, BMI, smoking and drinking status, diabetes mellitus, total cholesterol, high-density lipoprotein cholesterol, family history of CVD, SBP, and hypertensive medication use.

mm Hg SBP and 1.74 mm Hg DBP, and a 62% increased risk of developing hypertension in a follow-up period of 7.9 years. Although the variants have modest effects on BP, their presence may act over the entire life course and translate into comparatively large effects. It has been shown that such modest increments in population SBP and DBP are associated with substantial increases in CVD risk.[19,20] As expected, we found that joint effect of BP-related SNPs was an independent risk factor for incident CVD, even after accounting for baseline BP. We also observed that the association of GRS with incident stroke was stronger than that with incident CAD. Thus, our findings are reasonable and consistent with an effect of BP

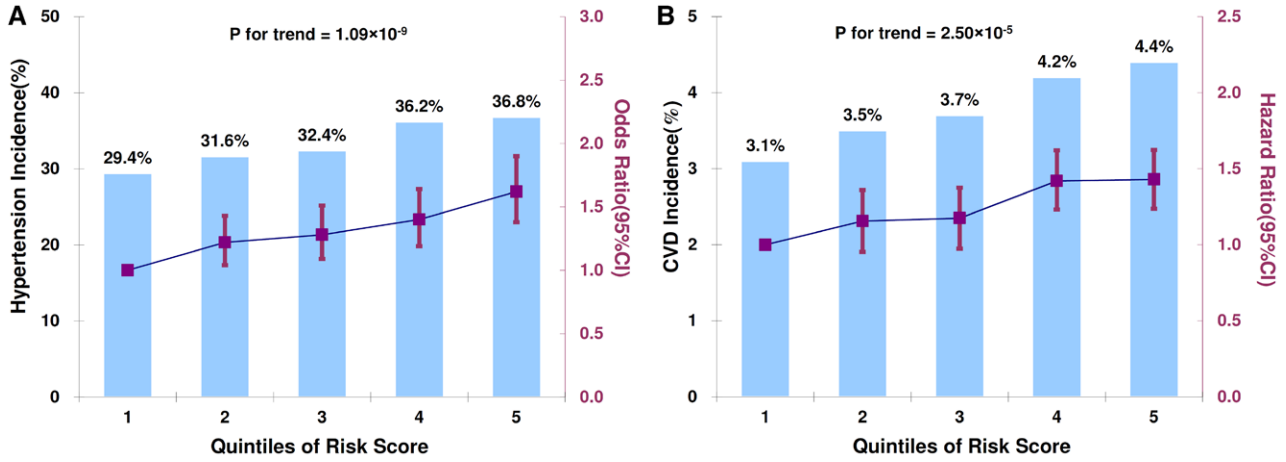

Figure 2. Combined effect of risk alleles on incident hypertension and cardiovascular disease (CVD). The blue columns show the incidence of hypertension (**A**) and CVD (**B**) according to quintile of genetic risk score. The effect sizes and their 95% confidence intervals (CIs) are indicated in red squares and bars, respectively.

Table 4. Discrimination After Addition of GRS to Traditional Risk Factors

Model	Discrimination, *C*-index (95% CI)		
	Model Without GRS	Model With GRS	*P* Value
Incident hypertension			
Model 1			
Age, sex, and BMI	0.650 (0.637–0.663)	0.655 (0.642–0.668)	0.011
Model 2			
Model 1+smoking, drinking, pulse rate, and education	0.683 (0.670–0.695)	0.687 (0.675–0.700)	0.014
Model 3			
Model 2+SBP and DBP	0.774 (0.763–0.785)	0.777 (0.766–0.787)	0.004
Incident CVD			
Model 1			
Age, sex, and BMI	0.774 (0.762–0.787)	0.776 (0.764–0.789)	0.035
Model 2			
Model 1+smoking, drinking, diabetes mellitus, TC, HDL-C, and CVD family history	0.782 (0.769–0.795)	0.784 (0.771–0.797)	0.028
Model 3			
Model 2+SBP, antihypertensive treatment	0.811 (0.799–0.823)	0.813 (0.801–0.825)	0.043

BMI indicates body mass index; CI, confidence interval; CVD, cardiovascular disease; DBP, diastolic blood pressure; GRS, genetic risk score; HDL-C, high-density lipoprotein cholesterol; SBP, systolic blood pressure; and TC, total cholesterol.

on CVD. These BP-associated SNPs may provide incremental information about cardiovascular risk beyond BP levels.

The issue of to what extent genetics can predict the incidence of future hypertension or cardiovascular events remains unanswered.[21–23] The studies in European populations indicated that BP GRS did not improve CVD risk prediction.[10,11,24] However, in the present study, we found that GRS could modestly improve risk prediction of incident CVD over the traditional risk factors. Our GRS consisted of a different set of SNPs from that used in European populations, which may explain the disparate results. We also observed a significant improvement in risk reclassification at the intermediate-risk group. Because risk categories of CVD have been proposed as clinical choices for treatment decisions,[25] identification of individuals at the intermediate-risk category may have public health benefits. Meanwhile, we note that the ability to predict CVD in our study is modest. It is most likely because of that the SNPs included in the GRS contributed to CVD primarily by affecting BP. Consequently, the magnitude and significance of GRS for CVD were somewhat reduced after adjustment for this intermediate phenotype (BP). The modest improvements we report for discrimination and reclassification confirm that genetic testing for cardiovascular risk prediction might be of limited clinical use. Additional studies evaluating the clinical use of adding a GRS in large samples of individuals are warranted.

The major strengths of our study included the use of large population-based cohorts for the assessment of both hypertension and CVD with minimal population stratification. Several limitations need to be acknowledged. First, although our GRS incorporated all the established genetic variants for BP in East Asian to date, it might account for only a small proportion of BP variation. Second, the established risk categories in our reclassification analyses were usually applied for a 10-year time frame and might not be directly applicable to our 6.9-year follow-up period. We have addressed this issue by performing a sensitivity analysis with 2% lower risk thresholds (Table S4). We observed a more significant improvement in reclassification (NRI=2.26%; $P=8.90\times10^{-4}$ and clinical NRI=8.44%; $P=8.44\times10^{-12}$). Given the current marginal improvement in risk prediction and ignoring potential gene–environment interactions in the prediction models, the further long-term follow-up studies and improvements in our understanding of interactions would be expected to improve genetic risk prediction models. Finally, our study was undertaken in individuals of Chinese, and hence it remains to be examined whether the results are generalizable to other ethnic groups.

In conclusion, a GRS based on 22 polymorphisms from GWAS in East Asian for BP was an independent risk factor for BP increase and incident hypertension and CVD. This SNP panel could modestly improve risk discrimination and reclassification of CVD over and above traditional risk factors. The modest improvement in discrimination and reclassification indicated that the clinical use was limited at present.

Perspectives

We demonstrate that many common genetic variants associated with higher BP confer an increased risk for incident hypertension and CVD, even after adjustment for baseline BP, consistent with a causal relationship of increasing BP to CVD risk. This SNP panel improved risk reclassification for CVD in participants who were at the intermediate risk on the basis of traditional risk factors. As our knowledge of genetic variation increases, the genetic information might be used clinically in hypertension and CVD risk prediction in the future.

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Disclosures

None.

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Novelty and Significance

What Is New?

- Genetic predisposition to higher blood pressure on risk of incident hypertension and cardiovascular disease (CVD) is uncertain, particularly among Chinese who may have different genetic and environmental exposures from Europeans.

What Is Relevant?

- A genetic risk score, based on 22 blood pressure variants established by genome-wide association studies in East Asian, is an independent risk factor for incident hypertension and CVD beyond baseline blood pressure levels and other established risk factors.
- This single nucleotide polymorphism panel could improve risk discrimination of hypertension and CVD and led to modest improvements in risk reclassification for CVD.

Summary

A lifelong effect on blood pressure of genetic variants is a significant predictor of incident hypertension and CVD. The potential clinical use of this panel of single nucleotide polymorphisms remains to be defined in future studies.

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SUPPLEMENTARY ONLINE CONTENT

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Table S1 Overview of 22 genotyped SNPs for blood pressure

Nearby gene	SNP	CHR	Position	Risk/no risk allele	Risk allele frequency	*P*-HWE	β SBP*	β DBP*
CASZ1	rs880315	1	10719453	C/T	0.61	0.15	0.97	0.46
MOV10	rs17030613	1	112971190	C/A	0.46	0.72	0.49	0.38
MOV10	rs10745332	1	112990576	A/G	0.82	0.52	0.96	0.53
FIGN	rs16849225	2	164615066	C/T	0.61	0.26	0.45	0.10
SLC4A7	rs820430	3	27523904	A/G	0.32	0.95	0.76	0.27
ULK4	rs9815354	3	41887655	A/G	0.18	0.08	0.10	0.43
CACNA1D	rs9810888	3	53610635	G/T	0.39	0.16	0.53	0.39
FGF5	rs1902859	4	81376727	C/T	0.40	0.98	1.34	0.71
ENPEP	rs6825911	4	111,601,087	C/T	0.47	0.61	0.6	0.39
GUCY1A3	rs13143871	4	156838654	T/C	0.79	0.34	0.96	0.49
NPR3	rs1173766	5	32,840,285	C/T	0.65	0.69	0.63	0.36
HFE	rs1799945	6	26199158	G/C	0.04	0.02	0.95	0.88
HLA-B	rs9266359	6	31440718	C/T	0.60	0.09	0.44	0.29
CYP21A2	rs2021783	6	32152829	C/T	0.78	0.01	0.68	0.49
CYP17A1	rs4409766	10	104606653	T/C	0.70	0.97	1.24	0.59
SOX6	rs4757391	11	16259515	C/T	0.28	0.55	0.67	0.36
ATP2B1	rs17249754	12	88584717	G/A	0.65	0.35	1.03	0.52
ALDH2	rs11066280	12	111302166	T/A	0.79	0.19	0.96	0.62
TBX3-TBX5	rs1991391	12	113837049	G/A	0.84	0.09	0.6	0.21
TBX3	rs35444	12	114036820	A/G	0.76	0.90	0.83	0.36
MED13L	rs11067763	12	114682724	A/G	0.61	0.29	0.81	0.51
JAG1	rs1887320	20	10913998	A/G	0.52	0.19	0.78	0.43

*SNP specific weights for genetic risk score calculation from blood pressure GWAS studies in East Asian population (*Nat Genet*. 2011; 43:531-538, *Hum Mol Genet*. 2015;24:865-874).

Table S2: Reclassification table of incident cardiovascular disease after addition of GRS to traditional risk factors

Model	Reclassification					
	NRI%*	*P*	NRI% (Continuous)	*P*	IDI%	*P*
Model 1 age,sex,bmi	2.08(0.08~4.08)	0.041	11.08 (5.00~17.16)	0.0004	0.10(0.03~0.16)	0.004
Model 2 Model 1 + smoking, drinking, diabetes, TC, HDL-c , CVD family history	2.53(0.60~4.46)	0.010	10.67 (4.59~16.75)	0.0006	0.08(0.04~0.15)	0.013
Model 3 Model 2 + SBP, antihypertensive treatment	1.73(0.33~3.14)	0.016	6.27 (0.18~12.36)	0.043	0.02(-0.02~0.06)	0.303

*Net reclassification improvement (NRI) was calculated using four risk categories: 0-5%, 5-10%, 10-20% and >20% for CVD. NRI, Net reclassification improvement; IDI, integrated discrimination index; GRS=Genetic Risk Score

Table S3 Reclassification of individuals in 4 risk categories after addition of GRS to a model with traditional risk factors

Model without GRS		Model with GRS				NRI	Clinical NRI
		0% to 5%	5% to 10%	10% to 20%	>20%		
0% to 5%	Events	318 (96.07%)	13 (3.93%)	0	0	1.73%	3.23%
	Nonevents	19295 (99.26%)	143 (0.74%)	0	0	(0.33%~3.14%)	(1.83%~4.63%)
						$P = 0.016$	$P = 1\times10^{-5}$
5% to 10%	Events	7 (2.29%)	283 (92.48%)	16 (5.23%)	0		
	Nonevents	176 (4.97%)	3279 (92.63%)	85 (2.40%)	0		
10% to 20%	Events	0	9 (3.03%)	279 (93.94%)	9 (3.03%)		
	Nonevents	0	86 (5.06%)	1589 (93.53%)	24 (1.41%)		
>20%	Events	0	0	5 (3.47%)	139 (96.53%)		
	Nonevents	0	0	29 (5.72%)	478 (94.28%)		

Traditional risk factors include sex, age, BMI, smoking and drinking status, diabetes, total cholesterol, high-density lipoprotein cholesterol, family history of CVD, SBP and hypertensive medication use.
Clinical NRI: Reclassification of those who were at intermediate risk (5%~20% risk category) in model without GRS.

Table S4 Reclassification of individuals in 4 risk categories after addition of GRS to a model with traditional risk factors – sensitivity analysis

Model without GRS		Model with GRS				NRI	Clinical NRI
		0% to 3%	3% to 8%	8% to 18%	>18%		
0% to 3%	Events	163(97.02%)	5(2.98%)	0	0	2.26%	3.52%
	Nonevents	15440(98.75%)	196(1.25%)	0	0	(0.93%~3.59%)	(2.51%~4.54%)
						$P = 8.90\times10^{-4}$	$P = 8.44\times10^{-12}$
3% to 8%	Events	1(0.28%)	334(93.56%)	22(6.16%)	0		
	Nonevents	217(3.36%)	6115(94.66%)	128(1.98%)	0		
8% to 18%	Events	0	9(2.37%)	358(94.46%)	12(3.17%)		
	Nonevents	0	93(3.84%)	2290(94.63%)	37(1.53%)		
>18%	Events	0	0	4(2.3%)	170(97.7%)		
	Nonevents	0	0	36(5.39%)	632(94.61%)		

Traditional risk factors include sex, age, BMI, smoking and drinking status, diabetes, total cholesterol, high-density lipoprotein cholesterol, family history of CVD, SBP and hypertensive medication use.
Clinical NRI: Reclassification of those who were at intermediate risk (3%~18% risk category) in model without GRS.
Sensitivity of the choice of categories was tested by lowering category thresholds by 2%.