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Genetic susceptibility to essential hypertension in the Chinese han population: a study on *GAB1*, *GAB2*, and *GAB3* gene polymorphisms

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Abstract

Background This study aims to examine the association between single nucleotide gene polymorphisms (SNPs) of *GAB1*, *GAB2*, and *GAB3* and the genetic susceptibility to essential hypertension in the Chinese Han population. The findings of this research will contribute to understanding the underlying causes of hypertension.

Methods A community-based sampling survey was conducted in two towns in the south of Jiangsu Province to investigate the correlation between gene polymorphisms and essential hypertension. The study included a total of 2119 cases of hypertension and 2317 healthy controls, with an average follow-up period of 10.75 years. The genotypes of seven tagging SNPs (*GAB1* rs300893 and rs11936966, *GAB2* rs7107174, rs2450135, and rs3740677, *GAB3* rs3813455 and rs5987015) were analyzed.

Results Regression analysis showed that after multifactor correction, only *GAB1* rs300893 dominant model was statistically associated with the risk of hypertension among 7 SNPs locis before Bonferroni correction. Subgroup analysis showed that there were associations between specific SNPS and the risk of hypertension in different subgroups, but after Bonferroni correction, these associations were no longer statistically significant. In the follow-up study, Cox proportional hazard regression analysis showed that there was no significant association between the seven SNPs locis and the risk of hypertension. However, subgroup analyses suggest that some gene variants are associated with a reduced or increased risk of hypertension in specific populations. After Bonferroni correction, the addition model of *GAB2* rs7107174 was still statistically significant in the specific stratified analysis. Plasma *GAB1*, *GAB2*, and *GAB3* mRNA expression showed no significant difference between the hypertensive group and the control group.

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Conclusion These findings provide additional support for the genetic role of *GAB1*, *GAB2* and *GAB3* in hypertension and blood pressure regulation.

Keywords *GAB* gene, Single nucleotide polymorphisms, Hypertension, mRNA expression

Background

The pathogenesis of hypertension is a complex process influenced by both genetic and environmental factors. It is associated with various complications and has multiple causal characteristics [1]. Hypertension plays a significant role in the development of cardiovascular and cerebrovascular diseases, such as coronary heart disease and stroke [2]. It is projected that by 2025, approximately 1.5 billion adults worldwide will have hypertension, and by 2030, the number of hypertension cases in China alone will rise to 352 million [3, 4]. This high incidence rate poses a serious threat to population health and imposes a substantial disease burden. Consequently, it is crucial to actively conduct research on the pathogenesis of hypertension and factors influencing blood pressure.

In recent years, Genome-wide association study (GWAS) has discovered significant associations between the development of hypertension and a variety of candidate genes in different populations [5, 6]. GAB family proteins, which are important signaling proteins involved in transmembrane receptor transport, have been found to bind to growth factor receptor binding protein 2 (Grb2). The GAB family proteins are currently classified into three subclasses: *GAB1*, *GAB2*, and *GAB3*. Among these subclasses, *GAB1* and *GAB2* are widely expressed in various tissues and organs of mammals, with the highest expression observed in the brain, kidney, lung, heart, testis, and ovary [7].

Studies have demonstrated that *GAB1* can undergo tyrosine phosphorylation in response to epidermal growth factor (EGF) and insulin stimulation. The recruitment of Src homology 2-containing protein tyrosine phosphatase 2 (SHP2) to *GAB1* can regulate vascular endothelial growth factor (VEGF)-induced migration [7, 8]. Additionally, animal experiments have revealed that *GAB1* knockout mice exhibit significant defects in vascular neovascularization and collateral circulation reconstruction, indicating the crucial role of the *GAB1-PKA-eNOS* signal transduction pathway in vascular endothelial cell remodeling [9]. *GAB1* serves as a vital signal transduction molecule that integrates VEGF-dependent and HGF-dependent signaling pathways, thereby regulating vascular cells in vascular cardiomyocytes. *GAB1/GAB2* double-knockout mice display ventricular dilation and decreased contractility associated with aging, highlighting the involvement of *GAB1* and *GAB2* in maintaining heart function and vascular regulation [10]. The latest GWAS [11] study conducted on the Australian population identified a susceptibility loci of GAB2, rs7107174, which is associated with essential hypertension. However, there are currently no reports on its correlation among the Chinese population. *GAB3* is primarily found in lymphoid tissues in the human body and shares a high sequence similarity with *GAB1*, but there are limited studies exploring their relationship.

This study aims to investigate the correlation between *GAB1*, *GAB2*, and *GAB3* polymorphisms and essential hypertension. It focuses on conducting a community-based molecular epidemiological study of the Han population in China. The primary objective is to provide a scientific basis for understanding the molecular mechanism underlying the development of hypertension and identifying potential therapeutic targets.

Materials and methods

Inclusion and exclusion criteria of the research object

In our epidemiological study, conducted from May to October 2009, we employed cluster sampling to select a rural population from two towns in Yixing city, Jiangsu Province. Our sample consisted of a total of 4436 participants, including 2119 individuals with hypertension and 2223 healthy controls. To ensure age-matching, we included 94 elderly subjects [12] with normal blood pressure. Hypertension was defined as a mean systolic blood pressure (SBP) of ≥140 mmHg and/or diastolic blood pressure (DBP) of ≥90 mmHg, or individuals currently undergoing antihypertensive therapy, even if their measured values were within normal range [13]. Blood pressure measurements for new cases were taken at different times on different days, with all three measurements meeting the diagnostic criteria for hypertension. The samples included in this study were selected based on the exclusion of individuals with acute and serious diseases that may affect blood pressure, such as severe liver and kidney diseases, organic cardiovascular and cerebrovascular diseases, and malignant tumors. Additionally, we selected 106 hypertension cases and 107 controls for the detection of *GAB1*, *GAB2*, and *GAB3* mRNA. This study was approved by the Ethics Committee of Wannan Medical College in Anhui Province, China, and each participant provided a written informed consent.

Collection of data and samples

Epidemiological baseline surveys were conducted on all subjects to gather basic information including age, gender, nationality, marital status, and education level. The surveys also collected general demographic characteristics such as height, weight, waist circumference, hip

circumference, and blood pressure. Additionally, epidemiological exposure history, such as previous disease history and family history, and lifestyle factors like smoking and drinking were recorded. For blood sample collection, subjects were instructed to fast for at least 10 h overnight before drawing blood. Peripheral venous blood was then collected on the morning of the second day.

A follow-up survey was conducted for a mean duration of 10.75 years until July 2020, involving 2116 control subjects. During this period, 637 new cases of hypertension were identified. The occurrence and progression of hypertension were assessed through face-to-face interviews and physical examinations. For participants who were unable to attend the on-site investigation, alternative methods such as telephone interviews or visits to close relatives were utilized to gather information about their health status. Participants who could not be contacted or had passed away were considered as lost to follow-up.

The study was registered with the local department of public health and met the requirements of the ethics committee. Written informed consents were obtained from all subjects during the study period.

SNPs screening and genotyping

The human *GAB1* gene is located on chromosome 4q31.21 (gene ID: 2549; NC_000004.12), while the *GAB2* gene is located on chromosome 11q14.1 (gene ID: 9846; NC_000011.10) and the *GAB3* gene is located on chromosome Xq28 (gene ID: 139716; NC_000023.11). The Beijing Han population genetic database used in this study was obtained from the National Genome Research Institute 1000 Genome Project Database (GRCh37, http://phase3browser.1000genomes.org/index.html). We used Haploview software (version 4.2) and the Snpinfo website (snpinfo, https://snpinfo.niehs.nih.gov/) to screen tagSNPs that satisfy the criteria of $r^2 \geq 0.8$ and minimum allele frequency (MAF) ≥ 0.05 based on SNP function prediction. Finally, we selected *GAB1* rs300893 (T > C) and rs11936966 (A > C) as well as *GAB2* rs2450135 (G > A), rs7107174 (C > T), and rs3740677 (G > T), and *GAB3* rs3813455 (C > G) and rs5987015 (A > G) as tagSNPs to investigate the genetic susceptibility of essential hypertension and its association with *GAB1*, *GAB2*, and *GAB3*. The biological information analysis and function prediction of the selected tagSNPs are presented in Table 1.

DNA was extracted from peripheral blood leukocytes using the standard phenol-chloroform method. Genotyping was performed using the Taqman method on the ABI 9700 real-time polymerase chain reaction (PCR) platform. The reaction conditions consisted of an initial denaturation step at 95℃ for 10 min, followed by 45 cycles of denaturation at 95℃ for 15 s, annealing at 60℃ for 1 min, and a final extension step at 15℃ for 10 min. The total reaction volume was 5 μl, with 1 μl of DNA template. The genotyping results were obtained using the SDS 2.32 allele recognition software on the ABI 7900 analyzer.

GAB1 GAB2 and *GAB3* mRNA measurement

Total RNA from peripheral blood mononuclear cells (PBMCs) was isolated using an RNA blood kit (Yuan, Yu-BR02-1, China). Complementary DNA (cDNA) was synthesized from messenger RNA (mRNA) using TAKARA reverse transcription kits (RR047A Takara PrimeScript RT reagent Kit with gDNA Eraser, Japan). In this study, glyceraldehyde – 3 - phosphate dehydrogenase (GAPDH) was employed as the internal reference. The primer sequences for GAB1, GAB2, and GAB3 can be found in Supplementary Table S1. The mRNA expression levels of GAB1, GAB2, and GAB3 were determined using SYBR Green real-time quantitative polymerase chain reaction (RT-qPCR). The relative mRNA expression was calculated using the 2-ΔΔCT method (where ΔΔCT case equals ΔCT case minus the mean of ΔCT control, and ΔΔCT control equals ΔCT control minus the mean of ΔCT control; ΔCT equals the target gene CT minus the housekeeping gene CT).

Statistical analysis

The software package Power for Genetic Association Analyses (PGA) was used to calculate the sample size. The significance level of the two-sided test was $\alpha = 0.05$, MAF0.05, with at least 80% statistical confidence to detect locis above OR = 1.3. All measured data were

Table 1 The biological information and function prediction of selected TagSNPs

No.	SNP	Chrom-osome	Position	Allele	TFBS	miRNA (miRanda)	RegPotent-ial	Conser-vation	Nearby Gene	Distance (bp)	MAF
1	rs300893	4	144,476,566	T/C	Y	--	0.508399	0.0	USP38‖GAB1	-114,476‖-934	0.265
2	rs11936966	4	144,564,620	A/C	Y	--	0.0	0.449	GAB1	87,120‖46,109	0.093
3	rs2450135	11	77,605,643	G/A	--	Y	0.0	0.0	GAB2	1653‖200,771	0.375
4	rs7107174	11	77,675,584	C/T	--	--	0.0	0.116	GAB2	71,594‖130,830	0.361
5	rs3740677	11	77,605,684	G/T	--	Y	0.041497	0.007	GAB2	1694‖200,730	0.262
6	rs3813455	X	153,557,329	C/G	--	Y	0.0	0.001	GAB3	609‖75,213	0.028
7	rs5987015	X	153,601,175	A/G	--	--	0.02323	0.001	GAB3	44,455‖31,367	0.349

presented as mean ± standard deviation (SD), median or inter-quartile range (IQR). T-test was used to compare two groups with a normal distribution, while ANOVA was used for multiple groups. Non-parametric tests were employed for data that did not conform to a normal distribution. Statistical data were expressed as composition ratio (%) and chi-square test was used for group comparisons. Logistic regression analysis was conducted to examine the association between different genotypes and the incidence of hypertension, with results reported as odds ratio (*OR*) and 95% confidence interval (95%*CI*). Stratification was performed based on age, gender, smoking, and drinking consumption. Cox proportional risk regression analysis was used to assess the risk of *GAB1*, *GAB2*, *GAB3*, and hypertension, with hazard ratio (HR) and 95% *CI* reported. Adjustments were made for covariates including age, gender, TCH, TG, HDL-C, LDL-C, BMI, GLU, smoking, and drinking consumption. Bonferroni correction was used for correcting the *p*-values for multiple comparisons. A significance level of $P < 0.05$ (two-sided) was considered statistically significant. SPSS 26.0 was utilized for all statistical analyses.

Result

General demographic and clinical characteristics of subjects

A total of 4436 subjects were included in this study, consisting of 2119 cases in the hypertension group and 2317 cases in the control group. The average ages of the hypertension group and control group were 62.68 ± 10.59 years and 59.39 ± 10.46 years, respectively. Although the ages were matched within a range of ± 5 years, the hypertension group had a slightly higher average age than the control group by 3.29 years ($P < 0.05$). There were no significant differences between the two groups in terms of gender, HDL-C level, smoking, and drinking status. However, compared to the control group, the hypertension cases had higher levels of SBP, DBP, BMI, TCH, TG, LDL-C, and GLU (Table 2).

A total of 637 (28.7%) subjects developed hypertension during the mean follow-up period of 2223 controls over 10.75 years. Among the new cases of hypertension, 162 (25.4%) were reported by the individuals themselves as taking antihypertensive drugs, and their medical records were further reviewed and validated. The remaining 451 cases (70.8%) were diagnosed based on standardized blood pressure measurements.

Logistic regression analysis between different genotypes and the incidence of hypertension

In addition to rs3813455, and rs5987015, the genotypes of the other five SNPs in the control group were consistent with Hardy-Weinberg Equilibrium (HWE) ($P > 0.05$). We analyzed the association between the *GAB1* loci (rs300893 and rs11936966), the *GAB2* loci (rs2450135, rs7107174, and rs3740677), and the *GAB3* loci (rs3813455 and rs5987015). Logistic regression results, adjusting for covariates such as age, gender, TCH, TG, LDL-C, HDL-C, BMI, GLU, smoking, and drinking, showed that only the *GAB1* rs300893 (TT vs. TC + CC) ($P = 0.037$) was statistically different in terms of hypertension risk, while the other SNPs showed no significant association with hypertension susceptibility ($P > 0.05$) (Table 3).

Table 2 Demographic and clinical characteristics of case-control study subjects

Characteristics	Group	Case($n = 2119$)	Control ($n = 2317$)	t/χ2	*P*
Gender	Male	872(41.2)	927 (40.0)	0.599	0.439
	Female	1247 (58.8)	1390(60.0)		
Age (years)		62.68 ± 10.59	59.39 ± 10.46	10.383	< 0.001
GLU (mmol/L)		5.81 ± 2.01	5.45 ± 1.57	6.718	< 0.001
TCH (mmol/L)		4.94 ± 1.05	4.79 ± 1.00	4.81	< 0.001
TG (mmol/L)		1.84 ± 1.54	1.53 ± 1.20	7.543	< 0.001
HDL-C (mmol/L)		1.36 ± 0.32	1.36 ± 0.33	0.052	0.959
LDL-C (mmol/L)		2.80 ± 0.88	2.65 ± 0.72	6.501	< 0.001
BMI (kg/m2)		24.7 ± 3.48	23.6 ± 3.20	11.024	< 0.001
Blood pressure	SBP	143.51 ± 14.53	124.21 ± 11.25	49.121	< 0.001
(mmHg)	DBP	87.23 ± 8.62	78.65 ± 6.79	36.587	< 0.001
Smoking	Yes	491(23.2)	540(23.3)	0.011	0.916
	No	1628(76.8)	1777(76.7)		
Drinking	Yes	433(20.4)	483(20.8)	0.114	0.735
	No	1686(79.6)	1834(79.2)		
Diabetes	Yes	297(14.0)	220(9.5)	22.196	< 0.001
	No	1817(86.0)	2096(90.5)		
Dyslipidemia	Yes	1363(64.5)	1296(56.0)	33.406	< 0.001
	No	751(35.5)	1020(44.0)		

Table 3 Analysis of the association between *GAB1*, *GAB2* and *GAB3* genes and essential hypertension

Gene	SNP	Group	WT/HT/MT	Crude OR(95%CI)[a]			Allele gene	P^b
				Additive	Dominant	Recessive	Major/minor	
			TT/TC/CC				T/C	
GAB1	rs300893	case	1164/812/130	1.104(1.000-1.219)	1.138(1.008–1.285)	1.090(0.845–1.405)	3140/1072	*0.728*
		control	1342/828/133	*P* = 0.050	***P* = 0.037**	*P* = 0.507	3512/1094	
			AA/AC/CC				A/C	
	rs11936966	case	1692/365/49	1.108(0.972–1.263)	1.135(0.973–1.325)	1.115(0.745–1.669)	3749/463	*0.447*
		control	1897/360/51	*P* = 0.124	*P* = 0.107	*P* = 0.597	4154/462	
			AA/AG/GG				A/G	
GAB2	rs2450135	case	1002/891/214	0.977(0.892–1.070)	0.979(0.868–1.104)	0.949(0.779–1.155)	2895/1319	*0.360*
		control	1081/984/245	*P* = 0.613	*P* = 0.725	*P* = 0.600	3146/1474	
			CC/CT/TT				C/T	
	rs7107174	case	719/1000/389	1.075(0.986–1.171)	1.057(0.932-1.200)	1.171(0.999–1.374)	2438/1778	*0.610*
		control	816/1121/369	*P* = 0.101	*P* = 0.388	*P* = 0.052	2753/1859	
			GG/GT/TT				G/T	
	rs3740677	case	1129/832/148	0.938(0.852–1.032)	0.945(0.838–1.066)	0.848(0.675–1.067)	3090/1128	0.799
		control	1197/923/183	*P* = 0.188	*P* = 0.358	*P* = 0.159	3317/1289	
			CC/CG/GG				C/G	
GAB3	rs3813455	case	1923/131/52	0.960(0.823–1.121)	0.941(0.762–1.162)	0.951(0.645–1.403)	3977/235	*< 0.05*
		control	2086/157/58	*P* = 0.608	*P* = 0.573	*P* = 0.800	4329/273	
			AA/AG/GG				A/G	
	rs5987015	case	1492/408/212	0.994(0.908–1.089)	0.981(0.859–1.121)	1.018(0.828–1.250)	3392/832	*< 0.05*
		control	1624/461/227	*P* = 0.904	*P* = 0.776	*P* = 0.868	3709/915	

WT: wild type, HT: heterozygous type, MT: mutant type;

Additive: WT vs. HT vs. MT, Dominant: WT vs. HT + MT, Recessive: WT + HT vs. MT;

a: Adjust the covariates such as age, gender, smoking, drinking, diabetes, dyslipidemia, etc.;

b: Hardy-Weinberg equilibrium test of the control group

Further stratified analysis by age, gender, smoking, drinking, and dyslipidemia revealed that the *GAB1* rs300893 T > C alternative was associated with an increased risk of hypertension in individuals aged ≥ 55 years, females, non-smokers, non-drinkers, and those without dyslipidemia (all $P < 0.05$). Additive models of GAB1 rs11936966 in the diabetic population, *GAB2* rs7107174 in males and drinkers, and *GAB3* rs5987015 in individuals aged < 55 years all suggested that the gene genetic variations increased the risk of hypertension (all $P < 0.05$). The additive model of *GAB2* rs3740677 in the nondyslipidemia population showed that the gene genetic variations played a protective role in hypertension ($OR = 0.849$, $P = 0.038$) (Supplement Table S2). These results were not valid after Bonferroni correction. The results of GAB2 haplotype analysis suggested that there was insufficient evidence for a significant association between this haplotype and the development of hypertension (Supplement Table S3).

Follow-up study analysis

The research analysis indicates that the proportional risk assumption is met in all situations. Cox proportional hazards regression analysis was conducted, adjusting for age, gender, GLU, TCH, TG, LDL-C, HDL-C, BMI, smoking, and drinking covariates. The results showed that the seven SNPs in the follow-up population were not statistically associated with the risk of hypertension (Supplement Table S4).

However, further stratified analysis revealed that certain genetic variations were associated with a reduced risk of hypertension in specific populations. For example, *GAB1* rs11936966 was associated with a reduced risk in the diabetic population, *GAB2* rs2450135 in males, rs3740677 in smokers and drinkers, and *GAB3* rs3813455 and rs5987015 in individuals aged ≥ 55 years and rs5987015 in abstainers and non-dyslipidemia. On the other hand, *GAB2* rs7107174 and *GAB3* rs3813455 in individuals aged ≥ 55 years, as well as rs7107174 in males, smokers, and drinking, suggested an increased risk of hypertension (all $P < 0.05$) (Table 4). After Bonferroni correction, the additive model of GAB2 rs7107174 was still statistically significant in the ≥ 55 years old, male, smoking stratification, and the additive and dominant models of GAB2 rs7107174 were also still correlated in the drinking stratification (P value×6). The detailed results of each level of analysis are shown in the supplement table S5-10.

Comparison of plasma *GAB 1/2/3* mRNA expression between hypertensive cases and controls

Based on the results of the Mann-Whitney U test, there was no significant difference in mRNA expression of

Table 4 Multivariate analysis of different stratification in association between genetic polymorphism and hypertension

Gene	SNP	Genotype	Group	HR(95%CI)[a]		
				Additive	**Dominant**	**Recessive**
GAB 1	rs11936966	AA	Diabetes	0.365(0.137–0.973)	0.358(0.130–0.984)	0.000(0.000–0.000)
		AC		***P*=0.044**	***P*=0.046**	*P*=0.967
		CC				
GAB 2	rs2450135	GG	male	0.839(0.700-1.007)	0.785(0.620–0.993)	0.849(0.570–1.265)
		GA		*P*=0.060	***P*=0.043**	*P*=0.421
		AA				
	rs7107174	CC	<55years	0.856(0.692–1.059)	0.943(0.697–1.276)	0.601(0.378–0.957)
		CT		*P*=0.152	*P*=0.704	***P*=0.032**
		TT				
		CC	≥55years	1.207(1.058–1.377)	1.271(1.040–1.553)	1.303(1.033–1.644)
		CT		***P*=0.005**	***P*=0.019**	***P*=0.025**
		TT				
		CC	male	1.294(1.093–1.533)	1.387(1.068–1.802)	1.438(1.071–1.929)
		CT		***P*=0.003**	***P*=0.014**	***P*=0.016**
		TT				
		CC	Smoking	1.342(1.087–1.658)	1.577(1.117–2.227)	1.404(0.973–2.024)
		CT		***P*=0.006**	***P*=0.010**	*P*=0.069
		TT				
		CC	Drinking	1.403(1.123–1.752)	1.677(1.177–2.391)	1.460(0.983–2.169)
		CT		***P*=0.003**	***P*=0.004**	*P*=0.061
		TT				
	rs3740677	GG	Smoking	0.783(0.606–1.014)	0.693(0.505–0.952)	0.946(0.525–1.704)
		GT		*P*=0.063	***P*=0.024**	*P*=0.853
		TT				
		GG	Drinking	0.708(0.542–0.926)	0.689(0.500-0.949)	0.521(0.242–1.120)
		GT		***P*=0.012**	***P*=0.023**	*P*=0.095
		TT				
GAB 3	rs3813455	CC	<55years	1.367(0.999–1.871)	1.529(1.005–2.327)	1.625(0.703–3.758)
		CG		*P*=0.051	***P*=0.047**	*P*=0.257
		GG				
		CC	≥55 years	0.765(0.582–1.005)	0.672(0.454–0.994)	0.644(0.341–1.217)
		CG		*P*=0.054	***P*=0.047**	*P*=0.175
		GG				
	rs5987015	AA	≥55 years	0.827(0.715–0.956)	0.767(0.617–0.952)	0.686(0.493–0.953)
		AG		***P*=0.010**	***P*=0.016**	***P*=0.025**
		GG				
		AA	male	0.861(0.733–1.012)	0.781(0.575–1.061)	0.714(0.514–0.992)
		AG		*P*=0.069	*P*=0.113	***P*=0.044**
		GG				
		AA	Nonsmoking	0.825(0.705–0.965)	0.799(0.651–0.981)	0.660(0.437–0.997)
		AG		***P*=0.016**	***P*=0.032**	***P*=0.049**
		GG				
		AA	Nondyslipidemia	0.793(0.649–0.969)	0.769(0.573–1.031)	0.539(0.331–0.877)
		AG		***P*=0.023**	*P*=0.079	***P*=0.013**
		GG				

a: Adjusted covariates such as age, gender, smoking, drinking, dyslipidemia, etc

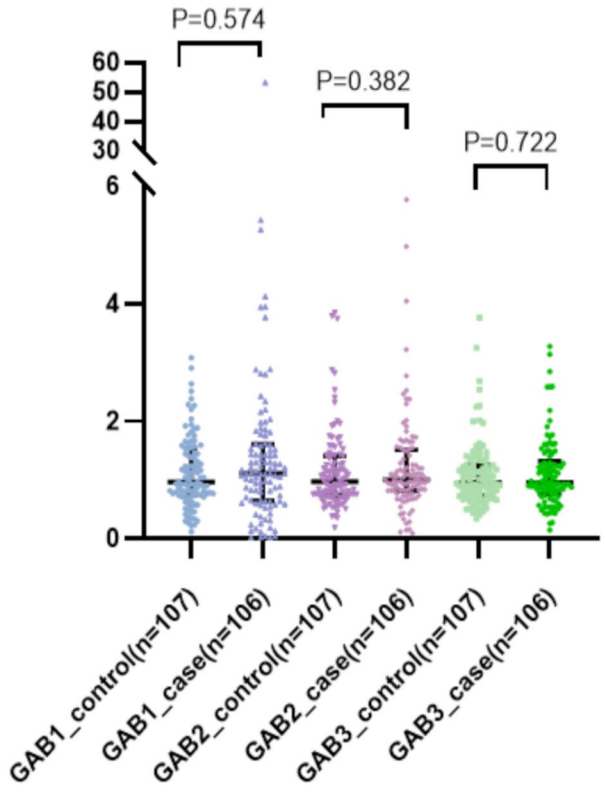

Fig. 1 The mRNA expression of *GAB1*, *GAB2* and *GAB3* in hypertensive cases and controls. (^{P} Mann-Whitney U test)

GAB 1/2/3 between the hypertension group and the control group. The *P* values for *GAB 1*, *GAB 2*, and *GAB 3* were 0.574, 0.382, and 0.722, respectively (Fig. 1).

Discussion

Grb2-related binding proteins, known as intracellular scaffold/docking molecules, act as downstream receptors on the cell surface and interact with various cytoplasmic signaling proteins [14, 15]. The renin-angiotensin system (*RAS*) is a hormone system that regulates plasma sodium concentration and arterial blood pressure, playing a crucial role in maintaining blood pressure, blood flow, and homeostasis [16]. Extracellular regulated protein kinases (*ERK*) *ERK1/2*, a member of the mitogen-activated protein kinase family, is involved in vasoconstriction and vascular smooth muscle cell growth. It is considered an effective target for hypertension treatment [17]. The GAB family participates in two classic signaling pathways, *SHP2/RAS/ERK* and *PI3K/AKT*, transmitting signals to downstream effector proteins. It plays a vital role in regulating angiogenesis, vascular endothelial function, and the pathological process of atherosclerosis [18, 19]. This study aims to investigate the correlation between single nucleotide polymorphisms (SNPs) in *GAB1*, *GAB2*, *GAB3*, and genetic susceptibility to hypertension through a combination of case-control studies and cohort studies.

This study is the first to discover an association between the rs300893 locus of the *GAB1* gene and the risk of hypertension in the population. It was found that individuals carrying the rs300893 TT gene had a 1.138 times higher risk of hypertension compared to those carrying the TC + CC gene. Animal experiments have shown that mice with a knocked-out *GAB1* gene exhibit severe defects in ischemic angiogenesis and collateral circulation reconstruction. This suggests that the '*GAB1-PKA-eNOS*' signal transduction pathway plays a crucial role in the remodeling of vascular endothelial cells [20]. *GAB1*, as a significant upstream signaling molecule, regulates the activation of Endothelial Nitric Oxide Synthase (eNOS) induced by VEGF and the formation of blood vessels [21]. Furthermore, studies have found a significant association between *NOS3* and genetic susceptibility to hypertension, indicating a potential close relationship between *GAB1* and hypertension genetic susceptibility.

Stratified analysis revealed that GAB2 rs2450135, rs7107174, and rs53740677 were found to be either risk or protective factors in different characteristic stratifications in both case controls and subsequent follow-up studies. These results suggest that age, sex, smoking, drinking, diabetes, and dyslipidemia may have some functional modifications in the process of gene SNPs allele alternative, potentially influencing the incidence of hypertension. Among these factors, rs7107174 consistently emerged as a risk factor for hypertension throughout the study. It has been reported that rs7107174 may exist on the putative transcription factor binding loci or enhancer element, and the protein expression can be regulated by binding the corresponding transcription factor [22]. The latest GWAS study demonstrates that the susceptible locus rs7107174 of the GAB2 gene is associated with essential hypertension in the Australian population [23], with no reports in other populations. *GAB2* plays a crucial role in the development of mononuclear phagocytes and serves as a regulator of macrophage recruitment during acute inflammation [23, 24]. These findings suggest that *GAB2* expression in inflammatory diseases may represent an important target for new therapies in inflammation and allergic diseases [11]. Studies have indicated that the inflammatory immune response may contribute to the development of hypertension [25]. Therefore, it can be speculated that the rs7107174 may alter the inflammatory immune function by regulating the specific expression of *GAB2* protein, thereby participating in the pathogenesis of hypertension.

In previous studies, it has been demonstrated that GAB family proteins possess immune functions in various animals. *GAB3* exhibits a high degree of sequence similarity to *GAB1* and *GAB2*. In mammals, *GAB3* plays a crucial

role in macrophage differentiation [26] and the innate immune response to viral infection, following stimulation by macrophage-colony stimulating factor (M-CSF) [27]. Subsequently, it was discovered that the *GAB3* rs5987015 acts as a protective factor against hypertension in stratifiable groups, such as age, sex, smoking, and dyslipidemia. These findings suggest that *GAB3* may also have immune-related functions in the hypertensive population. In conclusion, *GAB3* could potentially serve as a resistance gene to hypertension in the population and play a significant role in countering the development of hypertension.

In the Chinese Han population, the *GAB2* rs300893 may increase the risk of hypertension. Additionally, the risk of hypertension was found to be influenced by age and gender stratification of the rs300893 locus on *GAB1*, the rs7107174 locus on *GAB2*, and the rs5987015 locus on *GAB3*. Moreover, considering smoking significantly increased the risk of cardiovascular disease [28], in the stratification of smoking and drinking, the rs300893 locus on *GAB1* and the rs7107174 locus on *GAB2* were associated with hypertension. Similarly, in the stratification of diabetes and dyslipidemia, the rs300893 and rs11936966 loci on *GAB1*, and the rs7107174 and rs3740677 loci on *GAB2* were found to be associated with hypertension.

Although this study confirmed the correlation between the *GAB1*, *GAB2*, and *GAB3* gene polymorphism and the onset of hypertension, there are still certain limitations. The two groups were matched for conditions, but there is still an age difference between them, and the study may be affected by recall bias, which is common in case-control studies. Additionally, there was no significant difference in mRNA expression levels between the hypertension group and the control group, which could be attributed to the limited sample size and the substantial individual differences among patients. Moreover, we did not assess the expression level of GAB proteins or investigate their role in vasoconstriction, endothelial dysfunction, and the functional verification of the inflammatory response. Therefore, further research is needed to explore the specific molecular mechanisms involved.

Abbreviations

SNPs	Single Nucleotide Gene Polymorphisms
GWAS	Genome-Wide Association Study
Grb2	Growth Factor Receptor Binding Protein 2
EGF	Epidermal Growth Factor
SHP2	Src Homology 2-Containing Protein Tyrosine Phosphatase 2
VEGF	Vascular Endothelial Growth Factor
SBP	Systolic Blood Pressure
DBP	Diastolic Blood Pressure
PCR	Polymerase Chain Reaction
PBMCs	Peripheral Blood Mononuclear Cells
mRNA	Messenger RNA
cDNA	Complementary DNA
RT-qPCR	Real-Time Quantitative Polymerase Chain Reaction
SD	Standard Deviation
IQR	Inter-Quartile Range
95%CI	95% Confidence Interval
HR	Hazard Ratio
GLU	Glucose
TCH	Total Cholesterol
TG	Triglyceride
HDL-C	High-Density Lipoprotein Cholesterol
LDL-C	Low-Density Lipoprotein Cholesterol
BMI	Body Mass Index
RAS	Renin-Angiotensin System
ERK	Extracellular Regulated Protein Kinases
eNOS	Endothelial Nitric Oxide Synthase
M-CSF	Macrophage-Colony Stimulating Factor

Supplementary Information

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Supplementary Material 1

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Author contributions

YYS and JYL designed the study. XJJ, ZYR, XM, and YY contributed to literature searching, data collection and analysis. YYS and JYL assessed study quality. XJJ and ZLJ wrote the manuscript. ZWJ and CWW revised the manuscript. All authors read and approved the final manuscript.

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Data availability

The data that support the findings of this study are available from the Institute of Chronic Disease Prevention and Control, Wannan Medical College, Anhui Province, but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. The Data and full trial protocol are however available from Yuelong Jin author upon reasonable request and with permission of the Institute of Chronic Disease Prevention and Control, Wannan Medical College, Anhui Province. The contact information is the email address of the author Yuelong Jin.

Declarations

Ethics approval and consent to participate

This study was approved by the Ethics Committee of Nanjing Medical University. The trial adheres to the principles of the Helsinki declaration. Written informed consent has been obtained from all subjects or their caregivers.

Consent for publication

Consent for publication was obtained from the participants.

Competing interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Clinical trial number

Not applicable.

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