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Genetic Variation in the Human *SORBS1* Gene is Associated With Blood Pressure Regulation and Age at Onset of Hypertension

A SAPPHIRe Cohort Study

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Abstract: Essential hypertension is a complex disease involving multiple genetic and environmental factors. A human gene containing a sorbin homology domain and 3 SH3 domains in the C-terminal region, termed *SORBS1*, plays a significant role in insulin signaling. We previously found a significant association between the T228A polymorphism and insulin resistance, obesity, and type 2 diabetes. It has been hypothesized that a set of genes responsible for insulin resistance may be closely linked with genes susceptible to the development of hypertension. Identification of insulin resistance-related genetic factors may, therefore, enhance our understanding of essential hypertension. This study aimed to examine whether common *SORBS1* genetic variations are associated with blood pressure and age at onset of hypertension in an ethnic Chinese cohort.

We genotyped 9 common tagged single nucleotide polymorphisms of the *SORBS1* gene in 1136 subjects of Chinese origin from the Stanford Asia-Pacific Program for Hypertension and Insulin Resistance family study. Blood pressure was measured upon enrolment. The associations of the SORBS1 single nucleotide polymorphisms with blood pressure and the presence of hypertension were analyzed with a generalized estimating equation model. We used the false-discovery rate measure Q value with a cutoff <0.1 to adjust for multiple comparisons. In the Cox regression analysis for hypertension-free survival, a robust sandwich variance estimator was used to deal with the within-family correlations with age at onset of hypertension. Gender, body mass index, and antihypertension medication were adjustment covariates in the Cox regression analysis.

In this study, genetic variants of rs2281939 and rs2274490 were significantly associated with both systolic and diastolic blood pressure. A genetic variant of rs2274490 was also significantly associated with the presence of hypertension. Furthermore, genetic variants of rs2281939 and rs2274490 were associated with age at onset of hypertension after adjustment for gender, body mass index, and antihypertension medication.

In conclusion, we provide evidence for an association between common *SORBS1* genetic variations and blood pressure, presence of hypertension, and age at onset of hypertension. The biological mechanism of genetic variation associated with blood pressure regulation needs further investigation.

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Abbreviations: BH = body height, BMI = body mass index, BW = body weight, CAP = c-Cbl-associated protein, CHB = Chinese in Beijing, CVD = cardiovascular diseases, DBP = diastolic blood pressure, FDR = false-discovery rate, GEE = generalized estimating equation, GWAS = genome-wide association study, LD = linkage disequilibrium, SAPPHIRe = Stanford Asia-Pacific Program for Hypertension and Insulin Resistance, SBP = systolic blood pressure, SORBS1 = sorbin homology domain and 3 SH3 domains in the C-terminal region.

INTRODUCTION

Hypertension, currently defined as systolic blood pressure (SBP) >140 mm Hg or diastolic blood pressure (DBP) >90 mm Hg, is the most common risk factor for cardiovascular

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diseases.[1] Twenty-five percent of the world's adult population has hypertension, and this figure is likely to increase to 29% by 2025.[2] As blood pressure (BP) is known to be regulated by a network of interacting complex systems, essential hypertension is considered a complex disease involving multiple genetic and environmental factors.[3,4]

According to the most recent evidence, genetic factors are estimated to explicate approximately 30% to 50% of the variability of BP.[5] Although several specific causal genes have been demonstrated to be involved in the regulatory pathways of some rare familial forms of hypertension,[6] many metabolic pathways are involved in the regulation of BP and development of hypertension, which are considered as polygenic traits.[7] The progress of high-throughput genotyping assays has been expected to expedite the identification of susceptible loci of hypertension.[8–11] Although thirty-eight loci have been identified to be robustly associated with BP regulation through large-scale genome-wide association study (GWAS) meta-analyses,[8,12–14] the currently identified common variants were expected to explain only about 0.9% of the variability of BP, and a large proportion of unexplained heritability needs further exploration.[8] The unexplained heritability of BP could be explained by the significant genetic and phenotypic heterogeneity among different populations and the modest effect size of risk alleles.[15]

Metabolic syndrome is characterized by the simultaneous existence of glucose intolerance, dyslipidemia, obesity, and hypertension, which leads to a significant increase in cardiovascular morbidity and mortality.[16–18] Several experimental results have supported the role of impaired insulin signaling in the pathogenesis of essential hypertension. For example, patients with essential hypertension without antihypertensive medication have higher fasting and postprandial insulin levels than normotensive persons independent of body mass index.[19] Plasma insulin levels were also positively correlated with BP.[19,20] However, there is no significant association between plasma insulin levels and hypertension in individuals with secondary hypertension.[19] Thus, hypertension per se is not the attributed factor of insulin resistance and hyperinsulinemia, but hypertension and insulin resistance may share a common genetic predisposition. This concept is also supported by one report that abnormal glucose metabolism was observed in the offspring of hypertensive parents.[19,20] In biological studies, insulin induced vascular relaxation through stimulation of nitric oxide production, reduction of intracellular Ca^{2+} concentrations in vascular smooth muscle cell, and sensitization of Ca^{2+}-myosin light chain.[21–23]In normal physiological condition, insulin mediates both glucose disposal and increased blood flow. The individuals with insulin resistance lose the normal response to insulin. The phenomenon implicated that the induction of NO vascular production and vascular relaxation caused by insulin in endothelial cells are impaired in the subjects with insulin resistance.[24] Furthermore, it has been postulated that a set of genes account for insulin resistance may be closely linked with the susceptible genes of type 2 diabetes, dyslipidemia, obesity, and hypertension.[25–27] Identification of the genetic factors related to insulin resistance may, therefore, enhance our understanding of BP regulation and development of essential hypertension.

We previously cloned a human gene containing a sorbin homology domain and 3 SH3 domains in the C-terminal region, termed *SORBS1* [OMIM 605264, GenBank accession No. AF136380 and AF136381]. SORBS1 is a human homologue for c-Cbl-associated protein (CAP),[28] which involves in the signaling pathway of insulin-stimulated glucose uptake in the mouse.[29] Insulin stimulates phosphorylation of c-Cbl and leads to dissociation of c-Cbl–CAP complex from the insulin receptor and translocates to a lipid raft domain of the plasma membrane, and then the c-Cbl–CAP complex interacts with flotillin, Crka, C3G, and TC10, and results in the translocation of the vesicles containing glucose transporter 4 (GLUT4) from cytoplasm to the plasma membrane.[29] Therefore, *SORBS1* is an important adaptor protein in the insulin-signaling pathway, and its genetic polymorphism may be related to insulin resistance. A previous case-control study found a significant association between a polymorphism of the threonine/alanine amino acid substitution at codon 228, termed the T228A polymorphism, and insulin resistance, obesity, and type 2 diabetes.[30] In the present study, we used a family-based study design to identify differences between siblings, allowing us to further examine the association of a larger number of single nucleotide polymorphism (SNP) genotypes of the *SORBS1* gene with BP, prevalence of hypertension, and age at onset of hypertension in a cohort of ethnic Chinese family members from the Stanford Asia-Pacific Program for Hypertension and Insulin Resistance study.

METHODS

Study Design

This was a family-based observational multi-center study designed to examine the association of genetic variants of the *SORBS1* gene with BP and age at onset of hypertension.

Subjects

Individuals were recruited as part of the Stanford Asia-Pacific Program for Hypertension and Insulin Resistance study; details of this study population have been published previously.[31] In brief, index cases were recruited if they were aged 35 to 60 years at onset of hypertension or >60 years, but with available documentation of their hypertension status prior to age 60 years. Concordant sibling groups (all siblings with hypertension) and discordant sibling groups ($\geq$1 hypertensive sibling) were recruited for this study. In the present study, 1136 siblings from 492 ethnic Chinese nuclear families were genotyped. The study was approved by institutional review boards at all participating sites, including National Taiwan University Hospital, Taipei Veterans General Hospital, Tri-Service General Hospital, and Taichung Veterans General Hospital. Written informed consent was obtained from all subjects prior to their enrollment in the study.

Measurement of Anthropometric Parameters and BP

Body height (BH), body weight (BW), and body mass index [BMI: BW (kg)/BH^2 (m^2)] were obtained at recruitment. Resting SBP and DBP were determined using an oscillometric device (Critikon Dinamap model 1846 SX V.S.M. BP Monitor from MFI Medical Equipment, Inc; San Diego, CA). Subjects were seated with legs uncrossed and were asked to refrain from talking for 5 minutes. BP was measured 3 times, with at least a 1-minute time lapse between each consecutive reading, and the average of the second and third readings was used in the analysis.[31]

Extraction of Genomic DNA and Genotyping

Total genomic DNA was purified from peripheral blood leukocytes using a Puregene DNA extraction kit (Minneapolis, MN), in accordance with the manufacturer's protocol. Nine tag

TABLE 1. *SORBS1* SNPs Information

SNP	SNP Name	Relative Position*,† (bp)	Chromosome Position† (bp)	Location†	Major Allele/ Minor Allele	MAF	HWE *P* Value
1	rs7081076	146635	97164527	exon 8	G/T	0.08	0.05
2	rs2281939	146820	97164342	exon 8	A/G	0.11	0.24
3	rs3818540	155361	97155801	intron 10	C/T	0.38	0.48
4	rs2274490	179649	97131513	exon 15	T/C	0.37	0.88
5	rs61739184	179685	97131477	exon 15	C/T	0.07	0.98
6	rs726176	215007	97096155	exon 19	G/A	0.36	0.77
7	rs2296966	246748	97064414	exon 25, 3′UTR	C/T	0.34	1.00
8	rs17849148	247043	97064119	exon 25, 3′UTR	T/C	0.27	0.51
9	rs3193970	249164	97061998	exon 25, 3′UTR	A/G	0.37	0.46

MAF estimation and HWE test were implemented using Haploview.
HWE = Hardy-Weinberg equilibrium, MAF = minor allele frequency, SNP = single nucleotide polymorphism, UTR = untranslated region.
* Genomic position relative to transcription start site.
† The SNP position information is based on NM_015385.

SNPs were selected from the HapMap Chinese in Beijing (CHB) data bank (http://www.hapmap.org) using the Tagger program in Haploview 4.1 (http://www.broad.mit.edu/mpg/haploview/), with a minor allele frequency threshold of 5% and an r^2 of 0.8 (Table 1). Genotyping was performed using Applied Biosystems SNPlex assays. All SNPs were in Hardy–Weinberg equilibrium in the controls (all $P > 0.01$), as determined by the Haploview program. All methods were carried out in accordance with the approved guidelines, and all experimental protocols were approved by committees at National Taiwan University Hospital, Taipei Veterans General Hospital, Taichung Veterans General Hospital, and Tri-Service General Hospital.

Statistical Analysis

Continuous variables were summarized as mean values ± standard deviation (SD), and binary variables were summarized as count (percentage) of a specific category. Pairwise linkage disequilibrium (LD) measures D′ and r^2 among assayed *SORBS1* SNPs estimated by the Haploview program.[32] We examined the association of each *SORBS1* SNP with SBP, DBP, and the presence of hypertension using a generalized estimating equation (GEE) model,[33] which accounted for the correlated data within families.[34] Age, gender, and BMI were used as covariates for adjustment in all GEE analyses and use of antihypertension medication was also adjusted for BPs. The status of use of antihypertension medication was dichotomized as ''yes'' if the subject used at least 1 antihypertension drug and ''no'' if the subject did not use any antihypertension drug. For each test, the null hypothesis was rejected if the $P < 0.05$. The GEE analyses were implemented using IBM SPSS version 19.0. We also used QVALUE software[35] to calculate Q, which is a false discovery rate (FDR)-based measure of significance adjusted for multiple comparisons. The Q represents the probability that a rejection of the null hypothesis is false. In this study, an association with a $Q < 0.1$ was considered statistically significant.[35] This threshold of Q implicates 10% of the declared discoveries are expected to be false and it is therefore commonly employed in candidate gene studies nowadays.[36,37]

We used a Cox proportional hazard model[38] to test for associations between specific *SORBS1* SNPs and hypertension-free survival (namely age at onset of hypertension), which were adjusted for gender, BMI, and use of antihypertension medication. Cox regression analysis was implemented using the R package ''survival'' (version 2.38–3, downloaded from The Comprehensive R Archive Network (CRAN)), and the robust sandwich variance estimator[39] was used to deal with the within-family correlation of age of onset of hypertension. Cox proportional hazard regression assumes that the hazard ratio is constant over time. Therefore, Schoenfeld residuals test was performed to examine the proportional hazards assumption essential for Cox regression analysis.[40]

RESULTS

Demographic and Anthropometric Characteristics of Study Participants at Baseline

A total of 1136 participants were recruited for this study. Mean age of these participants was 49.49 ± 8.15 years, and 542 (47.70%) were male. The mean SBP was 130.44 ± 26.17 mm Hg, and the mean DBP was 77.73 ± 14.26 mm Hg. The mean BMI was 25.35 ± 3.41 kg/m^2. Seven hundred and eighty-four subjects (69.01%) had hypertension at recruitment, and 688 (60.56%) used antihypertension medication (Table 2).

TABLE 2. Characteristics of the Ethnic Chinese Participants in the SAPPHIRe Study

Variables	N	Mean ± SD
Age	1136	49.49 ± 8.15
Gender (male, %)	1136	542 (47.70%)
Hypertension (Baseline, %)	1136	784 (69.01%)
SBP, mm Hg	1136	130.44 ± 26.17
DBP, mm Hg	1136	77.73 ± 14.26
BMI (kg/m^2)	1135	25.35 ± 3.41
Use of antihypertension medication	1136	688 (60.56%)

BMI = body mass index, DBP = diastolic blood pressure, SBP = systolic blood pressure, SAPPHIRe = Stanford Asia-Pacific Program for Hypertension and Insulin Resistance.

TABLE 3. Effect of the Minor Allele of *SORBS1* on Each Trait Under the Recessive Model, Analyzed Using the GEE Approach

		Hypertension			SBP			DBP		
SNP	MAF	OR (95% CI)	*P*	*Q*	β (95% CI)	*P*	*Q*	β (95% CI)	*P*	*Q*
rs7081076	0.08	—	—	—	—	—	—	—	—	—
rs2281939	0.11	0.65 (0.16, 2.57)	0.54	0.78	−8.48 (−13.96, −3.00)	0.002	0.02	−6.88 (−8.94, −4.81)	7.2×10^{-11}	1.4×10^{-9}
rs3818540	0.38	1.1 (0.69, 1.75)	0.69	0.78	3.55 (−0.57, 7.68)	0.09	0.26	2.05 (−0.30, 4.40)	0.09	0.26
rs2274490	0.37	0.63 (0.44, 0.90)	0.011	0.06	−4.45 (−7.76, −1.14)	0.008	0.05	−2.12 (−3.98, −0.27)	0.025	0.10
rs61739184	0.07	1.19 (0.09, 15.18)	0.9	0.78	−2.99 (−17.66, 11.69)	0.69	0.78	0.46 (−11.91, 12.83)	0.94	0.78
rs726176	0.36	1.04 (0.70, 1.53)	0.85	0.78	0.16 (−3.76, 4.07)	0.94	0.78	0.33 (−1.78, 2.45)	0.76	0.78
rs2296966	0.34	0.92 (0.60, 1.43)	0.71	0.78	1.95 (−2.40, 6.29)	0.38	0.76	0.48 (−1.76, 2.71)	0.68	0.78
rs17849148	0.27	0.94 (0.53, 1.67)	0.94	0.78	−0.54 (−5.89, 4.81)	0.84	0.78	0.59 (−2.33, 3.50)	0.69	0.78
rs3193970	0.37	0.77 (0.54, 1.09)	0.14	0.35	−1.75 (−5.59, 2.08)	0.37	0.76	−0.76 (−2.75, 1.24)	0.46	0.78

CI = confidence interval, DBP = diastolic blood pressure, MAF = minor allele frequency, OR = odds ratio, SBP = systolic blood pressure, SNP = single nucleotide polymorphism.

Association of SNPs of *SORBS1* With SBP, DBP, and Presence of Hypertension

First, we explored the association of each *SORBS1* SNP genotype with SBP, DBP, and the presence of hypertension using a GEE model. Subjects carrying 2 minor alleles (GG genotype) of rs2281939 had lower SBP and DBP than those carrying 2 major alleles (AA genotype). Similarly, individuals carrying 2 minor alleles (CC genotype) of rs2274490 had lower SBP and DBP than those carrying 2 major alleles (TT genotype) (Supplementary Table 1, http://links.lww.com/MD/A754). We obtained the effects of the minor alleles of *SORBS1* SNPs under recessive models in subsequent analyses, based on genotypic association.

Individuals carrying 2 G alleles of rs2281939 had significantly lower SBP (β = −8.48, 95% CI 13.96 to −3.00, $Q = 0.02$) and DBP (β = −6.88, 95% CI −8.94 to −4.81, $Q = 1.4 \times 10^{-9}$) than those carrying the A allele. Individuals carrying 2 C alleles of rs2274490 had a significantly lower prevalence of hypertension (Odds ratio [OR] = 0.63, 95% CI 0.44–0.90, $Q = 0.06$), lower SBP (β = −4.45, 95% CI −7.76 to −1.14, $Q = 0.05$), and lower DBP (β = −2.12, 95% CI −3.98 to −0.27, $Q = 0.10$) than those carrying the T allele (Table 3).

Association of rs2281939 and rs2274490 With Age at Onset of Hypertension

Based on the results of Table 3, we selected rs2281939 and rs2274490 to perform Cox regression analysis to explore the association of these 2 SNPs with age at onset of hypertension. Results of Schoenfeld residuals tests indicated that the proportional hazards assumption was not violated in our data (Supplementary Table 2, http://links.lww.com/MD/A754). Individuals carrying the GG genotype of rs2281939 had a significantly older age at onset of hypertension than those carrying AA or AG genotypes (Table 4, Figure 1A). Individuals carrying the CC genotype of rs2274490 had a significantly older age at onset of hypertension than those carrying TT or TC genotypes (Table 4, Figure 1B).

Investigating Whether rs2281939 and rs2274460 Are Independently Associated With SBP, DBP, and Age at Onset of Hypertension

To investigate whether rs2281939 and rs2274490 are independently associated with SBP, DBP, and age at onset of hypertension, we reexamined the associations by incorporating these 2 SNPs into the models simultaneously (Table 5). For rs2281939, significant effects on SBP, DBP, and age at onset of hypertension remained in the 2-SNP models ($P = 0.049$, 8.2×10^{-6}, and 0.042, respectively). For rs2274490, the effect on SBP was significant ($P = 0.016$), but the effects on DBP and age at onset of hypertension were borderline ($P = 0.056$ and 0.094, respectively) in the 2-SNP model. The D′ of LD between rs2281939 and rs2274490 was 0.83.

DISCUSSION

We reported that 2 specific SNPs of *SORBS1* were associated with the prevalence of hypertension, SBP, and DBP. Furthermore, the 2 specific SNPs were also associated with age at onset of hypertension. To the best of our knowledge, this is the first study on the association of genetic variants of *SORBS1* with age at onset of hypertension.

It has been reported that deletion of the bone marrow-specific Cap gene protects against high-fat diet-induced insulin resistance.[41] Ribon et al[42] also reported that treatment with an insulin sensitizer may regulate the expression of this protein in insulin-target tissues. In addition, it has been shown that there is an inverse relationship between BMI and the expression level of the *SORBS1* gene in the visceral adipose tissue of non-diabetic women.[43] We previously reported that the G allele of rs2281939 (Ala allele of the T228A polymorphism) was associated with a leaner body build than that of subjects without this polymorphism. Furthermore, the G allele of this polymorphism was also associated with a lower insulin resistance index than the A allele

TABLE 4. Effect of the Minor Allele of rs2281939 and rs2274490 on Age at Onset of Hypertension Under a Recessive Model Analyzed Using Cox Regression Model

			Age at Onset of Hypertension	
SNP	SNP Name	MAF	HR (95% CI)	*P*
2	rs2281939	0.11	0.5 (0.28, 0.88)	0.016
4	rs2274490	0.37	0.83 (0.69, 0.99)	0.047

95% CI = 95% confidence interval, HR = hazard ratio, MAF = minor allele frequency, SNP = single nucleotide polymorphism.

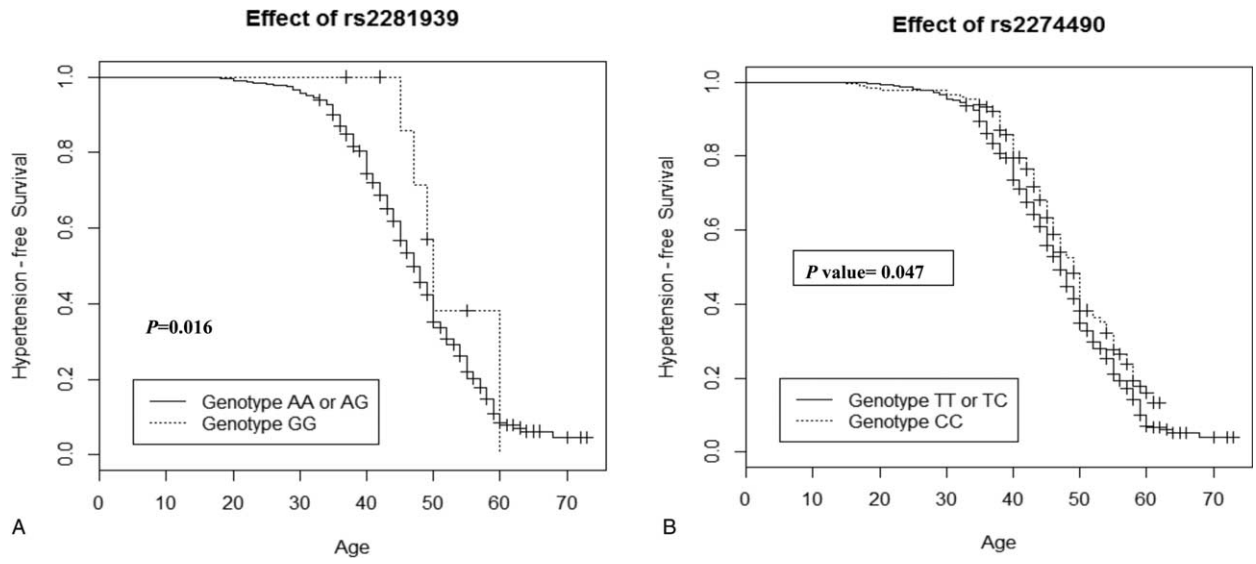

FIGURE 1. Probability of hypertension-free survival of participants carrying different genotypes of rs2281939 (A) and rs2274490 (B).

of rs2281939 (Thr allele of T228A). We also found that the G allele of this polymorphism was protective for both obesity and diabetes.[30] It has been reported that the GG genotype of the rs2281939 (Ala/Ala genotype of T228A) polymorphism may be a potential risk factor for lacunar infarction in a Japanese population.[44] The G allele of rs2281939 (Ala allele of the T228A polymorphism) in the *SORBS1* gene has also been reported to be a risk factor for hypertension in a Japanese population and to be associated with higher DBP in Japanese women.[45] In the present study, we genotyped 9 tag SNPs of *SORBS1* and found that the individuals carrying 2 G alleles of rs2281939 (Ala allele of the T228A polymorphism) had lower SBP, DBP and later age at onset of hypertension. This result is in contrast to findings in Japanese populations.[44,45] The discrepancy may be due to ethnic differences and the younger age of the participants in our study than that of the Japanese study group (49.49 ± 8.15 years in our group; Japanese women with hypertension: 64.4 ± 0.5 years, Japanese women without hypertension: 56.6 ± 0.4 years; Japanese men with hypertension: 63.2 ± 0.6 years, Japanese men without hypertension: 57.3 ± 0.4 years), and different sampling methods (family-based design in our study, and case-control design in the Japanese study). The A to G polymorphism of rs2281939 corresponds to a predicted phosphorylation site for mitogen-

TABLE 5. Effect of the Minor Allele of *SORBS1* (rs2281939 and rs2274490) on SBP, DBP, and Age at Onset of Hypertension Under the 1-SNP and 2-SNP Models

		Effect of rs2281939		Effect of rs2274490	
Trait	**Model**	**β or HR (95% CI)**	***P***	**β or HR (95% CI)**	***P***
Systolic blood pressure					
	1-SNP model: rs2281939	−8.48 (−13.96, −3.00)	0.002	—	—
	1-SNP model: rs2274490	—	—	−4.45 (−7.76, −1.14)	0.008
	2-SNP model: rs2281939 & rs2274490	−5.41 (−10.79, −0.03)	0.049	−4.19 (−7.61, −0.76)	0.016
Diastolic blood pressure					
	1-SNP model: rs2281939	−6.88 (−8.94, −4.81)	7.2×10^{-11}	—	—
	1-SNP model: rs2274490	—	—	−2.12 (−3.98, −0.27)	0.025
	2-SNP model: rs2281939 & rs2274490	−5.5 (−7.92, −3.09)	8.2×10^{-6}	−1.86 (−3.76, 0.05)	0.056
Age of onset of hypertension					
	1-SNP model: rs2281939	0.5 (0.28, 0.88)	0.016	—	—
	1-SNP model: rs2274490	—	—	0.83 (0.69, 0.99)	0.047
	2-SNP model: rs2281939 & rs2274490	0.56 (0.32, 0.98)	0.042	0.86 (0.71, 1.03)	0.094

Adjustment covariants: gender, BMI, antihypertension medication.
95% CI = 95% confidence interval, HR = hazard ratio, SNP = single nucleotide polymorphism.

activated protein kinase.[30] However, the exact mechanism of this amino acid variant in influencing BP regulation needs further study.

In this study, we found individuals carrying two C alleles of rs2274490 also had lower SBP and DBP, lower prevalence of hypertension, and later age at onset of hypertension. The association of rs2274490 with the above phenotype was first reported in this study. The MAF of rs2274490 was 0.37, which was higher than that of rs2281939. Therefore, the genetic variant of rs2274490 may also contribute to BP regulation to some degree. However, this needs further replication in other independent populations and different ethnic groups. Because D′ of the LD between rs2281939 and rs2274490 was 0.83, we further analyzed the association of the 2 SNPs with SBP, DBP, and age at onset of hypertension, respectively, under a 2-SNP model (Table 5). We found the associations of rs2281939 with SBP, DBP, and age at onset of hypertension were still statistically significant under the 2-SNP model, indicating the associations of rs2281939 with these phenotypes were independent of the LD with rs2274490. On the other hand, the association of rs2274490 with SBP was also significant under the 2-SNP model, which indicated the association of rs2274490 with SBP was independent of the LD with rs2281939. In contrast, the associations of rs2274490 with DBP and age at onset of hypertension were borderline significant under the 2-SNP model, indicating the associations of rs2274490 with these 2 phenotypes were partially from the LD between rs2281939 and rs2274490, with some effects from rs2274490 itself.

We further searched the open GWAS Central Database,[46] 18 GWAS for hypertension and 37 GWAS for BP were found (https://www.gwascentral.org/, searched on 12.26.2015). Then we searched the association between genetic variants of *SORBS1* and BP as well as hypertension based on the database of these GWAS. None of the associations attained genome-wide significance (5.0×10^{-8}). This may be partially explained that the underlying rationale for GWAS is based on the ''common disease, common variant'' hypothesis, assuming that common diseases are attributable in part to the common variants (allelic frequency more than 1%–5%) of the population.[47–49] However, most common variants individually or in combination confer relatively small odds ratio (1.1–1.5 fold) and explain only a small proportion of heritability.[50] Another limitation of GWAS is that the rarer variants (possibly with larger effects) are hardly detected by available genotyping arrays in GWAS.[51] Therefore, it is possible that the sample size of GWAS is not big enough to have the power to detect the effect of genetic variants in *SORBS1* on BP regulation. Another plausible explanation is that almost all the GWAS were under the assumption of additive genetic model, but we obtained the effects of the minor alleles of *SORBS1* SNPs under recessive models in this study based on genotypic association (Supplementary Table 1, http://links.lww.com/MD/A754). We found several SNPs of *SORBS1* associated with SBP, DBP, or hypertension with a $P < 0.05$ based on GWAS of SBP in a British population (HGVST307) or GWAS for BP and arterial stiffness of Framingham Heart Study 100K project (HGVST204) (Supplementary Table 3, http://links.lww.com/MD/A754).[52] We further searched the published SNPs of *SORBS1* from 1000 Genomes Project phase 3 in Han Chinese South (https://www.1000genomes.org/, searched on 1.2.2016), and then estimated D′ of LD among assayed 9 *SORBS1* SNPs in this study and 2 SNPs from British population and Framingham Heart Study (rs11188311 and rs10509693) using the Haploview program.[32] D′ of the LD between rs2281939 and rs11188311, and D′ of the LD between rs2274490 and rs10509693 were 1.0 (Supplementary Figure 1, http://links.lww.com/MD/A754). Therefore, the 2 significant SNPs rs2281939 and rs2274490 in this study were in strong linkage disequilibrium with the 2 previously GWAS published SNPs of *SORBS1* rs11188311 and rs10509693, respectively.

This study has several strengths. First, we adopted *Q* values as our measure of significance to reduce false-positive results derived from multiple tests. The *Q* value is similar to the more widely used *P* value, but it is a measure of significance in terms of the FDR rather than the false-positive rate.[35] The *Q* value provides a measure of each feature's significance, automatically controlling for the fact that multiple hypotheses are being simultaneously tested. This approach offers a sensible balance between the number of true and false positives, which is automatically calibrated and easily interpreted.[35] Second, this study examined SNPs associated with age at onset of hypertension in addition to prevalence of hypertension. However, a limitation of this study should be noted. The probands recruited in this study also had hypertension. Therefore, the statistical power for associations with hypertension may be hampered due to ascertainment bias.

In conclusion, we provided evidence for the associations of 2 common *SORBS1* genetic variants with SBP, DBP, and age at onset of hypertension. These findings, together with some earlier observations in different ethnic groups, support an involvement of the *SORBS1* gene in the pathogenesis of hypertension and provide a possible link between insulin resistance and essential hypertension.

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