

Research Article

Association of Antihypertensive Drug-Related Gene Polymorphisms with Stroke in the Chinese Hypertensive Population

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Background. Antihypertensive therapy is crucial for preventing stroke in hypertensive patients. However, the efficacy of antihypertensive therapy varies across individuals, partially due to therapy-related genetic variations among individuals. We investigated the association of antihypertensive drug-related gene polymorphism with stroke in patients with hypertension. Methods. Demographic information, medication, and outcome data were obtained from a hypertensive patient management system, and a PCR fluorescence probe technique was used to detect 7 gene polymorphic loci (CYP2D6 * 10, ADRB1, CYP2C9 * 3, AGTR1, ACE, CYP3A5 * 3, and NPPA), and these loci were compared between patients with and without stroke. Logistic regression was performed to analyze the association of these genetic variations with stroke risk in hypertensive patients while controlling for potential factors. Results. The prevalence of stroke in the hypertensive population in Changsha County of Hunan Province was 2.75%. The mutation frequencies of ADRB1 (1165G > C), CYP2D6 * 10, CYP2C9 * 3, AGTR1 (1166A > C), ACE (I/ D), NPPA (2238T > C), and CYP3A5 * 3 were 74.43%, 57.23%, 4.26%, 5.71%, 31.62%, 1.17%, and 69.58%, respectively. Univariate analysis revealed that *ADRB1* polymorphism was associated with stroke ($\chi^2 = 8.659$, P < 0.05), with a higher stroke risk in the *CC* group than in the GC and GG groups (GC+GG). Multivariate unconditional logistic regression analysis showed that the CC genotype in ADRB1 (vs. the GC + GG genotype) was associated with an increased risk of stroke [odds ratio (OR) = 1.184, P<0.05] in hypertensive patients. No association was observed between CYP2D6 * 10, CYP2C9 * 3, AGTR1 (1166A > C), ACE (I/D), CYP3A5 * 3, and NPPA (2238T > C) polymorphisms and stroke. Conclusions. ADRB1 (1165G > C) gene polymorphism is associated with the risk of stroke in Chinese hypertensive patients. The CC genotype is correlated with a higher risk of stroke than the GC + GG genotype.

1. Introduction

Stroke, which is the second leading cause of death globally, is a chronic noninfectious disease hampering public health [1]. Compared to that in 1990, the absolute number of stroke events worldwide increased by 70.0% in 2019, and the number of deaths increased by 40%. Currently, stroke is the leading cause of death and disability among adults in China; its morbidity, mortality, and number of cases are the highest worldwide [2, 3].

Hypertension is the most important and modifiable high-risk factor for stroke development [4–6]. The World Health Organization (WHO) estimates that approximately 54% of all stroke cases worldwide can be attributed to hypertension [7]. Hypertension control could significantly reduce the incidence of stroke [8]. The drugs for the treatment of hypertension are mainly divided into five categories: beta receptor blockers (BBs), angiotensin-II receptor antagonists (ARBs), angiotensin-converting enzyme inhibitors (ACEIs), calcium channel blockers (CCBs), and diuretics. However, community attainment of hypertension treatment remains dismal, with less than a quarter being controlled [9, 10]. Uncontrolled hypertension may significantly contribute to high mortality from stroke [11].

Hypertension is a polygenic disease, and differences in antihypertensive efficacy are partially associated with genetic variations among individuals [12, 13]. A previous study summarized the pharmacogenomics of hypertension treatment, and the most common genetic variants involved in the metabolism of the above five classes of drugs included *ADRB1* (*1165G* > *C*), *CYP2D6* * *10*, *CYP2C9* * *3*, *AGTR1* (*1166A* > *C*), *ACE* (*I/D*), *CYP3A5* * *3*, and *NPPA* (*2238T* > *C*) [14].

Differences in these gene polymorphisms in response to antihypertensive therapy have been described previously in the literature. Certain genotypes exhibit a greater reduction in blood pressure (BP) and/or long-term benefit with antihypertensive drug use [15]. In particular, the CC genotype of ADRB1 (1165G > C), DD genotype of ACE (I/D), C allele carrier of AGTR1 (1166A > C), and NPPA (2238T > C) are reported to be associated with a significant reduction in BP [16-19]. Mutations in cytochrome P450 enzyme family members, such as CYP2D6, CYP2C9, and CYP3A5, mainly affect the activities of metabolic enzymes. Patients using antihypertensive drugs and having an increased active CYP phenotype may have increased metabolic capacity; in contrast, those with an inactive CYP phenotype may display increased clinical effects and bradycardia following the use of metoprolol and other antihypertensive drugs [20]. A previous study reported that the CYP2C9 * 3 allele may be associated with a decrease in the activity of the CYP2C9 enzyme in the Asian population [21], while CYP3A5 * 3 is correlated with effective control of BP with amlodipine (CCB) in hypertensive patients following renal transplantation via decreasing the activity of the CYP3A5 enzyme [22]. The association of the CYP2D6 mutation with the outcome of antihypertensive therapy with BBs is controversial. CYP2D6 * 10 significantly affected the pharmacokinetics of metoprolol in the Chinese population [23]; however, no significant effect on the outcome of carvedilol and propranolol therapy was observed [24, 25].

ADRB1 (1165G > C), CYP2D6 * 10, CYP2C9 * 3, AGTR1 (*1166A* > *C*), *ACE* (*I*/*D*), *CYP3A5* * 3, and *NPPA* (*2238T* > *C*) are associated not only with BP reduction but also with disease prognosis. A few previous studies revealed that a mutation in ADRB1 (1165G > C) was associated with the survival of patients with heart failure by increasing the dose of BBs [26]. In patients with chronic heart failure and the ADRB1 CC genotype, the use of BBs also appears to reduce the risk for cardiovascular events [26, 27]. However, to the best of our knowledge, no studies have focused on the relationship between all above-mentioned genes and stroke. A community registry of hypertensive patients was started in Changsha County, Hunan Province, in 2013; this system registers the BP treatment and outcomes of hypertensive patients through follow-ups. In 2017, a test of the seven genes polymorphisms mentioned above was conducted in

hypertensive patients. Our study aimed to explore the association between different antihypertensive-related genotypes and stroke. It would provide some evidence for preferential selection of antihypertensive medication in the hypertensive population in Changsha County, Hunan Province.

2. Methods

2.1. Study Population. The study population was selected from hypertensive patients registered in the hypertension management system at each township health center and street health service center in Changsha County, Hunan Province, between January 1, 2013, and January 1, 2018.

Inclusion criteria for study participants: all the hypertensive patients registered in the management system; these patients were enrolled based on the criteria of the Chinese Guidelines for the Prevention and Treatment of Hypertension (2010 Revision) [28]. (1) participants had a systolic blood pressure (SBP) \geq 140 mmHg (1 mmHg = 0.133 kPa) or a diastolic blood pressure (DBP) \geq 90 mmHg three times on different days; (2) participants were previously diagnosed with hypertension; and (3) participants were currently taking BP medications. Exclusion criteria for study participants: (1) participants registered in the system but with no record of BP; (2) participants without any follow-up records; and (3) participants under the age of 18 years.

2.2. Data Source. All patient data were obtained from the same above-mentioned hypertension management system. This system is a part of the National Basic Public Health Service Project Management Information System, which records the medical information of all registered and followup hypertensive patients. According to the basic public health service guidelines, hypertensive patients were followed up face-to-face four times a year, and they had to undergo physical examinations yearly. Family doctors and public health personnel in the community health service centers were responsible for registering, following up, and managing patients with hypertension within their jurisdiction. The Centers for Disease Control and Prevention were responsible for developing technical programs, personnel training, and quality control of follow-up data. All medical follow-up information of the patients must be faithfully recorded in the system database by the physicians monitoring the patients. Strokes and other illnesses in follow-up patients must be documented in detail; stroke and other cardiovascular events must be diagnosed and confirmed by a high-level hospital.

This study was approved by the Ethics Committee of Xiangya School of Public Health, Central South University (approval number: XYGW-2022-73), and informed consent was taken from all individual participants.

2.3. Data Collection. Demographic information, medication, and outcome data were derived from the basic patient information module, physical examination information module, drug exposure module, and follow-up module in the hypertension patient management system in Changsha County, Hunan Province. International Journal of Hypertension

2.3.1. Basic Patient Information Module. Data exported from this module included participants' ID number, date of birth, sex, type of usual residence, education level, marital status, presence of coronary heart disease at the time of first registration, presence of diabetes at the time of first registration, presence of chronic obstructive pulmonary disease (COPD) at the time of first registration, presence of tumor at the time of first registration, family history of stroke, family history of hypertension, and family history of diabetes.

2.3.2. *Physical Examination Module.* Annual height and weight checks and positive physical examination results were exported from this module.

2.3.3. Follow-Up and Medication Modules. Data exported from these modules included the use and compliance of antihypertensive drugs, the drug names (trade names), usage times, and self-reported adverse reactions.

2.3.4. Genetic Polymorphism Data. Between January 1, 2017, and December 31, 2017, oral mucosa-shedding cells of hypertensive patients were collected using oral mucosa swabs during the annual physical examination conducted by community health services centers of Changsha County. And genomic DNA was extracted using a commercial nucleic acid separation kit (Promega, USA) and frozen at -80°C. PCR fluorescence probe technique was used to detect ADRB1 (1165G > C), CYP2D6 * 10, CYP2C9 * 3, AGTR1 (1166A > C), ACE (I/D), CYP3A5 * 3, and NPPA (2238T > C) polymorphisms (hypertension drug-related gene chip detection kit, sequencing primer, and other reaction fluids are products of Hunan Honghao Biopharma Co., Ltd., China). The PCR conditions are as follows: predenaturation at 95°C for 2 min; denaturing 40 s at 95°C; annealing 40 s at 60°C; extending 40 s at 72°C; a total of 40 cycles; and the final extension step at 72°C for 5 min. GenePix4 100A scanner was used to conduct quantitative analysis of the scan results with its own system, GenePix6.0, and the analysis software was used to interpret the genotype according to the set Cuff value. For genes and related polymorphisms, rs number, and interested genotypes, refer to the supplementary documents (Table S1).

2.4. Data Cleaning and Merging

2.4.1. Data Cleaning. This study included data derived from the basic information module with one record for each participant and from the physical examination follow-up and medication modules, generating multiple records for each participant. Therefore, we carried out data cleaning according to the following principles:

 For the physical examination module, height, weight, BP, and positive physical examination results (such as stroke, coronary heart disease, and kidney disease) were mainly extracted.

- (2) For follow-up and medication modules, the inpatient and outpatient diagnoses, the patient's main antihypertensive medication, and the duration of medication use were extracted. The antihypertensive drugs were classified into five categories: BBs, ARBs, ACEIs, CCBs, and diuretics. CCBs include dihydropyridine and nondihydropyridine drugs. Accumulated days of each antihypertensive drug taken by the patients were calculated according to the medication status with and without specific medicine, and compliance was recorded at each follow-up visit. If patients complied well with antihypertensive drugs, the duration of drug exposure was considered as 120 days during one follow-up period based on 4-month visit intervals. In the case of poor compliance of patients with drugs, the number of days of drug use during the follow-up period was registered or calculated by the time between the start and discontinuation of drug use.
- (3) Poststroke medication exposure was not analyzed.

2.4.2. Data Merge. Basic information, BP at each examination and visit, antihypertensive drug use, stroke, and other conditions were combined with "resident ID card" as the unique identification number and name for the checking information.

2.5. Research Variable Determination

2.5.1. Stroke Definition. In this study, stroke was defined as follow-up and physical examination records containing "stroke," "cerebral hemorrhage," "cerebral infarction," or records with diagnosis codes (ICD-10) containing I60–I64. The cases extracted from the follow-up records require the appropriate diagnostic basis (inpatient treatment in hospitals at or above the county level or with a high-resolution imaging diagnosis). If a "stroke" record with unique identity was detected in the follow-up or physical examination record, it will be recorded as one patient. If "stroke" records with the same identity were detected both in the follow-up and physical examination records, they will be recorded as one patient only.

2.5.2. Body Mass Index Classification. Body mass index (BMI) was calculated based on the height and weight of patients at their earliest registration dates and was divided into three categories: <18.5, 18.5~24, and >24 kg/m².

2.5.3. Age Classification. According to the age at the earliest registration dates in the system, participants were divided into three age groups: 18–45, 45–60, and >60 years.

2.5.4. Relevant Family History and Disease Incidence. Family history was defined as the patient's immediate family members with hypertension, stroke, diabetes, or other diseases. Presence of coronary heart disease, COPD, diabetes, or tumor refers to the occurrence of these diseases in the patients; the related data were generally obtained from the registration inquiry information belonging to the basic information data.

2.5.5. Control of SBP and DBP. According to the hypertension prevention and treatment guidelines, control of SBP and DBP is defined as follows: (1) general hypertension patients with BP of <140/90 mmHg, (2) hypertension comorbid with diabetes or heart failure with BP of <130/80 mmHg, (3) hypertension comorbid with coronary heart disease or chronic kidney disease with BP of <140/90 mmHg, and (4) older patients aged >65 years with BP of <150/90 mmHg. If the above criteria were met, BP was considered to be under control; otherwise, it was not controlled.

2.5.6. *History of Drug Exposure.* According to the WHO [29] and Chinese guidelines [30], if the antihypertensive effect is not good or does not achieve the goal level after 4 weeks of initial treatment, a combination of medications or a change of medication is required. Therefore, we defined a history of use of an antihypertensive drug as the drug being used for more than 28 days.

Administering antihypertensive drugs (BBs, ARBs, ACEIs, CCBs, and diuretics) refers to a patient's taking a specific antihypertensive drug for several days. According to Guidelines for Rational Drug Use of Hypertension in China (Second Edition) [30], the use of BBs, ARBs, ACEIs, CCBs, and diuretics should be changed or used in combination therapies after four weeks of administration. Therefore, we defined the exposure time of BBs, ARBs, ACEIs, CCBs, or diuretics as more than 4 weeks.

2.6. Statistical Analysis. SPSS 22.0 software and R Studio were used for data analyses. Quantitative data and categorical data were expressed as mean and standard deviation (SD) and as frequency or percentage, respectively. A chisquare test was performed to compare the genotypes and allele frequency and detect Hardy-Weinberg equilibrium (HWE). Logistic regression was used to determine the association of the polymorphisms of each antihypertensive drug-related gene with stroke, considering the possible confounding factors, including general demographic information, the presence of other main diseases, family history of disease, and antihypertensive drug use. All hypothesis tests were two-tailed, and P < 0.05 was considered statistically significant. A further subgroup analysis was performed, considering the clinical heterogeneity of hypertension patients.

3. Results

3.1. General Information. A total of 33,210 participants were registered in the system. We excluded 90 patients who were enrolled in the system but lacked genetic information and 3,458 patients who lacked BP records and follow-up records. One patient under 18 years was excluded. Finally, 29,661 patients with hypertension were included in the follow-up

analysis (Figure 1); among them, 816 (2.75%) had stroke. Significant differences were observed between the stroke patients and the nonstroke patients in terms of sex, age, BMI, educational level, presence of coronary heart disease, presence of COPD, presence of tumor, family history of stroke, family history of hypertension, and the use of ACEIs, diuretics, or CCBs (P < 0.05). In contrast, no significant differences were observed between these two groups in terms of resident type, marital status, control of SBP, control of DBP, presence of diabetes, family history of diabetes, ARBs exposure, and BBs exposure (P > 0.05) (Table 1).

3.2. Distribution of Drug-Related Genes in Hypertensive Patients and Their Relationship with Stroke. The mutation frequencies of ADRB1 (1165G > C),CYP2D6 * 10,CYP2C9 * 3, AGTR1 (1166A > C), ACE (I/D), NPPA (2238T > C), and CYP3A5 * 3 were 74.43%, 57.23%, 4.26%, 5.71%, 31.62%, 1.17%, and 69.58%, respectively (Table 2). Hardy-Weinberg balance test was conducted on the distribution of antihypertensive drug-related genotypes in the control group, and no significant difference was observed in ADRB1 (1165G > C), CYP2C9 * 3, ACE (I/D), and CYP3A5 * 3 polymorphism loci (P > 0.05). The polymorphism loci of CYP2D6 * 10, AGTR1 (1166A > C), and *NPPA* (2238*T* > *C*) did not conform to gene balance (P < 0.05) (Table 3). Univariate analysis revealed that the CC genotype of ADRB1 (1165G > C) was strongly associated with a higher stroke risk than the GC and CC genotypes ($\chi^2 = 8.659$, P < 0.05) (Table 3). This association remained significant after multivariate unconditional logistic regression analysis was performed adjusting for age, sex, BMI, type of usual residence, education, marital status, control of SBP, control of DBP, presence of disease, family history, and antihypertensive drug history. These observations revealed that the risk of stroke was 1.184 times higher in CC carriers with the dominant gene than in GC + GG genotype patients (95% confidence interval (CI): 1.026–1.365, P < 0.05) (Table 4). No association was observed between CYP2D6 * 10,CYP2C9 * 3, AGTR1 (1166A > C), ACE (I/D), CYP3A5 * 3, and NPPA (2238T > C) polymorphisms and stroke (Tables 3 and 4).

3.3. Subgroup Analysis of the Relationship between Antihypertensive Drug-Related Genes and Stroke in Hypertensive Patients. To further understand the specific association of ADRB1 (CC vs. GC+GG) with stroke in different subpopulations, we conducted regression analysis by dividing the study subjects into different subgroups according to the presence of diabetes mellitus, presence of coronary heart disease, presence of COPD, presence of tumor, and whether they were taking BBs, ARBs, ACEIs, CCBs, and diuretics. The results revealed that CC (vs GC+GG) of the ADRB1 (1165G > C) gene was associated with stroke occurrence in nondiabetic and noncoronary populations of hypertensive patients (OR: 1.20, 95% CI: 1.03-1.41; OR: 1.30, 95% CI: 1.09–1.56), in hypertensive patients who took BBs (OR: 2.43, 95% CI: 1.08-5.47; OR: 1.17, 95% CI: 1.010-1.348) or diuretics (OR: 1.707, 95% CI: 1.226-2.376) (Figure 2). No correlation was observed between CYP2D6 * 10, CYP2C9 * 3, AGTR1



FIGURE 1: Flowchart of participants.

TABLE 1:	Demographic	characteristics	and associa	ted risk	factors	of patients	with	stroke a	and healthy	controls.
	01					1				

Variables	Categories	Controls	Stroke patients	Р	
Sav	Male	11496 (39.9)	406 (49.8)	<0.001	
3ex	Female	17349 (60.1)	410 (50.2)	<0.001	
Age (y)		64.63 ± 9.89	67.20 ± 8.60	< 0.001	
BMI (kg/m ²)		23.88 ± 3.19	23.36 ± 3.10	< 0.001	
Trans of annual matching of	Country	27256 (94.5)	769 (94.2)	0.757	
Type of usual residence	City	1589 (5.5)	47 (5.8)	0.757	
	Unmarried	583 (2.0)	16 (2.0)		
Marital status	Married	25352 (87.9)	706 (86.5)	0.409	
	Divorced or widowed	2910 (10.1)	94 (11.5)		
	Primary school and below	15573 (54.0)	491 (60.2)		
Educational background	Junior high school	11234 (38.9)	273 (33.4)	0.002	
	High school and above	2038 (7.1)	52 (6.4)		
Control of SPD	No	16490 (57.2)	488 (59.8)	0 1 2 2	
	Yes	12355 (42.8)	328 (40.2)	0.133	
Control of DDD	No	11695 (40.5)	308 (37.7)	0.108	
Control of DBP	Yes	17150 (59.5)	508 (62.3)		
Diskatas	No	23664 (82.0)	654 (80.1)	0.1//	
Diabetes	Yes	5181 (18.0)	162 (19.9)	0.166	
Commune hourt discuss	No	23354 (81.0)	527 (64.6)	(0.001	
Coronary heart disease	Yes	5491 (19.0)	289 (35.4)	<0.001	
COPD	No	28494 (98.8)	815 (99.9)	0.001	
COPD	Yes	351 (1.2)	1 (0.1)	0.004	
Transar	No	28557 (99.0)	814 (99.8)	0.021	
Tumor	Yes	288 (1.0)	2 (0.2)	0.031	
Family history of hypertension	No	25416 (88.1)	692 (84.8)	0.004	
Family history of hypertension	Yes	3429 (11.9)	124 (15.2)	0.004	
Family history of studys	No	28494 (98.8)	796 (97.5)		
Family history of stroke	Yes	351 (1.2)	20 (2.5)	0.002	
Densile history of dishetse	No	28399 (98.5)	802 (98.3)	0.000	
ranny mistory of diabetes	Yes	446 (1.5)	14 (1.7)	0.699	
	No	22144 (76.8)	531 (65.1)	<0.001	
ACEIS	Yes	6701 (23.2)	285 (34.9)	< 0.001	

Variables	Categories	Controls	Stroke patients	Р
ARBs	No Yes	27532 (95.4) 1313 (4.6)	768 (94.1) 48 (5.9)	0.073
BBs	No Yes	27617 (95.7) 1228 (4.3)	785 (96.2) 31 (3.8)	0.522
Diuretics	No Yes	23762 (82.4) 5083 (17.6)	650 (79.7) 166 (20.3)	0.045
CCBs	No Yes	9474 (32.8) 19371 (67.2)	180 (22.1) 636 (77.9)	<0.001

TABLE 1: Continued.

COPD, chronic obstructive pulmonary disease; ACEI, angiotensin-converting enzyme inhibitor; ARBs, angiotensin-II receptor antagonists; BBs, beta receptor blockers; CCBs, calcium channel blockers.

TABLE 2: Genotypes and allele frequency distribution in hypertensive population.

Canalaci		Allel	Allele (%)		
Gene loci	WW	WM	MM	W	М
ADRB1 (1165G > C)	1971 (6.6)	11218 (37.8)	16472 (55.5)	15160 (25.6)	44162 (74.4)
CYP2D6 * 10	6255 (21.1)	12855 (43.3)	10551 (35.6)	25365 (42.8)	33957 (57.2)
CYP2C9 * 3	27204 (91.7)	2387 (8.0)	70 (0.2)	56795 (95.7)	2527 (4.3)
AGTR1 (1166A > C)	26458 (89.2)	3021 (10.2)	182 (0.6)	55937 (94.3)	3385 (5.7)
ACE (I/D)	13959 (47.1)	12646 (42.6)	3056 (10.3)	40564 (68.4)	18758 (31.6)
CYP3A5 * 3	2783 (9.4)	12473 (42.1)	14405 (48.6)	18039 (30.4)	41283 (69.6)
NPPA (2238T > C)	29091 (98.1)	443 (1.5)	127 (0.4)	58625 (98.8)	697 (1.2)

WW, wild-type homozygotes; WM, heterozygous mutation; MM, homozygous mutation; W, wild type; M. mutant.

TABLE 3: Distribution of polymorphisms in genes related to antihypertensive drugs.

0 1 :	0	Controls		Stroke patients		2	D
Gene loci	Genotype	n	%	п	%	X	P
	СС	15984	55.4	488	59.8	8.884	0.012
ADRB1 (1165G > C)	GC	10950	38.0	268	32.8		
	GG	1911	6.6	60	7.4		
HWE-P		>0.05					
	* 1/ * 1	6085	21.1	170	20.8	3.097	0.213
CYP2D6 * 10	* 1/ * 10	12522	43.4	333	40.8		
	* 10/ * 10	10238	35.5	313	38.4		
HWE-P		< 0.05					
	* 1/ * 1	26452	91.7	752	92.2	2.042	0.360
CYP2C9 * 3	* 1/ * 3	2323	8.1	64	7.8		
	* 3/ * 3	70	0.2	0	0.0		
HWE-P		>0.05					
	1166A/A	25721	89.2	737	90.3	1.585	0.453
AGTR1 (1166A > C)	1166A/C	2948	10.2	73	8.9		
	1166C/C	176	0.6	6	0.7		
HWE-P		< 0.05					
	II	13564	47.0	395	48.4	0.666	0.717
ACE (I/D)	ID	12305	42.7	341	41.8		
	DD	2976	10.3	80	9.8		
HWE-P		>0.05					
	* 1/ * 1	2700	9.4	83	10.2	1.537	0.464
CYP3A5 * 3	* 1/ * 3	12120	42.0	353	43.3		
	* 3/ * 3	14025	48.6	380	46.6		
HWE-P		>0.05					
	2238T/T	28291	98.1	800	98.0	0.128	0.938
$NPPA \ (2238T > C)$	2238T/C	430	1.5	13	1.6		
	2238C/C	124	0.4	3	0.4		
HWE-P		< 0.05					

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TABLE 4: Association between antihypertensive drug-related genes polymorphism and stroke occurrence in hypertensive patients (controls = 28846 and stroke = 816).

Gene loci	Crude OR (95% CI)	Adjusted OR [*] (95% CI)	Adjusted OR [§] (95% CI)	
ADRB1 (1165G > C)				
CC	1.197 (1.039-1.380)*	1.186 (1.029–1.368)*	1.184 (1.026–1.365)*	
GC + GG	1^{\dagger}	1^{\dagger}	1^{\dagger}	
GG	1.119 (0.857–1.461)	1.186 (1.029–1.370)	1.099 (0.840-1.438)	
GC + CC	1 [†]	1 [†]	1 [†]	
CYP2D6 * 10				
* 10/ * 10	1.131 (0.980-1.305)	1.119 (0.969–1.292)	1.115 (0.966-1.288)	
* 1/ * 1+ * 1/ * 10	1^{\dagger}	1^{\dagger}	1^{\dagger}	
* 1/ * 1	0.984 (0.829–1.168)	0.982 (0.827–1.166)	0.981 (0.825–1.166)	
* 1/ * 10+ * 10/ * 10	1*	1 [†]	1 [†]	
<i>CYP2C9</i> * 3				
* 1/ * 1	1.063 (0.821-1.377)	1.033 (0.796-1.339)	1.021 (0.787-1.324)	
* 1/ * 3+ * 3/ * 3	1^{\dagger}	1^{\dagger}	1^{\dagger}	
* 3/ * 3	Not available	Not available	Not available	
* 1/ * 3+ * 1/ * 1	1'	1'	1'	
AGTR1 (1166A > C)				
1166A/A	1.133 (0.896–1.433)	1.115 (0.881-1.412)	1.122 (0.885–1.421)	
1166A/C+1166C/C	1^{\dagger}	1^{\dagger}	1^{\dagger}	
1166C/C	1.207 (0.533–2.730)	1.293 (0.569–2.937)	$1.279 \ (0.562 - 2.911)$	
1166A/C+1166A/A	1'	1'	1'	
ACE (I/D)				
II	1.057 (0.920-1.215)	1.077 (0.936-1.239)	1.078 (0.937-1.240)	
ID + DD	1^{\dagger}	1^{\dagger}	1^{\dagger}	
DD	0.945 (0.748 - 1.194)	$0.921 \ (0.728 - 1.165)$	$0.923 \ (0.729 - 1.168)$	
ID + II	1'	1'	1'	
<i>CYP3A5</i> * 3				
* 3/ * 3	0.921 (0.801-1.059)	0.936 (0.814–1.077)	0.938 (0.815–1.079)	
* 1/ * 3+ * 1/ * 1	1'	1'	1'	
* 1/ * 1	1.096 (0.871-1.381)	1.072 (0.850–1.351)	$1.080 \ (0.856 - 1.362)$	
* 1/ * 3+ * 3/ * 3	1'	1'	1'	
NPPA (2238T > C)				
TT	0.979 (0.593–1.617)	0.973 (0.587–1.612)	$0.962 \ (0.580 - 1.595)$	
TC + CC	1'	1'	1'	
CC	0.855 (0.271–2.692)	$0.942 \ (0.296-2.994)$	$0.946 \ (0.297 - 3.010)$	
TC + TT	1'	1'	1'	

* P < 0.05. [†]Reference. [‡]Adjusted for age, sex, BMI, type of usual residence, education, marital status, control of SBP, control of DBP, presence of diabetes, presence of coronary heart disease, presence of COPD, presence of tumor, and family history related to hypertension, stroke, diabetes as covariates. [§]Adjusted for age, sex, BMI, type of usual residence, education, marital status, control of SBP, control of DBP, presence of coronary heart disease, presence of coronary heart disease, structure, education, marital status, control of SBP, control of DBP, presence of diabetes, presence of coronary heart disease, presence of COPD, presence of tumor, family history related to hypertension, stroke, diabetes, and whether taking BBs, ACEIs, ARBs, CCBs, and diuretics as covariates.

(1166A > C), ACE (I/D), NPPA (2238T > C), CYP3A5 * 3 genes polymorphism and stroke in hypertensive patients in subgroup analysis. For specific results, refer to the supplementary documents (Figures S1–S6).

4. Discussion

This study revealed that the prevalence of stroke in the hypertensive population in Changsha County of Hunan Province was 2.75%, which was significantly lower than the 10.04% reported in hospitalized hypertensive patients in the Anhui Province [31]. The difference may be a result of differences in the study population, with the hospitalized population having more difficulty in controlling BP and higher-grade hypertension than the community population.

Furthermore, the BMI and age were lower in the present study than in the previous one. The prevalence of stroke in male patients was higher than that in female patients possibly because female patients had better hypertension control and a lower incidence of stroke than male patients [9].

Our study showed that the mutation frequencies of antihypertensive drug-related genes varied from 5.71% to 74.43%. The mutation rate of the *ADRB1* (*1165G* > *C*) gene (74.43%) was slightly higher than that in Chinese patients with essential hypertension reported previously (59.8%) [32], while the mutation rate of *CYP3A5* * 3 (69.58%) was slightly lower than that reported previously (79.5%) [33]. The difference may be explained by the fact that the present study recruited hypertensive patients in the community, while the previous research subjects were hospitalized hypertensive patients [32]

Subgroup	CC (n/N)	GC+GG (n/N)	OR (95%CI)
Diabetes			
Yeses	96/2958	66/2385	1.179 (0.857-1.620)
No	66/2385	262/10804	1.202 (1.026-1.408)
Coronary hear	rt disease		
Yes	163/3234	126/2546	1.019 (0.803-1.294)
No	325/13238	202/10643	1.301 (1.089-1.554)
COPD			
Yes*			
No	487/16287	328/13022	1.193 (1.035-1.375)
Tumor			
Yes*			
No	486/16311	328/13060	1.192 (1.034-1.374)
ACEIs			
Yes	173/3915	112/3071	1.221 (0.958-1.557)
No	315/12557	216/10118	1.180 (0.990-1.405)
ARBs			
Yes	24/741	24/620	0.831 (0.467-1.479)
No	464/15731	304/12569	1.226 (1.059-1.420)
BBs			
Yes	23/689	8/570	2.426 (1.077-5.466)
No	465/15783	320/12619	1.167 (1.010-1.348)
Diuretics			
Yes	113/2936	53/2313	1.707 (1.226-2.376)
No	375/13536	275/10876	1.098 (0.938-1.286)
ССВ			
Yes	377/11148	259/8859	1.162 (0.990-1.365)
No	111/5324	69/4330	1.315 (0.971-1.781)
		0	1 2 3
*It was not ana	alyzed because the	he sample size was	ioo small

FIGURE 2: Forest plot of the association between ADRB1 gene and stroke occurrence in different subgroups.

or healthy individuals [33]. The frequency of CYP2D6 * 10, CYP2C9 * 3, and AGTR1 (1166A > C) was generally consistent with that reported for Chinese hypertensive patients in previous studies [21, 34]. In addition, we observed that CYP2D6 * 10, AGTR1 (1166A > C), and NPPA (2238T > C) genes do not conform to the Hardy–Weinberg equilibrium test. Another study conducted in Chinese Han hypertensive patients also found that CYP2D6 * 10, AGTR1 (1166A > C), and NPPA (2238T > C) genes were associated with the development of hypertension [23, 35, 36]. Studies revealed that alleles associated with disease etiology often deviate from the expected allele or genotype frequency [37].

Our results indicated that the *CC* genotype of *ADRB1* (*1165G* > *C*) is a risk factor for stroke in hypertensive patients, and the risk of stroke was 1.184 times higher for the *CC* genotype than for the *GC* + *GG* genotype (95% CI: 1.026–1.365). Studies had established that *ADRB1* (*1165G* > *C*) dominant allele *C* was a risk factor for hypertension [38–41]. It is reasonable to assume that *CC* may also contribute to the risk of developing stroke in hypertensive patients. In addition, previous studies indicated that mutation of *ADRB1* (*1165G* > *C*) was associated with shorter sleep duration in humans and mice; carriers of the mutation sleep two hours less per day on average than nonmutation carriers [42], and shorter sleep duration was an independent risk factor for future stroke events in

hypertensive patients [43]. Therefore, ADRB1 (1165G > C) might also affect the occurrence of stroke by affecting sleep. Our study was inconsistent with the results of a study on ADRB1 (1165G > C) polymorphism and ischemic stroke in North India, which recruited 224 patients and 224 age- and sexmatched controls and discovered no association between ADRB1 (GC + GG vs. CC) and overall ischemic stroke [44]. The following reasons can explain the difference: (1) The difference of interested diseases: Our study recruited all patients diagnosed with ICD codes ranging from I60 to I64, while the Indian study only included patients with ischemic diseases (I63); (2) heterogeneity of design methods: This study is a cross-sectional study and the previous one is case-control study; and (3) the sample difference: This study had a larger number of subjects derived from the community, and the case control had a smaller sample size and was hospital-based. Although both studies had some bias, we believe that genes are generally associated with stroke.

To further analyze the relationship between *ADRB1* (1165G > C) polymorphism and stroke, we performed a subgroup analysis. The results indicated that *ADRB1* (1165G > C) polymorphism was significantly associated with stroke risk in patients with noncoronary heart disease and nondiabetic diseases, while not significantly associated with stroke risk in patients with coronary heart disease and diabetes. This finding suggests that hypertensive patients

comorbid with coronary heart disease or diabetes may modify the association of ADRB1 (1165G > C) polymorphisms with stroke. In patients only with elevated BP, the *CC* genotype was the main risk factor for stroke; in hypertensive patients with other comorbid conditions, many nongenetic factors related to coronary heart disease or diabetes, such as smoking, physical activities, and dietary factors [31, 45, 46], might affect stroke development and conceal the association of ADRB1 (1165G > C) gene polymorphism with stroke. Similarly, a meta-analysis revealed no significant association of ADRB1 (1165G > C) polymorphisms with cardiovascular events in patients with coronary artery disease [47].

The result of subgroup analysis revealed that polymorphisms in the *ADRB1* (1165G > C) gene were consistently associated with stroke in hypertensive patients regardless of BBs use. The OR values were 2.426 (95% CI: 1.077–5.466) and 1.167 (95% CI: 1.010–1.348) in hypertensive *CC* and *GC*+*GG* carriers, respectively. Numerous studies have demonstrated that the CC genotype is associated with a better antihypertensive response to metoprolol treatment in different racial populations of healthy volunteers and hypertensive patients [26, 48]. A recent study assessed the role of *ADRB1* (1165G > C) gene polymorphisms on BBs response in a population with heart failure, revealing that the patients with the CC genotype seemed to receive the most benefit from a high BBs dose. However, our study showed the opposite result. The discrepancy could be explained by the following reasons:

- (1) BBs are the first-line pharmacological treatment for hypertensive patient comorbid with other conditions, such as heart failure and coronary disease, but not the first-line treatment for simple blood pressure-elevated patients. Therefore, for those simple blood pressure elevated patients with the *CC* genotype, BBs treatment was prescribed until "trial and error" treatment failed or developed with other conditions, the benefit from BBs prescription of CC genotype patients may have been delayed, and lead to a higher risk of stroke.
- (2) Although we excluded the data of poststroke drug usage, the patients may have experienced a prolonged period of uncontrolled BP before the stroke, and during this period, BBs may have been used. A study showed that there may be a higher risk of stroke due to greater variability in BP when treated with BBs [49], increasing the risk among patients with BBs. Our results indicated that ADRB1 (1165G > C) was not associated with stroke occurrence in hypertensive patients without diuretics, and ADRB1 (1165G > C) was associated with stroke risk in hypertensive patients with diuretics, possibly because the patients without diuretics were those with a shorter course of the disease and a lower BP level. The antihypertensive effect of diuretics was relatively weak when used as antihypertensive drugs in hypertensive patients for a long time [50]. Therefore, long-term use of diuretics may lead to poor BP control and increase the risk of stroke.

We did not establish an association of CYP2D6 * 10, CYP2C9 * 3, AGTR1 (1166A > C), ACE (I/D), CYP3A5 * 3, and NPPA (2238T > C) gene polymorphisms with stroke susceptibility. The result of a study conducted in India was consistent with our observations, in that no significant association of ACE (I/D) gene polymorphisms with ischemic stroke exists in hypertensive patients [51]. The secondary C allele of the NPPA (2238T > C) gene is associated with a higher risk of stroke [52]; however, no association between the NPPA (2238T > C) gene and stroke susceptibility was detected in other studies [19]. Regarding the AGTR1 (1166A > C) gene, studies revealed that its C allele was associated with increased BP in hypertensive patients [35]; currently, there are no studies on its relationship with stroke in hypertensive patients. Therefore, the association of CYP2D6 * 10, CYP2C9 * 3, AGTR1 (1166A > C), ACE (I/D), CYP3A5 * 3, and NPPA (2238T > C) gene polymorphisms with stroke in hypertensive patients needs further studies.

This study has some limitations. First, stroke is a disease with complex pathogenesis; hemorrhagic stroke and ischemic stroke have different mechanisms, conditions, and prognoses. The data used in this study could not distinguish between ischemic and hemorrhagic stroke. Therefore, the study could not analyze the differences between these two types of stroke. Second, all the participants were Han people, and there may be genetic variations among different ethnic groups. In future studies, we will verify the results of this study with data from other groups. Third, the stroke cases identified in the hypertension management system were mainly prevalent cases; therefore, the study was inclined to generate a Neiman bias. As we explained in the previous paragraph, although we excluded the poststroke data, the patients may have experienced a long period of uncontrolled BP before the stroke, and during this period, medications and lifestyles may have changed, leading to a bias. Therefore, new cases should be selected, and more accurate exposure assessment methods are needed in future studies. However, our study systematically investigated the association of antihypertensive drugrelated gene polymorphisms and the occurrence of stroke in hypertensive patients by including a large number of participants to obtain reliable data through a hypertension management system and adjusting for possible nongenetic factors that may influence the occurrence of stroke, such as sex, age, marital status, education level, BMI, family history, and antihypertensive medications.

Data Availability

The data used to support the findings of this study are available from the corresponding author upon request.

Ethical Approval

This study was approved by the Ethics Committee of Xiangya School of Public Health, Central South University (approval number: XYGW-2022-73), and informed consent was taken from all individual participants.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Authors' Contributions

Jing Deng, Huixia Liu, and Hua Zhong designed the study. Huixia Liu, Hua Zhong, and Ying Lin collected basic data and samples. Huixia Liu, Hua Zhong, Linzhi Han, and Tao Tang analyzed the data. Huixia Liu, Hua Zhong, Jing Deng, Ying Lin, and Mengshi Chen contributed to the discussion and reviewed/edited the manuscript. Huixia Liu and Hua Zhong wrote the manuscript. Jing Deng and Mengshi Chen supervised the study and were the guarantors of this work. All authors read and approved the final manuscript. Huixia Liu and Hua Zhong have contributed equally to the work. Huixia Liu and Hua Zhong as co-authors.

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Supplementary Materials

Supplementary Table 1: rs number of genes and interested genotype. Supplementary Figure 1: forest plot of the association between CYP2D6 * 10 gene and stroke occurrence in different subgroups. Supplementary Figure 2: forest plot of the association between CYP2C9 * 3 gene and stroke occurrence in different subgroups. Supplementary Figure 3: forest plot of the association between AGTR1 (1166A > C) gene and stroke occurrence in different subgroups. Supplementary Figure 4: forest plot of the association between ACE (I/D) gene and stroke occurrence in different subgroups. Supplementary Figure 5: forest plot of the association between CYP3A5 * 3 gene and stroke occurrence in different subgroups. Supplementary Figure 6: forest plot of the association between NPPA (2238T > C) gene and stroke occurrence in different subgroups. (Supplementary Materials)

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