Am J Cardiovasc Dis 2023;13(4):264-271
www.AJCD.us /ISSN:2160-200X/AJCD0150289

Original Article

CYP2D6 and *ADRB1* genetic polymorphisms and the selection of antihypertensive beta-receptor blockers for hypertensive patients

Keping Chen[1], Ying Li[1], Chuankun Yang[1], Peng Xiao[1], Guochun Li[2], Yurong Xu[1]

[1]*Clinical Laboratory, Zhongda Hospital, School of Medicine, Southeast University, Nanjing 210009, Jiangsu, China;* [2]*Nanjing Central Hospital, Nanjing Municiple Government Hospital, Nanjing 210009, Jiangsu, China*

Received March 22, 2023; Accepted July 16, 2023; Epub August 15, 2023; Published August 30, 2023

Abstract: Background: Genetic factors contribute to the variability in individual response to antihypertensive medications. We sought to investigate the frequencies of allele and genotype for *CYP2D6* and *ADRB1* genetic polymorphisms and explore their potential impact in influencing the selection of antihypertensive beta-receptor blockers. Methods: The study population was selected from the Han Chinese patients in Zhongda Hospital, which contained 2419 Han Chinese hypertensive individuals and 151 normotensive controls. Each of the above participants underwent venous blood sampling. Then, the gene chip platform was adopted to evaluate the *CYP2D6* and *ADRB1* genetic polymorphisms. The allele as well as genotype frequencies for each gene, along with the combined genotypes, were subjected to analysis. Results: The frequency of *1/*1 wild-type homozygous for *CYP2D6* was 9.71%, while the frequency of *1/*10 heterozygous or *10/*10 mutant homozygous was 59.16% or 31.13%, respectively, as established by gene chip analysis. Similarly, we observed that the genotype frequencies of GG wild-type homozygous for *ADRB1* was 10.29%, while that of GC heterozygous, or CC mutant homozygous was 44.98%, or 44.73%, respectively. Notably, combined genotypes *1/*10 + CC (25.88%) and *1/*10 + CG (27.78%) had the highest frequencies. Importantly, no substantial differences in the distributions of *CYP2D6* and *ADRB1* polymorphism were noted between hypertensive patients and normotensive controls, or among all different grades of hypertension. Conclusion: These findings provide insights into the *CYP2D6* and *ADRB1* polymorphisms in hypertensive patients from Han Chinese, which show significant differences compared to other geographic groups of Han Chinese hypertensive patients. These results offer valuable information for future prospective clinical studies on the antihypertensive effects of beta-receptor blockers in Han Chinese hypertensive patients.

Keywords: *CYP2D6*, *ADRB1,* genetic polymorphism, hypertension, beta-receptor blockers, Han Chinese

Introduction

Hypertension is strongly linked to the morbidity and mortality of cardiovascular disease [1]. A nationwide hypertension survey conducted between 2012 and 2015 revealed that hypertension among adults in China aged 18 years and above had a prevalence of 27.9% [2]. The Chinese population's lifestyle is characterized by a diet high in salt, fat, and sugar, high psychosocial stress, and low physical activity [3]. Consequently, with the growing elderly population and inappropriate lifestyles, the prevalence of hypertension is projected to increase in China. Failure to adequately control hypertension will undoubtedly pose a prominent public health challenge in the coming decades [4]. Currently, improvement in blood pressure management is an effective approach to control hypertension. Although the approval of numerous antihypertensive drugs, the control rate of hypertension in the Chinese population is still unpromising, at 15.3% [2]. Patients with hypertension often experience a trial-and-error process in finding the right drug due to variable responses. Genetic factors may influence the inter-individual variability in response to hypertensive therapeutic agents, including beta-receptor blockers, calcium-channel blockers, and angiotensin receptor antagonists [5].

Genes encoding the metabolic enzymes, particularly the cytochrome P450 (CYP), are involved in the biotransformations that occur in

phase I and phase II and have an impact on the interindividual variations in antihypertensive drug response [6]. Over the past few years, various CYP enzymes have been investigated, and these enzymes include *CYP1A2*, *CYP2C9*, *CYP2C19*, and *CYP2D6* [7]. The *CYP2D6* enzyme, in particular, exhibits considerable genetic diversity, with more than 100 different alleles identified, categorized as nonfunctional alleles (e.g. *3, *4, *5, *6, *7, *8, *11, *13, *15), reduced functional alleles (e.g. *9, *10, *14, *41, *49, *59), and functional alleles (e.g. *1, *2) [8]. Homozygous individuals for the nonfunctional alleles were established as poor metabolizers (PM), individuals with heterozygous nonfunctional alleles or homozygous diminished functional alleles were defined as intermediate metabolizers (IM), while those with homozygous or heterozygous functional alleles were considered extensive metabolizers (EM). Different metabolism phenotypes result in variant responses to antihypertensive beta-receptor blockers. Numerous studies reveal the involvement of *CYP2D6* in the metabolism of beta-receptor blockers, for instance, carvedilol and metoprolol [6, 9, 10]. Specifically, the clearance and concentration of carvedilol have been reported to be influenced by the *CYP2D6* genotype [6, 9]. Metoprolol is mainly metabolized by *CYP2D6* [6, 9]. The *CYP2D6* genotype has been shown to impact the metabolic ratio, with patients lacking *CYP2D6* metabolic capacities experiencing greater reductions in diastolic and systolic blood pressure during metoprolol treatment compared to patients with active *CYP2D6* phenotypes [11]. The Dutch Pharmacogenomics Working Group (DPWG) also recommends *CYP2D6* genotyping when using metoprolol, suggesting alternate drug selection or a 75% dose decrease for PM, a 50% dose decrease for IM, and a dose increase for EM [12].

The beta1-adrenergic receptor, encoded by the *ADRB1* gene, serves as the primary target protein for all beta-receptor blockers [9]. Variants of the *ADRB1* gene have been identified as predictors of antihypertensive drug response [13]. Among the *ADRB1* polymorphisms, the most extensively studied ones are Ser49Gly (rs1801252) and Gly389Arg (rs1801253), which may lead to remarkable changes in the functioning of beta-receptor blockers. Of particular interest is the Gly389Arg polymorphism, as its different variants have been associated with variations in antihypertensive treatment responses among diverse populations [13-17]. The substitution of Gly with Arg at residue 389 (Gly389Arg) due to the G→C exchange at 1165 bp is the focus of attention. Two studies have reported that Chinese hypertension patients carrying the Gly389Gly genotype for the Gly389Arg polymorphism demonstrate a significantly improved antihypertensive effect when treated with metoprolol in contrast with patients with other genotypes [13, 18]. Additionally, Chinese hypertensive patients carrying the Arg389Arg genotype experience a great reduction in BP when treated with carvedilol in contrast with individuals carrying the Gly allele [19].

Beta-receptor blockers are widely utilized in the treatment of hypertension. Previous studies have established a connection between the antihypertensive efficacy of beta-receptor blockers and genetic variations in *CYP2D6* and *ADRB1* polymorphisms. Beta-receptor blockers are mainly metabolized by *CYP2D6*, while *ADRB1* serves as their target protein. *The CYP2D6*10* allele is the most prevalent in the Asian population [8], and the presence of the *CYP2D6*10* genotype significantly impacts the pharmacokinetics of metoprolol [18]. Notably, several studies find *ADRB1* Gly389Arg polymorphisms are linked to different responses to hypertensive therapeutic agents among Chinese hypertensive patients. Consequently, this study focused on investigating the frequencies of *CYP2D6*10* and *ADRB1* allele and genotype polymorphisms and exploring the link between hypertension grades and *CYP2D6* and *ADRB1* polymorphisms in Han Chinese hypertensive patients. The study findings may potentially provide useful insights for the selection of beta-receptor blockers, for instance, carvedilol and metoprolol, in the treatment of hypertensive patients of Han Chinese descent.

Materials and methods

Study subjects

This retrospective study was conducted in accordance with the Ethics committee of Zhongda Hospital, Southeast University (No. 2020ZDSYLL014-P01). The baseline characteristics of hypertensive patients had been described previously [20]. Briefly, 2570 Han patients were included in the present study

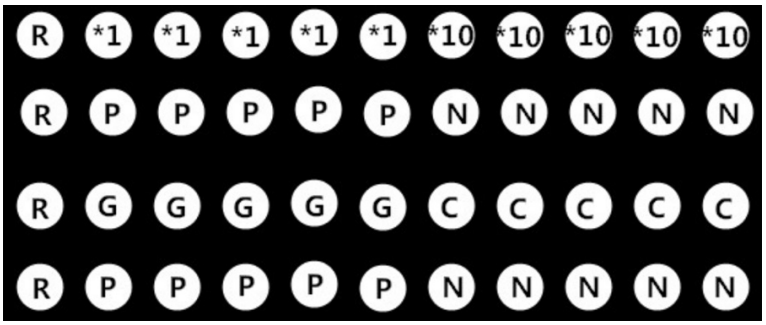

Figure 1. Schematic diagrams of the *CYP2D6* and *ADRB1* gene chip. R is the chip hybridization positioning reference, *1 and *10 are the wild-type and mutant-type probe sites of *CYP2D6* gene, respectively. G and C are the wild-type and mutant-type probe sites of *ADRB1* gene, respectively. P is the positive reference probe site for *CYP2D6* and *ADRB1,* while N is the negative reference probe site. There are 5 replicates of wild-type probe, mutation-type probes, positive reference probes, and negative reference probes.

from February 2017 to December 2019, encompassing 2419 hypertensive patients and 151 normotensive controls. Further to note, all the subjects in the study were patients from the Zhongda Hospital. Upon admission, blood pressure measurements were taken. Hypertension was denoted as systolic blood pressure (SBP) >140 mmHg and diastolic blood pressure (DBP) >90 mmHg. The essential hypertensive population included in this study had not received any antihypertensive medication prior to participation. Among the hypertensive patients, aged from 20 to 98 years old, there were 1405 males and 1014 females. Patients with secondary hypertension like endocrine diseases or kidney disease were not included in this study.

Genotyping procedures for CYP2D6 and ADRB1

CYP2D6 and *ADRB1* alleles and genotypes were estimated by gene chip. Briefly, DNA extraction was carried out from the whole blood utilizing an automatic nucleic acid extraction and purification system (NP968-C), following the instruction of the DNA extraction kit. The protocol followed to carry out the polymerase chain reaction (PCR) is as follows: 94°C for 3 min for pre-denaturation, then at 94°C for 30 s, 56°C for 30 s, and extension at 70°C for 30 s for 40 cycles, and at 70°C for 2 min for elongation. PCR was performed following the manufacturer's specifications by the ABI7500 real-time PCR system. Subsequently, 3 μL amplification products of *CYP2D6* or *ADRB1* were dispensed into the gene chip and incubated at 41°C for hybridization. The genotypes of *CYP2D6* and *ADRB1* for each sample were scanned by the GenePix4100A scanner and determined by the GenePix6.0 software. The gene chip schematic diagrams for *CYP2D6* and *ADRB1* were depicted in **Figure 1**.

Statistical analysis

Statistical Package for the Social Sciences for Windows (IBM SPSS Statistics, version 26) was utilized for data analysis. The allele and genotype frequencies were computed as per the observed number of occurrences. Categorical variables were presented as numbers and frequencies. Comparisons between different groups were performed by means of a chi-square test. A value of $P<0.05$ was statistically significant.

Results

The allele and genotype frequency of CYP2D6 and ADRB1 polymorphisms in Han Chinese hypertensive patients

The allele frequency, as well as genotype distributions of *CYP2D6* or *ADRB1* in Han hypertensive patients, were depicted in detail in **Tables 1** and **2**, correspondingly. Pertaining to *CYP2D6*, we observed allelic frequencies of 39.29% and 60.71% for the *CYP2D6*1* and *CYP2D6*10* alleles, correspondingly. Further evaluations depicted that the frequency of wild-type homozygotes genotype (*1/*1) was 9.71%. On the other hand, the frequency of mutant heterozygotes (*1/*10) or homozygotes (*10/*10) was 59.16% or 31.13%. For *ADRB1*, we identified a frequency of 32.78% for G alleles and 67.22% for C alleles. While the frequency of the wild-type homozygotes (GG) genotype was 10.29%, the frequency of mutant heterozygotes genotype (GC) or homozygotes genotype (CC) was 44.98% or 44.73%. We compared the allele frequencies of *CYP2D6* and *ADRB1* with respect to previously published reports in Han and other ethnic Chinese hypertensive populations. There were significant differences in *ADRB1* allele frequencies and *CYP2D6* and *ADRB1* genotype frequencies among the different geo-

Table 1. The *CYP2D6* and *ADRB1* allele frequencies of Chinese hypertensive patients in the present study and previous studies

Populations	Number	Allele frequencies of *CYP2D6*			Allele frequencies of *ADRB1*		
		CYP2D6*1 (%)	CYP2D6*10 (%)		ADRB1-G (%)	ADRB1-C (%)	
Jiangsu-Han	4838	39.29	60.71	χ^2=5.521[a] P=0.137[a]	32.78	67.22	χ^2=33.5[a] P<0.001[a]
Fujian [13]	522	35.40	64.6	χ^2=1.845[b] P=0.174[b]	40.2	59.8	χ^2=1.716[b] P=0.190[b]
Fujian [21]	186	41.40	58.60		38.71	61.29	
Hunan [22]	446	-	-		23.9	76.1	
Hunan-Han [18]	250	43.6	56.4		28.8	71.2	

a: χ^2 and *p* value among geographic Chinese hypertensive patients; b: χ^2 and *p* value between geographic Han Chinese hypertensive patients.

Table 2. The genotype frequencies of *CYP2D6* and *ADRB1* in Han Chinese hypertensive patients

Populations	Number	Genotype frequencies of *CYP2D6*				Genotype frequencies of *ADRB1*			
		*CYP2D6*1/*1*	*CYP2D6*1/*10*	*CYP2D6*10/*10*		ADRB1-GG	ADRB1-GC	ADRB1-CC	
Jiangsu-Han	2419	9.71	59.16	31.13	χ^2=66.37 P<0.001	10.29	44.98	44.73	χ^2=55.81 P<0.001
Fujian [13]	261	15	44.4	40.2		18	45.2	37	
Fujian [21]	93	24.73	33.33	41.94		24.73	27.96	47.31	
Hunan [22]	223	-	-	-		6.6	34.6	58.9	
Hunan-Han [18]	125	21.60	44.00	34.40		6.40	44.80	48.80	

Table 3. The combined genotype distributions of *CYP2D6* and *ADRB1* in Han Chinese hypertensive patients

CYP2D6 genotype	*ADRB1* genotype	Reactions for β-receptors blockers		Frequencies % (N)
		Metabolizing capacity	Sensitivity	
*1/*1	CC	EM	normal	4.13 (100)
*1/*1	GC	EM	Slightly increased	4.38 (106)
*1/*1	GG	EM	Significantly increased	1.20 (29)
*1/*10	CC	IM	normal	25.88 (626)
*1/*10	GC	IM	Slightly increased	27.78 (672)
*1/*10	GG	IM	Significantly increased	5.50 (133)
*10/*10	CC	PM	normal	14.72 (356)
*10/*10	GC	PM	Slightly increased	12.82 (310)
*10/*10	GG	PM	Significantly increased	3.60 (87)

EM: Extensive metabolizers, IM: Intermediate metabolizers, PM: Poor metabolizers.

graphic hypertensive populations (P<0.05) [13, 18, 21, 22]. However, the *CYP2D6* and *ADRB1* allele frequencies in this study were consistent with other studies conducted in Han Chinese hypertensive patients [18].

The combined genotype and phenotype of CYP2D6 and ADRB1 in Han Chinese hypertensive patients

Among the 2,419 Han hypertensive Chinese individuals included in this study, the most combined genotype of *CYP2D6* and *ADRB1* were *1/*10 + GC and *1/*10 + CC, whose frequencies were 27.78% (672/2419) and 25.88% (626/2419). The least combined genotype was *1/*1 + GG, whose frequency was just 1.62% (29/2419). All results were showed in **Table 3**.

The relationships between the genotype distributions of CYP2D6 and ADRB1 and various grades of hypertension among Han Chinese hypertensive patients

In the study examining the genetic polymorphisms of *CYP2D6* and *ADRB1* among various grades of hypertension among Han hypertensive Chinese, the participants were divided into three grades based on their blood pressure

Table 4. The genotype distributions of *CYP2D6* and *ADRB1* in different grades of hypertensive patients and normotensive controls

Genotype	Normotensive % (N)	The grades of hypertension (N)			*P* value
		Grade 1	Grade 2	Grade 3	
CYP2D6*1/*1	6.62 (10)	9.29 (13)	10.11 (62)	9.60 (160)	χ^2=1.58[c] P=0.45[c]
CYP2D6*1/*10	60.93 (92)	60.00 (84)	58.24 (357)	59.42 (990)	χ^2=0.35[d] P=0.99[d]
CYP2D6*10/*10	32.45 (49)	30.71 (43)	31.65 (194)	30.97 (516)	
ADRB1-CC	42.38 (64)	43.57 (61)	42.74 (262)	45.56 (759)	χ^2=4.71[c] P=0.10[c]
ADRB1-GC	41.72 (63)	48.57 (68)	46.00 (282)	44.30 (738)	χ^2=2.95[d] P=0.57[d]
ADRB1-GG	15.89 (24)	7.86 (11)	11.26 (69)	10.14 (169)	

c: *p* value between normotensives and hypertensive patients; d: *p* value among all three grades of hypertensive patients.

(BP) levels. The criteria were defined as follows for each grade: grade 1 (systolic BP 140-159 mmHg or diastolic BP 90-99 mmHg); grade 2 (systolic BP 160-179 mmHg or diastolic BP 100-109 mmHg); grade 3 (systolic BP ≥180 mmHg or diastolic BP ≥110 mmHg) [20]. As depicted in **Table 4**, statistical analysis revealed no remarkable differences in genetic polymorphisms of *CYP2D6* and *ADRB1* between normotensives control individuals and hypertensive patients, as well as among the three grades of hypertensive patients.

Discussion

Hypertension is a polygenic and multifactorial ailment. The efficacy of antihypertensive medications relies on factors including age, ethnicity, gender, gene-gene interactions, and gene-environment interplay. Genetic factors play a pivotal function in characterizing an individual's response to antihypertensive drugs. Therapies tailored to genetic polymorphisms have shown remarkable effectiveness, aiding in the prevention of major adverse events and reducing treatment costs. This study investigated the frequencies of alleles and genotypes in hypertensive patients of Han Chinese descent. Furthermore, the study revealed that the combined genotypes *1/*10 + CC and *1/*10 + CG were the most prevalent among the Han hypertensive population. Notably, no substantial variations were seen in the genotype distributions of *CYP2D6* and *ADRB1* between normotensive individuals and hypertensive patients within the Han Chinese population, or among the three hypertension grades.

*CYP2D6*10* stands as the predominant allele in the Chinese population [23]. Previous studies have shown that the frequency of the *CYP2D6*10* allele is up to 64.6% in Chinese hypertensive patients (**Table 1**). In this study, which encompassed a substantial sample size, the frequency of the *CYP2D6*10* allele was 60.71% in Han Chinese hypertensive patients living in Jiangsu province, which was consistent with Han Chinese hypertensive patients living in Hunan province [18]. However, the *CYP2D6* genotype frequencies of *1/*1, *1/*10, and *10/*10 were 9.71%, 59.16%, and 31.13% in the present study, respectively, which was inconsistent with other studies in different ethnic and geographic populations [13, 18, 21]. Therefore, a significant difference in the *CYP2D6* genotype polymorphisms among different ethnic and geographic populations becomes evident, thereby accentuating the significance of the study. Moreover, the *CYP2D6* genotype frequencies of the Han Chinese hypertensive population in the present study did not align with those reported by Liu et al., in their investigation involving 125 Han Chinese hypertensive patients from Hunan province [18]. Different geographic populations and sample sizes contribute to the contradictory results. Hiltunen et al., have affirmed that a small sample size had inadequate power to identify the single nucleotide polymorphism [24]. Collectively, these results indicated most Han hypertensive patients carried the *CYP2D6*10* mutation allele. Consequently, individuals harboring this mutation are anticipated to exhibit reduced drug clearance, resulting in elevated concentrations of antihypertensive beta-receptor blockers. Decreased drug dose is recommended to control blood pressure for individuals carrying the mutation.

In addition, the allele frequencies of *ADRB1-G* in Chinese hypertensive patients are up to

40.2% in the previous studies, and the allele frequencies were relatively low in Hunan province (**Table 1**). So, there was a significant difference in the *ADRB1-G* allele frequencies among the different geographic hypertensive populations. However, the G allele frequency in the present study was 32.78% in 2419 Han Chinese hypertensive patients living in Jiangsu province, which is similar to that in the previous study of Han Chinese hypertensive patients living in Hunan province (P>0.05) [18]. In addition, there was a significant difference in the *ADRB1* genotype frequencies among the different geographic hypertensive populations [13, 18, 21, 22]. Liu et al. reported the genotype frequencies of *ADRB1* were 6.40% for GG, 44.80% for GC, and 48.80% for CC in a small Han Chinese hypertensive population living in Hunan [18]. The genotype frequencies of *ADRB1* in this study were 10.29% for GG, 44.98% for GC, and 44.73% for CC in Han Chinese hypertensive patients, which was consistent with Liu et al. reports (P>0.05).

Importantly, the study additionally examined the combined genotypes of *CYP2D6* and *ADRB1*. The results showed *1/*10 + CC (25.88%) and *1/*10 + CG (27.78%) were the two combined genotypes with the highest frequencies. Beta-receptor blocker of antihypertensive drugs is primarily metabolized by *CYP2C9*, and *ADRB1* is the target protein of beta-receptor blocker. It can be inferred that just half of Han Chinese hypertension patients (53.66%) poses an intermediate metabolizing capacity, along with nearly normal sensitivity to beta-receptor blockers for antihypertensive treatment as per our outcomes.

The study did not depict any substantial differences in the genotype distributions of *CYP2D6* and *ADRB1* between normotensive individuals and hypertensive patients within the Han Chinese population, nor among the three different grades of hypertensive patients. However, according to Wang et al., for *ADRB1* polymorphism, individuals carrying the GG genotype exhibited a more pronounced response to metoprolol in Han Chinese hypertensive patients [14]. Conversely, two European prospective studies did not ascertain any link between *ADRB1* polymorphism and the antihypertensive response to beta-receptor blockers [25, 26]. Moreover, under strictly regulated conditions, Hiltunen et al. did not establish any correlation between *ADRB1* and *CYP2D6* polymorphisms and the antihypertensive impact of beta-receptor blockers utilizing the GWAS technology [25]. The contradictory results could be attributed to variations in ethnic groups and sample sizes. Thus, the antihypertensive response to beta-receptor blockers appears to be complex. It is advisable to monitor the plasma concentration of these drugs and the risk of adverse reactions to optimize the dosage when administering beta-receptor blockers to Han Chinese hypertensive patients. Furthermore, further research, particularly prospective multicenter studies involving Han Chinese hypertensive patients with different genotypes, is necessary to establish reliable recommendations.

Conclusions

In conclusion, this study provides insights into the polymorphism characteristics of CYP2D6 and ADRB1 in Han Chinese hypertensive patients, demonstrating significant differences compared to other ethnic and geographic Chinese hypertensive populations. The most frequent genotypes observed in the combined CYP2D6 and ADRB1 analysis were *1/*10 + CC and *1/*10 + CG. Importantly, no significant differences in polymorphism distributions were discovered between normotensive individuals and hypertensive patients, nor among the different grades of hypertensive patients. However, it is important to consider the limitations of these findings. Firstly, only the dominant variants of CYP2D6 and ADRB1 were detected due to their remarkable frequencies in the Han Chinese population. Secondly, while there was a substantial number of hypertensive patients in this study, there was a relatively small sample size for normotensive controls. Lastly, the evaluation of the pharmacokinetics of beta-receptor blockers in individuals carrying various CYP2D6 and ADRB1 genotypes was not performed.

Acknowledgements

The Medical Science and Technology Development Foundation, Nanjing Municipality Health Bureau (Grant No: YKK17287). We thank Bullet Edits Limited for the linguistic editing and proofreading of the manuscript.

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Keping Chen, Clinical Laboratory, Zhongda Hospital, School of Medicine, Southeast University, Dingjiaqiao Road 87, Nanjing 210009, Jiangsu, China. Tel: +86-13505157582; ORCID: 0000-0002-8601-7481; E-mail: keping2001@hotmail.com

References

[1] Al Attar AA, Fahed GI, Hoballah MM, Pedersen S, El-Yazbi AF, Nasser SA, Bitto A, Orekhov AN and Eid AH. Mechanisms underlying the effects of caloric restriction on hypertension. Biochem Pharmacol 2022; 200: 115035.

[2] Wang Z, Chen Z, Zhang L, Wang X, Hao G, Zhang Z, Shao L, Tian Y, Dong Y, Zheng C, Wang J, Zhu M, Weintraub WS and Gao R; China Hypertension Survey Investigators. Status of hypertension in China: results from the China hypertension survey, 2012-2015. Circulation 2018; 137: 2344-56.

[3] Rosengren A, Teo K, Rangarajan S, Kabali C, Khumalo I, Kutty VR, Gupta R, Yusuf R, Iqbal R, Ismail N, Altuntas Y, Kelishadi R, Diaz R, Avezum A, Chifamba J, Zatonska K, Wei L, Liao X, Lopez-Jaramillo P, Yusufali A, Seron P, Lear SA and Yusuf S. Psychosocial factors and obesity in 17 high-, middle- and low-income countries: the prospective urban rural epidemiologic study. Int J Obes (Lond) 2015; 39: 1217-23.

[4] Wang JG. Unique approaches to hypertension control in China. Ann Transl Med 2018; 6: 296.

[5] Rysz J, Franczyk B, Rysz-Gorzynska M and Gluba-Brzozka A. Pharmacogenomics of hypertension treatment. Int J Mol Sci 2020; 21: 4709.

[6] Eadon MT and Chapman AB. A physiologic approach to the pharmacogenomics of hypertension. Adv Chronic Kidney Dis 2016; 23: 91-105.

[7] Jang JS, Cho KI, Jin HY, Seo JS, Yang TH, Kim DK, Kim DS, Seol SH, Kim DI, Kim BH, Park YH, Je HG, Jeong YH and Lee SW. Meta-analysis of cytochrome P450 2C19 polymorphism and risk of adverse clinical outcomes among coronary artery disease patients of different ethnic groups treated with clopidogrel. Am J Cardiol 2012; 110: 502-8.

[8] Pratt VM, Cavallari LH, Del Tredici AL, Gaedigk A, Hachad H, Ji Y, Kalman LV, Ly RC, Moyer AM, Scott SA, van Schaik RHN, Whirl-Carrillo M and Weck KE. Recommendations for clinical CYP2D6 genotyping allele selection: a joint consensus recommendation of the Association for Molecular Pathology, College of American Pathologists, Dutch Pharmacogenetics Working Group of the Royal Dutch Pharmacists Association, and the European Society for Pharmacogenomics and Personalized Therapy. J Mol Diagn 2021; 23: 1047-64.

[9] Sehrt D, Meineke I, Tzvetkov M, Gultepe S and Brockmoller J. Carvedilol pharmacokinetics and pharmacodynamics in relation to CYP2D6 and ADRB pharmacogenetics. Pharmacogenomics 2011; 12: 783-95.

[10] Shahin MH, Sa AC, Webb A, Gong Y, Langaee T, McDonough CW, Riva A, Beitleshees AL, Chapman AB, Gums JG, Turner ST, Boerwinkle E, Scherer SE, Sadee W, Cooper-DeHoff RM and Johnson JA. Genome-wide prioritization and transcriptomics reveal novel signatures associated with thiazide diuretics blood pressure response. Circ Cardiovasc Genet 2017; 10: e001404.

[11] Meloche M, Khazaka M, Kassem I, Barhdadi A, Dube MP and de Denus S. CYP2D6 polymorphism and its impact on the clinical response to metoprolol: a systematic review and meta-analysis. Br J Clin Pharmacol 2020; 86: 1015-33.

[12] Swen JJ, Nijenhuis M, de Boer A, Grandia L, Maitland-van der Zee AH, Mulder H, Rongen GA, van Schaik RH, Schalekamp T, Touw DJ, van der Weide J, Wilffert B, Deneer VH and Guchelaar HJ. Pharmacogenetics: from bench to byte--an update of guidelines. Clin Pharmacol Ther 2011; 89: 662-73.

[13] Chen L, Xiao T, Chen L, Xie S, Deng M and Wu D. The association of ADRB1 and CYP2D6 polymorphisms with antihypertensive effects and analysis of their contribution to hypertension risk. Am J Med Sci 2018; 355: 235-9.

[14] Wang H, Liu J, Liu K, Liu Y, Wang Z, Lou Y, Niu Q, Gu W, Wang L, Li M, Zhu X and Wen S. Beta1-adrenoceptor gene Arg389Gly polymorphism and essential hypertension risk in general population: a meta-analysis. Mol Biol Rep 2013; 40: 4055-63.

[15] Liu H, Xing X, Huang L, Huang Z and Yuan H. The expression level of myocardial beta1-adrenergic receptor affects metoprolol antihypertensive effects: a novel mechanism for interindividual difference. Med Hypotheses 2013; 81: 71-2.

[16] Yip VL and Pirmohamed M. Expanding role of pharmacogenomics in the management of cardiovascular disorders. Am J Cardiovasc Drugs 2013; 13: 151-62.

[17] McCrink KA and Lymperopoulos A. Beta1-adrenoceptor Arg389Gly polymorphism and heart disease: marching toward clinical practice integration. Pharmacogenomics 2015; 16: 1035-8.

[18] Liu J, Liu ZQ, Liu YZ, Tan ZR, Hu DL, Li Z, Wang D, Zhang W and Zhou HH. Effects of β1-adrenergic receptor and CYP2D6 genetic polymorphism on metoprolol pharmacokinetics

and pharmacodynamics in antihypertension therapy. Chinese Journal of Clinical Pharmacology & Therapeutics 2007; 12: 1130-1137.

[19] Si D, Wang J, Xu Y, Chen X, Zhang M and Zhou H. Association of common polymorphisms in beta1-adrenergic receptor with antihypertensive response to carvedilol. J Cardiovasc Pharmacol 2014; 64: 306-9.

[20] Chen K, Xiao P, Li G, Wang C and Yang C. Distributive characteristics of the CYP2C9 and AGTR1 genetic polymorphisms in Han Chinese hypertensive patients: a retrospective study. BMC Cardiovasc Disord 2021; 21: 73.

[21] Wu D, Li G, Deng M, Song W, Huang X, Guo X, Wu Z, Wu S and Xu J. Associations between ADRB1 and CYP2D6 gene polymorphisms and the response to beta-blocker therapy in hypertension. J Int Med Res 2015; 43: 424-34.

[22] Liu J, Liu ZQ, Yu BN, Xu FH, Mo W, Zhou G, Liu YZ, Li Q and Zhou HH. Beta1-adrenergic receptor polymorphisms influence the response to metoprolol monotherapy in patients with essential hypertension. Clin Pharmacol Ther 2006; 80: 23-32.

[23] He L, Chen S, Li J, Xie X, Huang L, Kuang Y, Xu K, Huang W, Zhao Y, Yang G and Guo C. Genetic and phenotypic frequency distribution of CYP2C9, CYP2C19 and CYP2D6 in over 3200 Han Chinese. Clin Exp Pharmacol Physiol 2020; 47: 1659-63.

[24] Hiltunen TP, Donner KM, Sarin AP, Saarela J, Ripatti S, Chapman AB, Gums JG, Gong Y, Cooper-DeHoff RM, Frau F, Glorioso V, Zaninello R, Salvi E, Glorioso N, Boerwinkle E, Turner ST, Johnson JA and Kontula KK. Pharmacogenomics of hypertension: a genome-wide, placebo-controlled cross-over study, using four classes of antihypertensive drugs. J Am Heart Assoc 2015; 4: e001521.

[25] Suonsyrja T, Donner K, Hannila-Handelberg T, Fodstad H, Kontula K and Hiltunen TP. Common genetic variation of beta1- and beta2-adrenergic receptor and response to four classes of antihypertensive treatment. Pharmacogenet Genomics 2010; 20: 342-5.

[26] Filigheddu F, Argiolas G, Degortes S, Zaninello R, Frau F, Pitzoi S, Bulla E, Bulla P, Troffa C and Glorioso N. Haplotypes of the adrenergic system predict the blood pressure response to beta-blockers in women with essential hypertension. Pharmacogenomics 2010; 11: 319-25.