Exploring CYP2D6 polymorphisms and angiotensin receptor blocker response in the Bai hypertensive population

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Objective **The CYP2D6 enzyme is crucial for the metabolism and disposition of a variety of drugs. This study was conducted to examine the relationship between CYP2D6 gene polymorphisms and the response to angiotensin receptor blocker (ARB)-based treatment in patients of Chinese Bai ethnicity with hypertension.**

Methods **Seventy-two hypertensive adults from the Chinese Bai ethnic group, exhibiting systolic blood pressure (SBP) ≥ 140 mmHg or diastolic blood pressure (DBP) ≥ 90 mmHg, were recruited. Targeted regional sequencing was utilized to genotype single nucleotide polymorphisms in the CYP2D6 gene, aiming to assess their frequency and to evaluate their influence on the therapeutic efficacy of ARB medications.**

Results **Our research identified nine significant CYP2D6 polymorphisms associated with the efficacy of ARB treatment in the Bai hypertensive cohort. Specifically, patients possessing certain mutant genotype at rs111564371 exhibited substantially greater reductions in SBP and DBP, with *P*-values of 0.021 and 0.016, respectively, compared to those carrying the wild genotype. Additionally, these mutant genotype at rs111564371 and rs112568578 were linked to approximately 20% higher overall efficacy rates and a 10% increased achievement rate relative to the wild genotype.**

Conclusion **Our research with the Bai hypertensive group shows that certain CYP2D6 polymorphisms significantly influence ARB treatment outcomes. Mutations at rs111564371 led to better blood pressure control (*P*-values: 0.021 for SBP, 0.016 for DBP), improving ARB efficacy by appromixately 20% and increasing treatment goal achievement by 10% over the wild-type genotype.**

Statements **Our investigation into CYP2D6 polymorphisms within the Bai hypertensive cohort marks a substantial advancement towards personalized healthcare, underscoring the pivotal influence of genetic constitution on the effectiveness of ARB therapy.**

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Keywords: angiotensin receptor blocker response, Bai hypertensive population, CYP2D6 polymorphisms, hypertension treatment, targeted region sequencing

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Introduction

Hypertension remains a global health challenge and a primary risk factor for cardiovascular diseases. The WHO reports that in China alone, approximately 270 million individuals are afflicted with hypertension, yet a mere 13.8% have successfully managed their condition [(WHO) (https://www.who.int/china/health-topics/hypertension#)]. This issue is particularly acute in southwestern China, where the prevalence of hypertension reaches an alarming 38.4% [1].

Angiotensin receptor blockers (ARBs), which operate by selectively inhibiting angiotensin II type 1 (AT1) receptors, play a crucial role in blood pressure regulation through vasoconstriction [2]. Due to their safety and tolerability [3,4], ARBs are endorsed in the Chinese Guidelines for Prevention and Treatment of Hypertension [5] and are often preferred over other antihypertensive agents.

Genetic predisposition is estimated to accounts for approximately 20–30% of the variability observed in drug responses [6]. The cytochrome P450 2D6 (CYP2D6)

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enzyme, a prominent member of the cytochrome P450 family, features a heme-binding domain critical for its metabolic function. This unique domain structure enables the enzyme to oxidize a wide range of pharmaceutical compounds. Responsible for metabolizing nearly a quarter of all clinically used drugs, including adrenergic antagonists [7,8] and ARBs [9], CYP2D6 exhibits considerable polymorphic diversity. To date, over 172 CYP2D6 gene variants have been identified (https://www.pharmvar.org/, last accessed: 11 December 2023), with many of which are linked to reduced enzymatic function, potentially affecting drug efficacy [10,11]. Moreover, variations in CYP2D6 genotype frequencies are observed across different ethnicities and regions [12–14]. Our study not only examines the genotype frequencies of CYP2D6 within the previously underexplored Bai hypertensive population but also uniquely assesses the impact of CYP2D6 variations on ARB treatment outcomes in this group. This approach addresses a significant gap in current pharmacogenomic research, providing valuable insights into personalized medicine.

The Bai ethnic group, primarily situated in the Dali Bai Autonomous Prefecture in Yunnan, China, exhibits a notably high hypertension prevalence of 42.1% [15]. This increased risk is attributed to dietary habits high in salt and the high-altitude environment of the region [16]. While pharmacogenomic research has investigated various genetic polymorphisms associated with hypertension in the Chinese population [8,17–21], studies focusing on the frequencies of CYP2D6 genotypes and their impact on the efficacy of antihypertensive drugs, especially ARBs, within the Bai community are scarce.

To bridge this research gap, we conducted targeted region sequencing of CYP2D6 single nucleotide polymorphisms (SNPs) in the Bai population. This methodology allowed us to analyze the genotype frequencies and their effects on ARB response in Bai hypertensive patients, enriching the pharmacogenomic understanding of hypertension treatment in this unique demographic.

Materials and methods

Study participants

In our study, we enrolled hypertensive adults from the Bai ethnic group in China, all of whom exhibited a SBP of ≥140 mmHg or a DBP of ≥90 mmHg. Recruitment was conducted at the No.1 People's Hospital of Dali City between December 2021 and October 2023. We meticulously collected the detailed demographic data, including gender, age, weight, and BMI, in addition to comprehensive disease histories. After implementing an exclusion criterion for concurrent conditions including tumors, myocardial infarction, cerebral thrombosis, and coronary heart disease, a cohort of 72 participants was selected to undergo treatment with ARBs for an average duration of 3 weeks. Blood pressure measurements were meticulously taken three times in succession by our trained nursing staff, with a 5-min minimum interval between readings. The mean of these three readings was then recorded as the official blood pressure measurement for each session. Our study was conducted in strict adherence to the Declaration of Helsinki, ensuring that informed consent was obtained from all participants. Ethical approval was granted by the Ethics Committee of Xiangya Hospital, Central South University, China, under Ethics Number: K22144.

Genomic DNA sequencing

For genomic analysis in this study, we collected 2 ml of peripheral blood from each participant. The extraction of genomic DNA extraction was carried out using the Tiangen Biochemical DP329 magnetic beads blood genome extraction kit, with subsequent quantification adhering to the Qubit dsDNA HS Assay Kit protocol (Yeasen, Shanghai, China). The selection of CYP2D6 and its variants was guided by current literature and the Pharmacogenomics Knowledgebase (PharmGKB). We then proceeded to enrich the CYP2D6 gene using amplicon-based methods. Sequencing was conducted on the DNBSEQ-T7 (BGI, Shenzhen, China) platform, producing 150 bp paired-end reads.

Single nucleotide polymorphism calling and genotyping

Sequencing data underwent quality filtering with Trimmomatic (v0.36) [22], which removed adapters and low-quality bases. Alignment to the human reference genome (hg19) was executed using the Burrows-Wheeler Aligner (BWA, v0.7.15) [23]. The Genome Analysis Toolkit (GATK, v3.8) [24] was utilized for SNP and indel realignment, quality score recalibration, variant calling, and genotyping via the Haplotype Caller module.

Statistical analysis

In this study, the reductions in SBP and DBP were quantitatively assessed. The percentage changes in SBP and DBP (deltaSBP and deltaDBP, respectively) were calculated from the baseline at enrollment to the conclusion of the 3-week medication regimen. To evaluate the correlation between CYP2D6 gene polymorphisms and changes in blood pressure postmedication, the Wilcoxon rank-sum test was employed. A *P*-value of less than 0.05 was considered to indicate statistical significance in these associations. Further, we investigated the patterns of linkage disequilibrium and haplotype structures within the CYP2D6 gene. These analyses were conducted using Haploview (v4.2) software [25], a tool widely recognized for its efficacy in studying genetic associations and linkage disequilibrium in complex datasets.

Results

Demographic and clinical characteristics of the study cohort

Our study enrolled 72 hypertensive patients from the Bai ethnic group in China, comprising 31 females and 41 males. Detailed demographic characteristics,

including age, gender, weight, and BMI, were recorded (Table 1). The mean age of participants was 54.43 years (SD = 12.54 years), and the average BMI was calculated at 25.23 kg/m² (SD = 3.38).

Identification and categorization of CYP2D6 polymorphisms

In this pharmacogenomic investigation focusing on the Bai ethnic group, we identified a total of 39 CYP2D6 polymorphisms. These polymorphisms have been comprehensively listed in Table 2 and are classified based on their functional implications into splicing, nonsynonymous, synonymous, and intronic variants.

Notably, two splicing-related polymorphisms, rs377725912 and rs3892097, were identified, albeit in a limited number of patients (found in 1 and 4 patients, respectively). Among the nonsynonymous polymorphisms, three variants demonstrated a higher frequency within our cohort: rs1135840, detected in 33 patients; rs16947, found in 66 patients; and rs1065852, observed in 51 patients. In terms of synonymous polymorphisms, rs28371713, rs1058164, and rs1081003, each were present in at least 33 patients and rs28371724 was identified in 4 patients. The majority of the polymorphisms ($n = 22$), accounting for 56.4% of the total, were located in introns. Of these, 15 variants were observed in more than five patients each, reflecting a significant proportion of intronic variation within the CYP2D6 gene in this population.

Table 1 Characteristics of Bai ethnic patients

Characteristics	All patients ($n = 72$)
Gender, *n* (%)	
Female	31
Male	41
Age, years (mean ± SD)	54.43 ± 12.54
Weight, kg (mean ± SD)	67.51 ± 10.81
BMI (mean ± SD)	25.23 ± 3.38

Continuous data are given as mean ± SD. Categorical variables are presented as numbers (%).

Comparative analysis of allele frequencies with public genomic databases

In this pharmacogenomic study, we analyzed allele frequencies of CYP2D6 polymorphisms in the Chinese Bai

Table 2 The frequency and annotations of CYP2D6 gene's polymorphisms identified in our study

rsID	gDNA_coordinate	Wild type (freq)	Heterozygous (freq)	Homozygous (freq)	Variant annoations
rs1135840	chr22:42522613G>C	39 (0.5417)	24 (0.3333)	9 (0.125)	Nonsynonymous
rs28371730	chr22:42523209T>C	17 (0.2361)	7 (0.0972)	48 (0.6667)	Intronic
rs2004511	chr22:42523211T>C	48 (0.6667)	0 (0.0000)	24 (0.3333)	Intronic
rs889634980	chr22:42523260G>T	70 (0.9722)	2 (0.0278)	0 (0.0000)	Intronic
rs1985842	chr22:42523409G>T	41 (0.5694)	31 (0.4306)	0 (0.0000)	Intronic
rs77312092	chr22:42523459C>T	71 (0.9861)	1 (0.0139)	0 (0.0000)	Nonsynonymous
rs61737946	chr22:42523505C>T	71 (0.9861)	1 (0.0139)	0 (0.0000)	Nonsynonymous
rs1058172	chr22:42523528C>T	71 (0.9861)	1 (0.0139)	0 (0.0000)	Nonsynonymous
rs28371725	chr22:42523805C>T	66 (0.9167)	6 (0.0833)	0 (0.0000)	Intronic
rs140513104	chr22:42523855G>A	68 (0.9444)	4 (0.0556)	0 (0.0000)	Nonsynonymous
rs28371724	chr22:42523857A>G	68 (0.9444)	4 (0.0556)	0 (0.0000)	Synonymous
rs16947	chr22:42523943A>G	6 (0.0833)	17 (0.2361)	49 (0.6806)	Nonsynonymous
rs28371722	chr22:42524130C>T	69 (0.9583)	2 (0.0278)	1 (0.0139)	Intronic
rs377725912	chr22:42524353C>T	71 (0.9861)	0 (0.0000)	1 (0.0139)	Splicing
rs79331140	chr22:42524369G>C	70 (0.9722)	2 (0.0278)	0 (0.0000)	Intronic
rs28371715	chr22:42524490G>A	69 (0.9583)	3 (0.0417)	0 (0.0000)	Intronic
rs2267447	chr22:42524696T>C	23 (0.3194)	30 (0.4167)	19 (0.2639)	Intronic
rs111564371	chr22:42524708T>C	48 (0.6667)	24 (0.3333)	0 (0.0000)	Intronic
rs112568578	chr22:42524713C>G	50 (0.6944)	22 (0.3056)	0 (0.0000)	Intronic
rs113889384	chr22:42524743G>A	55 (0.7639)	17 (0.2361)	0 (0.0000)	Intronic
rs28371713	chr22:42524795A>G	33 (0.4583)	39 (0.5417)	0 (0.0000)	Synonymous
rs3892097	chr22:42524947C>T	68 (0.9444)	4 (0.0556)	0 (0.0000)	Splicing
rs76326664	chr22:42525003T>C	71 (0.9861)	1 (0.0139)	0 (0.0000)	Intronic
rs200002499	chr22:42525010T>G	71 (0.9861)	1 (0.0139)	0 (0.0000)	Intronic
rs5030865	chr22:42525035C>T	70 (0.9722)	2 (0.0278)	0 (0.0000)	Nonsynonymous
rs1058164	chr22:42525132G>C	39 (0.5417)	24 (0.3333)	9 (0.125)	Synonymous
rs1135822	chr22:42525182A>T	69 (0.9583)	3 (0.0417)	0 (0.0000)	Nonsynonymous
rs537872336	chr22:42525361G>A	71 (0.9861)	1 (0.0139)	0 (0.0000)	Intronic
rs1081003	chr22:42525756G>A	21 (0.2917)	28 (0.3889)	23 (0.3194)	Synonymous
rs28371704	chr22:42525811T>C	71 (0.9861)	1 (0.0139)	0 (0.0000)	Nonsynonymous
rs28371703	chr22:42525821G>T	71 (0.9861)	1 (0.0139)	0 (0.0000)	Nonsynonymous
rs28371702	chr22:42525952C>A	43 (0.5972)	21 (0.2917)	8 (0.1111)	Intronic
rs28371701	chr22:42526049C>G	70 (0.9722)	0 (0.0000)	2 (0.0278)	Intronic
rs28371699	chr22:42526484A>C	64 (0.8889)	0 (0.0000)	8 (0.1111)	Intronic
rs1081000	chr22:42526549C>T	11 (0.1528)	13 (0.1806)	48 (0.6667)	Intronic
rs28695233	chr22:42526561G>T	14 (0.1944)	10 (0.1389)	48 (0.6667)	Intronic
rs1080996	chr22:42526573T>G	10 (0.1389)	14 (0.1944)	48 (0.6667)	Intronic
rs1080995	chr22:42526580G>C	10 (0.1389)	14 (0.1944)	48 (0.6667)	Intronic
rs1065852	chr22:42526694G>A	21 (0.2917)	28 (0.3889)	23 (0.3194)	Nonsynonymous

gDNA_coordinate was based on hg19. Values were presented as number (frequency).

Table 3 The allele frequency of the found polymorphisms in our study and public databases

rsID	alleleFreq	maxM allele frequency in database	1000g2015aug_ all	1000g2015aug_ afr	1000g2015aug_ eas	1000g2015aug_ eur	1000g2015aug_ sas	1000g2015aug_ amr	gnomAD_ genome_ ALL	gnomAD_ genome_ allele frequency R	gnomAD_ genome_ AMR	gnomAD_ genome_ EAS
rs1135840	0.2917	0.5652	0.4012	0.3238	0.2956	0.4543	0.4724	0.5245	0.4196	0.3487	0.5652	0.278
rs28371730	**0.7153**	0.8581	0.6695	0.5552	0.8581	0.6581	0.636	0.6772	0.6479	0.5805	0.7119	0.8554
rs2004511	**0.3333**	0.6021	0.2424	0.1157	0.5823	0.2058	0.1656	0.1513	0.2076	0.1313	0.1534	0.6021
rs889634980	0.0139	0.0005							0.0002	0.0005	0	0
rs1985842	0.2153	0.3914							0.3144	0.2695	0.3914	0.199
rs77312092	0.0069	0							0	0	0	0
rs61737946	0.0069	0.0231							0.0224	0.0231	0.0087	0.0152
rs1058172	0.0069	0.1511							0.1091	0.0333	0.118	0.0012
rs28371725	0.0417	0.1523	0.0635	0.0182	0.0377	0.0934	0.1217	0.062	0.0603	0.0241	0.0493	0.0319
rs140513104	0.0278	0.001	0.0002		0.001				0.0003	0.0006	0	0.0006
rs28371724	0.0278	0.0012	0.0002		0.001				0.0002	0.0001	0	0.0012
rs16947	**0.7986**	0.8601	0.6408	0.4463	0.8601	0.6571	0.638	0.6729	0.615	0.4759	0.7	0.8514
rs28371722	0.0278	0.0268	0.006		0.0268	0.003			0.0032	0.0001	0	0.0254
rs377725912	0.0139	0.001	0.0002		0.001							
rs79331140	0.0139	0.0069	0.0014		0.0069				0.0001	0	0	0.0012
rs28371715	0.0208	0.0159	0.0034		0.0159		0.001		0.0006	0	0	0.0106
rs2267447	**0.4722**	0.5754	0.2406	0.1233	0.5754	0.2008	0.1605	0.1484	0.188	0.1235	0.1322	0.5642
rs111564371	0.1667	0.3717							0.2741	0.1828	0.3717	0.181
rs112568578	0.1528	0.3754							0.2784	0.1881	0.3754	0.186
rs113889384	0.1181	0.3821							0.2882	0.1982	0.3821	0.2177
rs28371713	**0.2708**	0.3861							0.2947	0.2074	0.3861	0.2163
rs3892097	0.0278	0.2053	0.0931	0.0605	0.002	0.1859	0.1094	0.1297	0.1363	0.0763	0.1123	0.0037
rs76326664	0.0069	0.0101	0.0024		0.005			0.0101	0.0007	0.0001	0.0072	0.0074
rs200002499	0.0069	0.0031	0.0012	0.0015		0.001	0.0031		0.0003	0.0006	0	0.0006
rs5030865	0.0139	0.0099	0.002		0.0099				0.0003	0	0	0.0056
rs1058164	0.2917	0.5692	0.401	0.3275	0.2907	0.4563	0.4673	0.5274	0.4233	0.3528	0.5692	0.2731
rs1135822	0.0208	0.0081							0.0006	0.0001	0.0024	0.0081
rs537872336	0.0069	0.0068	0.0006		0.003				0.0004	0.0002	0	0.0068
rs1081003	**0.5139**	0.5752	0.1669	0.0923	0.5704	0.0239	0.0818	0.0504	0.0702	0.0843	0.0564	0.5752
rs28371704	0.0069	0.173	0.0693	0.0204	0.001	0.173	0.0808	0.0951	0.1133	0.0359	0.0768	0.0012
rs28371703	0.0069	0.173	0.0693	0.0204	0.001	0.173	0.0808	0.0951	0.1118	0.0346	0.0749	0.0012
rs28371702	0.2569	0.5622	0.37	0.2292	0.2748	0.4523	0.4693	0.5173	0.3884	0.2504	0.5622	0.241
rs28371701	**0.0278**	0.8711	0.624	0.6301	0.8562	0.4821	0.5501	0.585	0.4959	0.5922	0.5612	0.8711
rs28371699	**0.1111**	0.5604	0.3684	0.2163	0.2857	0.4533	0.4693	0.513	0.3917	0.2512	0.5604	0.2666
rs1081000	**0.7569**	0.8571	0.6927	0.646	0.8571	0.6571	0.6319	0.6801	0.6675	0.6638	0.7077	0.8504
rs28695233	**0.7361**	0.8571	0.6929	0.6467	0.8571	0.6571	0.6319	0.6801	0.6641	0.6588	0.7054	0.8455
rs1080996	**0.7639**	0.8571	0.6929	0.646	0.8571	0.6571	0.6329	0.6801	0.6642	0.6594	0.7064	0.8447
rs1080995	**0.7639**	0.8571	0.6929	0.646	0.8571	0.6571	0.6329	0.6801	0.6643	0.6592	0.7083	0.8453
rs1065852	**0.5139**	0.5812	0.238	0.1127	0.5714	0.2018	0.1646	0.1484	0.1921	0.1214	0.1343	0.5812

Values presented in bold denote CYP2D6 polymorphisms exhibiting allele frequency differences greater than 0.05, as compared to East Asian records in these databases.
1000g2015aug, 1000 Genomes Project (August 2015 release); AFR, African/African American; alleleFreq, allele frequency; AMR, Admixed American; EAS, East Asian; EUR, European; gnomAD, GenomeAggregation database; maxMAF, maximum minor allele frequency; SAS, South Asian.

ethnic group, comparing these with frequencies reported in public genomic databases, as summarized in Table 3. Notably, the allele frequency of rs2004511 in our cohort (0.3333) showed a significant deviation from those in the East Asian population, as reported in the 1000 Genomes Project (1000g2015aug) and the Genome Aggregation Database (gnomAD), where the frequencies are 0.5823 and 0.6021, respectively. Additionally, 12 other polymorphisms demonstrated allele frequency discrepancies exceeding 0.05 when compared to East Asian data in these databases.

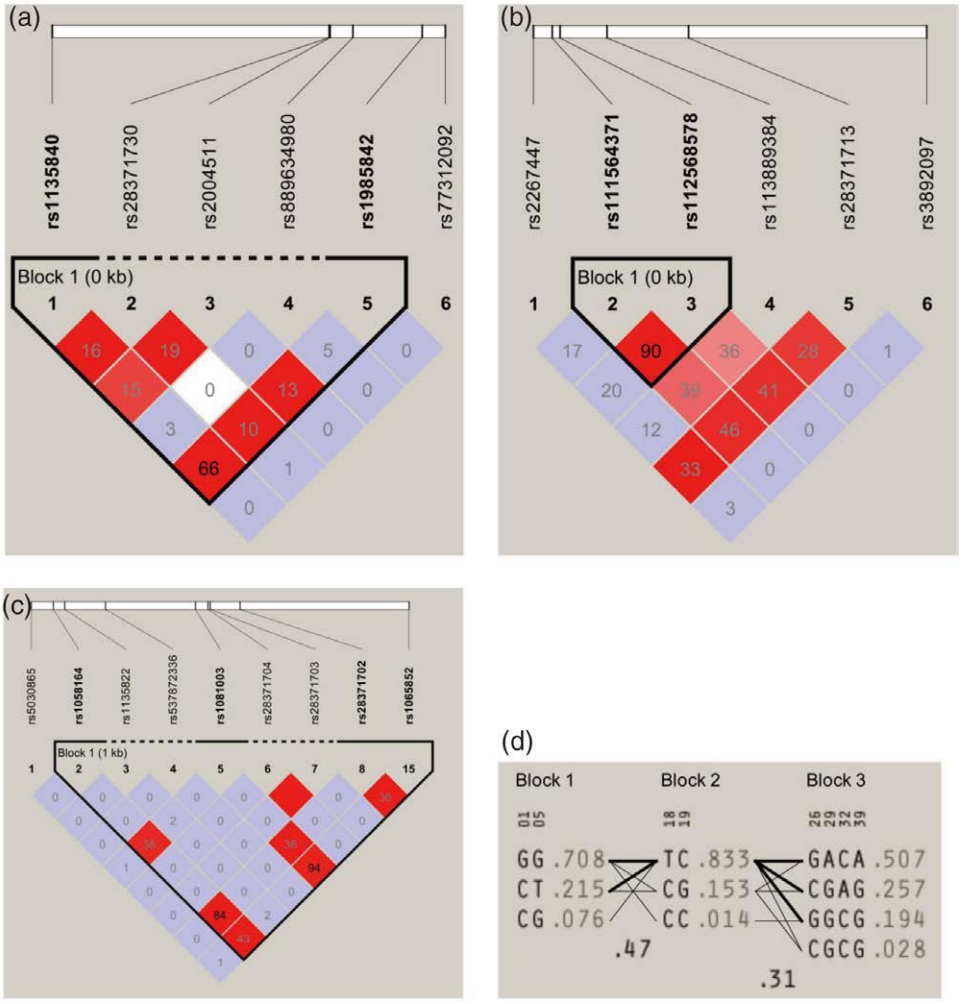
In contrast, the allele frequencies of the remaining polymorphisms were more closely aligned with those reported for the East Asian population in gnomAD, with differences between the Bai ethnic group and the broader East Asian population remaining within a 0.05 margin.

Linkage disequilibrium and haplotype structure in CYP2D6 polymorphisms

The polymorphisms rs1135840 and rs28371702, rs111564371 and rs112568578, rs1058164 and rs1065852, often co-occur in patients. Subsequently, the identified CYP2D6 polymorphisms were extensively analyzed for linkage disequilibrium and haplotype structuring among the Bai ethnic group. This analysis identified a complex linkage disequilibrium block composed of three linkage disequilibrium subblocks, each with distinct polymorphism interactions and haplotype frequencies.

First linkage disequilibrium subblock featured a linkage ($r^2 = 0.66$) between rs1135840 and rs1985842, and included four additional variants (Fig. 1). The most prevalent haplotype was 'GG' (frequency: 0.708), followed by 'CT' and 'CG' with frequencies of 0.215 and 0.076,

Fig. 1



Linkage disequilibrium subblocks and haplotypes of CYP2D6 polymorphisms. Panels (a)–(c) depict the linkage disequilibrium blocks and their r^2 values. Panel (d) illustrates the phased haplotypes within these subblocks, detailing their population frequencies and recombination rates.

Table 4 The association of CYP2D6 polymorphisms with clinical blood pressures at enrollment

Genotype	gDNA_coordinate	Wild type (variant)	SBP (wild type greater *P*-value)	SBP (wild type less *P*-value)	DBP (wild type greater *P*-value)	DBP (wild type less *P*-value)
rs1135840	chr22:42522613G>C	39 (33)	0.278	0.722	0.968	**0.032**
rs28371730	chr22:42523209T>C	17 (55)	0.287	0.713	0.954	**0.046**
rs2004511	chr22:42523211T>C	48 (24)	0.293	0.707	0.314	0.686
rs1985842	chr22:42523409G>T	41 (31)	0.514	0.486	0.972	**0.028**
rs28371725	chr22:42523805C>T	66 (6)	0.597	0.403	**0.044**	0.956
rs16947	chr22:42523943A>G	6 (66)	0.295	0.705	0.597	0.403
rs2267447	chr22:42524696T>C	23 (49)	0.644	0.356	0.913	0.087
rs111564371	chr22:42524708T>C	48 (24)	0.761	0.239	0.973	**0.027**
rs112568578	chr22:42524713C>G	50 (22)	0.69	0.31	0.961	**0.039**
rs113889384	chr22:42524743G>A	55 (17)	0.744	0.256	0.842	0.158
rs28371713	chr22:42524795A>G	33 (39)	0.691	0.309	0.954	**0.046**
rs1058164	chr22:42525132G>C	39 (33)	0.278	0.722	0.968	**0.032**
rs1081003	chr22:42525756G>A	21 (51)	0.473	0.527	0.429	0.571
rs28371702	chr22:42525952C>A	43 (29)	0.683	0.317	0.985	**0.015**
rs28371699	chr22:42526484A>C	64 (8)	0.305	0.695	0.514	0.486
rs1081000	chr22:42526549C>T	11 (61)	0.219	0.781	0.469	0.531
rs28695233	chr22:42526561G>T	14 (58)	0.23	0.77	0.815	0.185
rs1080996	chr22:42526573T>G	10 (58)	0.265	0.735	0.926	0.074
rs1080995	chr22:42526580G>C	10 (58)	0.265	0.735	0.926	0.074
rs1065852	chr22:42526694G>A	21 (51)	0.473	0.527	0.429	0.571

gDNA_coordinate was based on hg19. Values were presented as number (patients' number); the relative decrease of clinical blood pressure after ARB therapy were compared by Wilcoxon rank-sum test. Values presented in bold represent statistical significance, with *P*-values less than 0.05.

respectively (Fig. 1a and d). Additionally, rs1135840 and rs28371702 were strongly linked ($r^2 = 0.84$) (Supplemental Fig. 1, Supplemental Digital Content 1, *http://links.lww.com/FPC/B482*).

Second linkage disequilibrium subblock exhibited a strong linkage ($r^2 = 0.90$) between rs111564371 and rs112568578. The dominant haplotype 'TC' had a population frequency of 0.833, with the 'CG' haplotype occurring at a frequency of 0.153 (Fig. 1b and d).

Third linkage disequilibrium subblock demonstrated strong linkages between rs1058164 and rs28371702 ($r^2 = 0.84$), rs1081003 and rs1065852 ($r^2 = 0.94$), with additional associated polymorphisms. The leading haplotype 'GACA' had a frequency of 0.507 (Fig. 1c and d).

Recombination rates observed were 0.47 between the first and second subblocks, and 0.31 between the second and third subblocks (Fig. 1d). This analysis highlights the complex genetic architecture of the CYP2D6 gene and its significance in pharmacogenomic studies.

Influence of CYP2D6 polymorphisms on initial blood pressure levels in hypertensive patients

Our study analyzed the impact of CYP2D6 polymorphisms, with variant and wild-type alleles identified in more than five patients, on initial clinic-measured blood pressure levels in hypertensive patients. The comprehensive results are outlined in Table 4. We identified nine CYP2D6 polymorphisms significantly correlated with DBP readings in the clinic setting. Notably, six of these polymorphisms were associated with higher DBP in patients carrying the wild-type alleles, exhibiting *P*-values between 0.015 and 0.046. In contrast, the rs28371725 polymorphism displayed an inverse relationship, with carriers of the wild-type allele showing lower DBP compared to those with the variant allele (*P*-values: 0.044). This analysis underscores the importance of CYP2D6 genetic variations in blood pressure regulation and their potential role in personalized hypertension management.

Influence of CYP2D6 polymorphisms on angiotensin receptor blocker medication efficacy

Our extensive pharmacogenomic study investigated the association between CYP2D6 polymorphisms and the efficacy of ARB medications in hypertension management. This analysis, focusing on polymorphisms present in more than five patients, assessed their impact on SBP and DBP reductions postmedication. Key findings are summarized in Tables 5 and 6.

Associations with SBP and DBP reductions: ARB medications showed variable BP-lowering effects depending on specific CYP2D6 genetic variants. Particularly, patients with the variant allele of rs111564371 experienced more significant SBP reductions (*P*-values: 0.021, Fig. 2a). This polymorphism was also associated with greater DBP reductions in carriers of variant allele compared to those with wild-type allele (*P*-values: 0.016, Fig. 2b).

Specific alleles and DBP reduction: Eight polymorphisms were significantly associated with DBP reduction. Notably, six alleles (rs1135840, rs1985842, rs112568578, rs28371713, rs1058164, and rs28371702) showed higher DBP reductions in patients with variant alleles (*P*-values shown in Supplemental Fig. 2a–h, Supplemental Digital Content 1, *http://links.lww.com/FPC/B482*). In contrast, rs2004511 and rs28371725 displayed opposite effects.

Efficacy of ARB therapy: Polymorphisms rs111564371, rs112568578 and rs28371713, with their variant alleles, demonstrated appromixately 15% higher efficacy rates than their wild counterparts. Specifically, variant alleles

Table 5 **The association of CYP2D6 polymorphisms with the relative decrease of clinical blood pressures after ARB therapy**

rsID	gDNA_coordinate	Wild type (variant)	Δ%SBP (wild type greater *P*-value)	Δ%SBP (wild type less *P*-value)	Δ%DBP (wild type greater *P*-value)	Δ%DBP (wild type less *P*-value)
rs1135840	chr22:42522613G>C	39 (33)	0.833	0.167	0.983	**0.017**
rs2004511	chr22:42523211T>C	48 (24)	0.298	0.702	**0.024**	0.976
rs1985842	chr22:42523409G>T	41 (31)	0.86	0.14	0.991	**0.009**
rs28371725	chr22:42523805C>T	66 (6)	0.455	0.545	**0.038**	0.962
rs111564371	chr22:42524708T>C	48 (24)	0.979	**0.021**	0.984	**0.016**
rs112568578	chr22:42524713C>G	50 (22)	0.947	0.053	0.958	**0.042**
rs28371713	chr22:42524795A>G	33 (39)	0.912	0.088	0.988	**0.012**
rs1058164	chr22:42525132G>C	39 (33)	0.833	0.167	0.983	**0.017**
rs28371702	chr22:42525952C>A	43 (29)	0.912	0.088	0.998	**0.002**

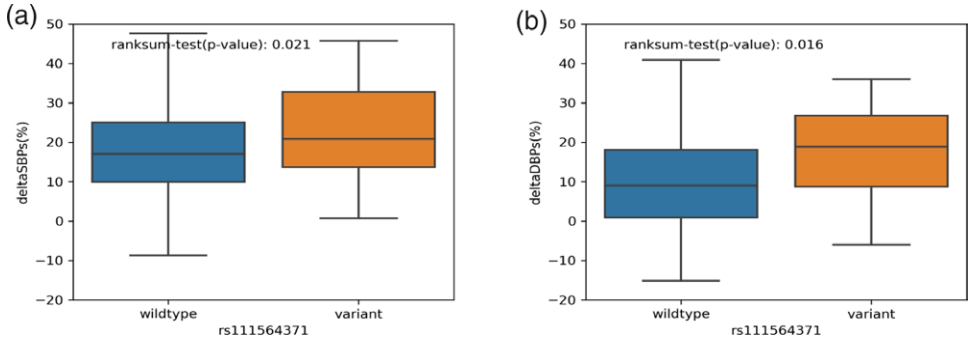
gDNA_coordinate was based on hg19. Values were presented as number (patients' number); the relative decrease of clinical blood pressure after ARB therapy were compared by Wilcoxon rank-sum test, values presented in bold represent statistical significance, with *P*-values less than 0.05.
$\Delta\%SBP = 100 \times (SBP_{post\text{-}mediaction} - SBP_{enrollment})/SBP_{enrollment}$; $\Delta\%DBP = 100 \times (DBP_{post\text{-}mediaction} - DBP_{enrollment})/SBP_{enrollment}$.
DBP, diastolic blood pressure; SBP, systolic blood pressure.

Table 6 **The association of CYP2D6 polymorphisms with the efficacy of ARB therapy**

	Wild type (patients)				variant(patients)			
	Patients	Achievement (%)	Improvement (%)	Efficacy (%)	Patients	Achievement (%)	Improvement (%)	Efficacy (%)
rs1135840	39	46.15	33.33	79.49	33	57.58	30.30	87.88
rs2004511	48	50.00	33.33	83.33	24	54.17	29.17	83.33
rs1985842	41	46.34	34.15	80.49	31	58.06	29.03	87.10
rs28371725	66	54.55	28.79	83.33	6	16.67	66.67	83.33
rs111564371	48	45.83	31.25	77.08	24	62.50	33.33	**95.83**
rs112568578	50	48.00	30.00	78.00	22	59.09	36.36	**95.45**
rs28371713	33	42.42	33.33	75.76	39	58.97	30.77	**89.74**
rs1058164	39	46.15	33.33	79.49	33	57.58	30.30	87.88
rs28371702	43	46.51	34.88	81.40	29	58.62	27.59	86.21

Achievement (%): The percentage of patients in this group whose first follow-up clinic blood pressure reached the normal blood pressure standards. Improvement (%): The percentage of patients in this group whose first follow-up clinic blood pressure did not reach the normal blood pressure standards, but the reduction in blood pressure was not less than 10%. Efficacy (%): The percentage of patients in this group whose first follow-up clinic blood pressure either met the standards or had a reduction in blood pressure meeting the standards. This rate is the sum of the achievement rate and the improvement rate. Values highlighted in bold indicate instances where the efficacy in carriers of variant alleles exceeded that of wild-type allele carriers by over 10%.

Fig. 2



The impact of rs111564371 polymorphism on ARB medication efficacy. Graphs (a) and (b) depict the relative changes in SBP and DBP in patients with different genotypes post-ARB treatment. ARB, angiotensin receptor blocker; DBP, diastolic blood pressure; SBP, systolic blood pressure.

at rs111564371 and rs112568578 showed over 95% efficacy rates. The rs28371725 polymorphism with wild-type allele yielded the highest achievement and efficacy rates (54.55 and 83.33%).

These findings underscore the influence of CYP2D6 genetic variations on ARB medication effectiveness, highlighting the potential of tailoring hypertension treatments based on individual genetic profiles.

Discussion

In this research, we enrolled 72 patients from the Bai ethnic group to investigate the impact of CYP2D6 polymorphisms on the efficacy of ARB medications in hypertension treatment. While previous studies have explored CYP2D6 variants in healthy Bai individuals [26] and the MTHFR gene's role in hypertension susceptibility [27], our study is the first to assess the effect of CYP2D6 polymorphisms on ARB response in Bai hypertensive patients.

The metabolism of ARBs by CYP2C9, has been a focal point of recent pharmacogenomic research. Studies have investigated the relationship between CYP2C9 polymorphisms and the response to irbesartan [28], utilizing physiologically based pharmacokinetic (PBPK) modeling for predicting drug pharmacokinetics across various CYP2C9 genotypes [29]. Despite these efforts, research by Liu *et al*. did not conclusively link CYP2C9 polymorphisms with the antihypertensive effects of valsartan [16]. Similarly, Prieto-Pérez *et al*. underscored the significance of both CYP2C9 and CYP2C8 genotypes in the metabolism of losartan and valsartan, but not for candesartan or elmisartan [30].

Furthermore, recent findings have broadened our understanding of the CYP2D6 enzyme. Notably, its association with portal hypertension in liver cirrhosis patients has been elucidated [31]. In addition, research by Soria-Chacartegui suggested a potential involvement of CYP2D6 in the metabolism of valsartan [9]. These developments suggest a more complex and nuanced role for CYP2D6 in drug metabolism, particularly concerning ARBs. The neuroprotective properties of ARBs further accentuate their therapeutic significance [32], highlighting the need for deeper pharmacogenomic investigations in this area.

Alternative splicing plays a critical role in gene regulation by creating diverse mRNA isoforms. Aberrations in this process, however, can lead to disease-causing protein abnormalities. In our research, we identified two polymorphic sites implicated in alternative splicing: rs377725912 and rs3892097. These polymorphisms were observed at lower frequencies within the Bai population, detected in only 1 and 4 individuals, respectively. While there are no existing publications addressing rs377725912, a connection was noted between rs3892097 carriage and the hemodynamic effects of propranolol in patients with liver cirrhosis in a Russian population [31]. This polymorphism, however, was not associated with primary hypotensive events [33].

Our pharmacogenomic analysis identified nine significant CYP2D6 polymorphisms that influence the efficacy of ARB medications in hypertension treatment. These polymorphisms are closely associated with notable reductions in both SBP and DBP following ARB therapy (Supplemental Table 1, Supplemental Digital Content 2, *http://links.lww.com/FPC/B483*). Particularly, patients with mutant genotype at rs111564371 demonstrated reductions in SBP and DBP exceeding 20 mmHg (Supplemental Fig. 3, Supplemental Digital Content 1, *http://links.lww.com/FPC/B482*). This observation is clinically relevant, considering that a reduction of 10 mmHg in SBP is linked to significant decreases in cardiovascular events and mortality [34,35]. The scarcity of literature on these specific polymorphisms underscores the novelty and potential impact of our findings.

Additionally, our study sheds light on various CYP2D6 polymorphisms with distinct allele frequencies and clinical correlations. For example, rs1135840 and rs1058164 presented lower allele frequencies compared to those observed in malaria patients in Yunnan Province [36], China (Supplemental Table 2, Supplemental Digital Content 2, *http://links.lww.com/FPC/B483*). Intriguingly, the T allele of rs2004511 was more effective in reducing DBP than the C allele, displaying a lower frequency in the Uygur population [19,37] and East Asian populations in genomic databases (Table 3). Moreover, polymorphisms such as rs28371725 and rs28371702 were associated with different clinical conditions, highlighting their potential roles in personalized medicine strategies [31,38–40].

While this study provides valuable insights into the impact of CYP2D6 polymorphisms on the efficacy of ARB medications in the Bai hypertensive population, it acknowledges certain limitations. The primary constraints include a relatively small sample size and a focus exclusively on the Bai ethnic group, without a comparative control group. These factors potentially limit the broader applicability and generalizability of our findings. To build upon these initial insights, future research involving larger and more ethnically diverse cohorts is imperative. The inclusion of control groups in such studies would further strengthen the validity of the results. Furthermore, this study did not investigate the impact of factors such as smoking, alcohol consumption, and potential drug interactions, all of which could influence blood pressure outcomes. Expanding this research is crucial for enhancing our understanding of the role of pharmacogenomics in personalized hypertension management. It will allow for a more comprehensive exploration of the genetic factors influencing ARB metabolism and its therapeutic efficacy.

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C.Y. designed the study and carried out the experiments. G.Z. and C.S. analyzed data and wrote the manuscript. Y.T. L.L. and Z.L. wrote the manuscript and made modifications to the manuscript. Q.T. and Z.W. carried out experiments and analyzed data. N.S., L.Y., and S.H. designed the research, critically revised the manuscript, and contributed equally as corresponding authors. All authors have read and approved the final manuscript.

The datasets presented in this article are not readily available because sharing of genomic data in the public domain is not allowed according to the requirements of the Institutional Ethics Committee. Requests to access the datasets should be directed to the corresponding authors.

Ethical approval for this study was granted by the Ethics Committee of Xiangya Hospital, Central South University, China (Ethics Number: K22144).

All authors provided their consent for the publication of this report.

Conflicts of interest

There are no conflicts of interest.

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