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Research Progress on CYP2D6 and ADRB1 Gene Polymorphisms in the Individualized Treatment of Hypertension with β-Blockers

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Abstract: *Hypertension is an independent risk factor for cardiovascular and cerebrovascular diseases and a major public health problem worldwide. β-blockers are one of the main drugs used clinically for hypertension treatment. A large number of clinical practices have found that there are significant individual differences in the clinical response to β-blockers among different patients, and such individual differences are closely related to polymorphisms in the cytochrome P450 2D6 (CYP2D6) and β1-adrenergic receptor (ADRB1) genes. In July 2024, the Clinical Pharmacogenomics Implementation Consortium (CPIC) issued the latest guidelines for the individualized use of β-blockers. This article reviews the recent research progress on the effects of CYP2D6 and ADRB1 gene polymorphisms on the treatment of hypertension with β-blockers, aiming to provide a theoretical basis for precision medicine in hypertension.*

Keywords: *Hypertension, β-blocker, Precision medicine, CYP2D6, ADRB1, Genetic polymorphism*

1. Introduction

Hypertension is one of the most common chronic diseases, closely associated with the incidence and mortality of cardiovascular and cerebrovascular diseases, and constitutes a major global public health issue. Studies have shown that among more than 1.7 million urban and rural community residents aged 35-75 in China, the prevalence of hypertension is 37.2%, while the awareness rate, treatment rate, and control rate of hypertension are 36.0%, 22.9%, and 5.7% respectively [1]. The Chinese lifestyle is characterized by a high-salt, high-fat, and high-sugar diet, high psychosocial stress, and low physical activity [2]. With the aging population and unhealthy lifestyles, the prevalence of hypertension in China continues to rise, but the control rate remains relatively low. Currently, the main clinical methods for controlling hypertension include non-pharmacological interventions such as dietary and lifestyle modifications, as well as pharmacological treatment. Among these, pharmacological treatment is the most effective measure for blood pressure control [3]. However, significant individual differences exist in the clinical response to antihypertensive drugs among different patients, which may be related to multiple factors such as gender, age, weight, lifestyle, and genetic factors [4]. Among these, genetic factors are one of the most important, as they are not only associated with elevated blood pressure but also serve as the main cause of individual differences in drug response [5-6].

β-blockers are widely used in the clinical treatment of hypertension. Their main target protein is the β1-adrenergic receptor encoded by the ADRB1 gene, and they are mainly metabolized by the CYP2D6 enzyme in the body. Previous studies have confirmed that the antihypertensive efficacy of β-blockers is correlated with CYP2D6 and ADRB1 gene polymorphisms [4,7]. The Guidelines for Rational Use of Antihypertensive Drugs (2nd Edition) recommend that clinicians detect ADRB1 gene polymorphisms before prescribing β-blockers to guide dosage selection and improve efficacy [8], but do not mention CYP2D6 gene testing. In July 2024, the CPIC issued the latest guidelines for the individualized use of β-blockers. The guidelines summarize the latest clinical research findings, evaluate the relationship between β-blockers and their metabolic enzymes, transporters, and target genes (CYP2D6, ADRB1, ADRB2, ADRA2C, GRK4, GRK5) in terms of drug exposure and response. Ultimately, it was concluded that the evidence level for the association between CYP2D6 genetic polymorphisms and metoprolol exposure and heart rate response is extremely high, and dosage recommendations for metoprolol can be provided based on CYP2D6 metabolic phenotypes [9]. However, previous research

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conclusions on the impact of CYP2D6 and ADRB1 gene testing on the antihypertensive efficacy of β-blockers are not entirely consistent. Therefore, this article reviews the recent research progress on the relationship between CYP2D6 and ADRB1 gene polymorphisms and the treatment of hypertension with β-blockers, in order to provide a theoretical basis for the precision treatment of hypertension.

2. Antihypertensive Mechanism and Classification of β-Blockers

Hypertension refers to the sustained elevation of systemic arterial blood pressure, a clinical syndrome that can lead to changes in the heart, brain, kidneys, and blood vessels. Its pathogenesis involves multiple systems, including genetic regulation, the renin-angiotensin-aldosterone system (RAAS), the sympathetic nervous system, vascular endothelial function, and metabolism [10]. β-blockers are a class of drugs that selectively bind to β-adrenergic receptors, thereby antagonizing the agonist effects of neurotransmitters and catecholamines on β-receptors. The antihypertensive mechanisms of these drugs include: (1) Binding to β-adrenergic receptors to inhibit neural transmission, reducing the agonist effects of catecholamines on β-receptors to lower blood pressure; (2) Blocking RAAS activity, exerting a favorable antihypertensive effect in high-renin hypertension; (3) Binding to cardiac β-receptors to reduce heart rate, weaken myocardial contractility, decrease cardiac output, and lower myocardial oxygen consumption, achieving significant reductions in both supine and standing blood pressure; (4) Reducing sympathetic tone and inhibiting excessive activation of the sympathetic nervous system, thereby lowering blood pressure and protecting cardiovascular function [11-12].

Based on their selectivity for β1-adrenergic receptors, β-blockers are classified into selective β-blockers (including metoprolol, atenolol, bisoprolol, etc.) and non-selective β-blockers (including propranolol, etc.). Based on pharmacokinetic characteristics, they are divided into lipophilic β-blockers (including metoprolol, labetalol, etc.), hydrophilic β-blockers (including atenolol, etc.), and amphiphilic β-blockers (bisoprolol) [13].

3. CYP2D6 Gene Polymorphism and β-Blockers

3.1 CYP2D6 Gene Polymorphism

The CYP450 enzyme system is the main enzyme system involved in drug biotransformation in the body, playing a crucial role in the metabolism of certain endogenous and exogenous substances. CYP2D6 is an important member of the CYP450 family and participates in the metabolism of various drugs. The CYP2D6 gene, which encodes the CYP2D6 enzyme, is located on human chromosome 22 (22q13.1) and consists of 9 exons and 8 introns [14]. Extensive research on the CYP2D6 gene has identified more than 100 allelic variants [15]. Based on the functional status of each allele, CYP2D6 alleles are classified into normal or enhanced function group (CYP2D6*1, *2, 35, etc.), reduced function group (CYP2D69, *10, 17, 41, etc.), and non-functional group (CYP2D63～6, *11, etc.). According to the different activity levels of alleles, the predicted phenotypes of CYP2D6 genotypes are categorized into: Ultrarapid metabolizers (UM), Extensive metabolizer (EM), Normal Metabolizer (NM), Intermediate metabolizer (IM), and Poor metabolizer (PM).

CYP2D6 gene polymorphism not only exhibits individual differences but also significant ethnic and geographical variations. CYP2D64 has a high mutation frequency in European and American populations, CYP2D641 is more common in Middle Eastern populations, and CYP2D617 is prevalent in African populations [16]. The most common mutation sites in Asian populations include CYP2D610, CYP2D61, and CYP2D62, among which CYP2D610 is the most frequent allelic mutation in the Chinese population [17]. Relevant studies have shown that the frequencies of CYP2D61 and CYP2D6*10 alleles in Chinese hypertensive patients are 39.29% and 60.71% respectively [18]. In addition, the metabolic phenotypes of the CYP2D6 gene vary among different ethnic groups: PM is more common in European and American populations, while IM is predominant in Asian populations [19]. It has been reported that the overall polymorphism frequency of CYP2D6 in the Chinese population is 88.04%, with metabolic phenotype frequencies of NM (95.43%), IM (3.35%), and PM (0.52%) [20].

3.2 Impact of CYP2D6 Gene Polymorphism on the Pharmacokinetics of β-Blockers

Commonly used β-blockers in the market, such as metoprolol, carvedilol, propranolol, labetalol,

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nebivolol, and timolol, are all substrates of CYP2D6 and are mainly metabolized by the CYP2D6 enzyme in the body. CYP2D6 gene polymorphism significantly affects the pharmacokinetic parameters of metoprolol [21]. Yang et al. conducted an in-depth study on the interaction between CYP2D6 variant genes (1, 2, 10, 39) and metoprolol, confirming that CYP2D6 polymorphism has a significant impact on metoprolol metabolism [22]. A meta-analysis of CYP2D6 metabolic phenotypes and metoprolol pharmacokinetics showed that the plasma concentration of metoprolol in CYP2D6 PM patients may be nearly 5 times higher than that in NM patients, which may increase the risk of various side effects [23]. Anstensrud AK et al. [24] reported that the adjusted plasma concentration of metoprolol in CYP2D6 PM patients was more than 6 times higher than that in EM patients, and the maximum heart rate increase achieved during exercise was lower. A study on the effects of CYP2D6 and CYP3A5 polymorphisms on the pharmacokinetics and pharmacodynamics of bisoprolol in Chinese hypertensive patients showed that bisoprolol 2.5 mg daily effectively reduces blood pressure and heart rate, but the tested CYP2D6 and CYP3A5 gene polymorphisms do not appear to be useful for predicting the hemodynamic response to bisoprolol in these patients [25]. Mohammed et al. [26] reported that the CYP2D62A genotype may be associated with the plasma concentration of bisoprolol. A study on the pharmacokinetics of nebivolol in healthy Chinese subjects showed that the peak plasma concentration and area under the curve of nebivolol in subjects with CYP2D65 and CYP2D610/10 polymorphisms were significantly higher than those in subjects with wild-type CYP2D6 (CYP2D61/1), while the plasma clearance was significantly reduced in CYP2D610/10 carriers and CYP2D65 carriers [27]. Research on the pharmacokinetics of carvedilol in healthy Korean volunteers showed that CYP2D610/*10 carriers had a lower clearance rate of carvedilol and a higher area under the curve of O-desmethylcarvedilol, indicating that CYP2D6 gene polymorphism affects the pharmacokinetic characteristics of carvedilol [28]. In addition, a population pharmacokinetic-pharmacodynamic model study of carvedilol showed that CYP450 2D6 gene polymorphism contributes to the inter-individual variability in carvedilol pharmacokinetics but has no significant impact on pharmacodynamics [29].

3.3 Relationship between CYP2D6 Gene Polymorphism and the Antihypertensive Efficacy of β-Blockers

Different β-blockers vary in their degree of metabolism by the CYP2D6 enzyme, and CYP2D6 affects their efficacy by influencing pharmacokinetic parameters. Different CYP2D6 metabolic phenotypes lead to significant differences in the antihypertensive efficacy of β-blockers in hypertension treatment [30]. A meta-analysis on the impact of CYP2D6 gene polymorphism on the response to metoprolol showed that compared with non-PM patients (Table 1) , PM patients had greater reductions in heart rate, diastolic blood pressure, and systolic blood pressure during metoprolol treatment [31]. A meta-analysis by Dou Xiaotao et al. [32] evaluating the effect of CYP2D6 gene polymorphism on the efficacy of metoprolol found that metoprolol had a better antihypertensive effect (mainly in reducing diastolic blood pressure) in PM patients than in UM, EM, and IM groups, but was less effective in controlling heart rate. Poulussen FCP et al. [33] reported that the CYP2D6 genotype is associated with the maintenance dose of metoprolol, and patients with the CYP2D6 PM phenotype may benefit from a lower initial dose of metoprolol. The Dutch Pharmacogenetics Working Group (DPWG) also recommends CYP2D6 genotyping when using metoprolol, suggesting a 75% dose reduction for PM patients, a 20%-50% dose reduction for IM patients, and alternative drugs for UM patients [34]. Carvedilol exhibits stereoselective metabolism: compared with CYP2D6 NM patients, PM patients showed reduced clearance of R-carvedilol [35].

CYP2D6 gene polymorphisms associated with reduced activity lead to slowed metabolism of β-blockers in the body, thereby increasing their plasma concentration and efficacy. Conversely, polymorphisms associated with increased activity may result in rapid drug metabolism and reduced efficacy. Therefore, understanding the patient's CYP2D6 genotype is helpful for selecting appropriate β-blocker types and dosages to improve treatment outcomes.

Table 1 Studies on the Relationship between CYP2D6 Gene Polymorphism and the Antihypertensive Efficacy of β-Blockers

Author	Year	Metabolic Phenotype	Study Population	Drug	Sample Size	Main Findings
Meloche et al. [31]	2022	PM	General population	Metoprolol	/	Compared with non-PM patients, PM patients had

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						greater reductions in heart rate, diastolic blood pressure, and systolic blood pressure during metoprolol treatment.
Dou Xiaotao et al. [32]	2021	UM, EM, IM, PM	General population	Metoprolol	/	Metoprolol had a better antihypertensive effect in PM patients than in UM, EM, and IM groups, but was less effective in controlling heart rate.
Poulussen et al. [33]	2019	PM	Dutch population	Metoprolol	105	The CYP2D6 genotype is associated with the maintenance dose of metoprolol, and patients with the CYP2D6 PM phenotype may benefit from a lower initial dose.
Swen et al. [34]	2011	PM, IM, UM	Dutch population	Metoprolol	/	DPWG recommends CYP2D6 genotyping when using metoprolol: 75% dose reduction for PM patients, 20%-50% dose reduction for IM patients, and alternative drugs for UM patients.
Lymperopoulos et al. [35]	2015	UM, EM, IM, PM	/	Carvedilol, Metoprolol	/	Carvedilol exhibits stereoselective metabolism; compared with CYP2D6 NM patients, PM patients showed reduced clearance of R-carvedilol.

3.4 CPIC Guidelines for Adjusting Metoprolol Dosage Based on CYP2D6 Metabolic Phenotype

In some studies, patients carrying different genotypes showed significant pharmacokinetic differences after using the above drugs, but the clinical responses after medication were mostly inconsistent among different studies. Only studies on metoprolol consistently confirmed that differences in heart rate and blood pressure responses after medication are associated with the CYP2D6 genotype. Evidence suggests that CYP2D6 poor metabolizers have significantly increased exposure to metoprolol during treatment, leading to greater reductions in metoprolol-related blood pressure (systolic blood pressure: approximately 3-6 mmHg; diastolic blood pressure: 2-6 mmHg) and heart rate (approximately 3-8 beats per minute). This heart rate response to metoprolol may increase the risk of bradycardia in patients. The guidelines suggest that compared with initiating metoprolol at the standard dose, a regimen of starting with a low dose in poor metabolizers and gradually increasing the dose based on the patient's post-medication response (heart rate and blood pressure) results in a lower risk of adverse reactions [9]. The guidelines provide metoprolol dosage recommendations based on CYP2D6 gene polymorphism (Table 2), aiming to minimize the risk of adverse reactions in CYP2D6 poor metabolizers using metoprolol.

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Table 2 Metoprolol Dosage Recommendations Based on CYP2D6 Phenotype

Metabolic Phenotype	Genotype Examples	Impact	Recommendation	Recommendation Level
Ultrarapid Metabolizer	*1/*1xN, *1/*2xN, *2/*2xN	Increased metoprolol metabolism leads to decreased drug concentration; it is unclear whether this results in clinically significant changes in heart rate, blood pressure, or clinical outcomes.	Metoprolol is not recommended.	No recommendation
Normal Metabolizer	*2x2/*10, *1/*1, *1/*2, *1/*10x3, *1/*17, *2/*29, *1/*10, *1/*41, *1/*9	Normal metabolism of metoprolol	Initiate treatment at the standard dose	Strong
Intermediate Metabolizer	*1/*5, *10/*17, *29/*41, *10/*10, *41/*41, *10/*41, *4/*10, *4/*41	Decreased metoprolol metabolism leads to increased drug concentration; no significant impact on heart rate, blood pressure, or clinical outcomes.	Initiate treatment at the standard dose	Moderate
Poor Metabolizer	*3/*4, *4/*4, *5/*5, *5/*6	Decreased metoprolol metabolism leads to significantly increased drug concentration; results in greater reductions in heart rate and blood pressure.	Initiate treatment at the lowest recommended starting dose. Gradually titrate the dose upward to the guideline-recommended dose or a maintenance dose with stable clinical effects, while monitoring for bradycardia. Alternatively, consider alternative β-blockers.	Moderate
Unknown Metabolizer	*1/*22, *1/*25, *22/*25	/	No recommendation	No recommendation

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4. ADRB1 Gene Polymorphism and β-Blockers

4.1 ADRB1 Gene Polymorphism

ADRB1 encodes the β1-adrenergic receptor, which is mainly distributed in cardiomyocytes. Stimulation by neurotransmitters and catecholamines can increase heart rate and enhance myocardial contractility. As the main target of β-blockers, the β1-adrenergic receptor is encoded and regulated by the ADRB1 gene. The ADRB1 gene is located on human chromosome 10 (10q24-q26), and its two main single nucleotide polymorphisms are rs1801252 (ADRB1 145A＞G; Ser49Gly), which causes a serine-to-glycine change at amino acid position 49, and rs1801253 (ADRB1 1165G＞C; Gly389Arg), which causes a glycine-to-arginine change at amino acid position 389. The Ser49Gly variant increases agonist-promoted downregulation, while the Gly389Arg variant alters the expression and regulation of G protein-coupled receptors, reducing adenylate cyclase activity and thereby attenuating cAMP production. These two polymorphisms lead to changes in the structure and function of the β1-adrenergic receptor, thereby affecting the efficacy of β-blockers [36-38]. There are ethnic differences in the allele frequency distribution of the ADRB1 1165G＞C polymorphism: the frequency of the C allele in different ethnic groups is ranked as follows: Chinese ＞ Caucasians ＞ Spaniards ＞ African Americans, with the C allele frequency in African Americans being significantly lower than in other ethnic groups [39].

4.2 Relationship between ADRB1 Gene Polymorphism and the Antihypertensive Efficacy of β-Blockers

β-blockers are among the most widely used drugs for the treatment of cardiovascular diseases. A pharmacogenomic review related to the metabolism and response of β-blockers showed that in numerous studies (Table 3) , patients with the ADRB1 Arg389Arg genotype had better β-blocker efficacy [40]. A study by Wu et al. showed that the ADRB1 1165G＞C polymorphism and the duration of β-blocker treatment are independent factors associated with the therapeutic effect of β-blockers [41]. A meta-analysis by Dou Xiaotao et al. [42] showed that the ADRB1 1165G＞C polymorphism has a significant impact on the reduction of diastolic and systolic blood pressure by metoprolol. Shen Juanqin et al. [43] reported that carriers of the ADRB1 1165 CC genotype had the most significant effects of metoprolol sustained-release tablets on lowering blood pressure and slowing heart rate, followed by the GC genotype, and the GG genotype had the weakest effect. Chen et al. [44] found that compared with patients with other genotypes, Chinese hypertensive patients carrying the ADRB1 Gly389Gly genotype had significantly improved antihypertensive efficacy when treated with metoprolol. A study on healthy volunteers showed that compared with the Arg389Arg genotype, the Gly389Gly genotype was associated with reduced plasma renin activity and decreased resting and exercise-induced heart rate responses during intervention with different doses of metoprolol [45]. A meta-analysis by Castaño-Amores et al. [46] showed that the ADRB1 Gly389Arg polymorphism had no significant impact on the blood pressure-lowering effect of bisoprolol in cardiovascular patients. A study by Zhang Tianqi et al. [47] concluded that the ADRB1 Gly389Arg polymorphism had no significant effect on the improvement of diastolic blood pressure, systolic blood pressure, or left ventricular ejection fraction by bisoprolol. A study by Zeng et al. [48] also reported that the two common polymorphisms of the ADRB1 gene were not significantly correlated with blood pressure and heart rate responses to bisoprolol in hypertensive patients. In addition, during the treatment of essential hypertension with carvedilol, the reduction rate of diastolic blood pressure in patients with the ADRB1 Arg389 homozygous genotype was approximately 4 times that of patients with the ADRB1 Gly389 homozygous genotype, indicating that ADRB1 polymorphism plays an important role in the diastolic blood pressure response to carvedilol in patients with essential hypertension [49]. Furthermore, the ADRB1 Gly49 genotype was significantly associated with a higher baseline heart rate in healthy volunteers and the effect of carvedilol on exercise-induced heart rate [50].

ADRB1 gene polymorphism affects the sensitivity of receptors to β-blockers, leading to changes in drug efficacy. Therefore, detecting ADRB1 gene polymorphism before treatment is of great significance for improving the efficacy of β-blockers in hypertension treatment.

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Table 3 Studies on the Relationship between ADRB1 Gene Polymorphism and the Antihypertensive Efficacy of β-Blockers

Author	Year	Gene Locus	Study Population	Drug	Sample Size	Main Findings
Wu et al. [41]	2015	ADRB1 1165G＞C	Chinese population	Metoprolol	93	The ADRB1 1165G＞C polymorphism and the duration of β-blocker treatment are independent factors associated with the therapeutic effect of β-blockers.
Dou Xiaotao et al. [42]	2020	ADRB1 1165G＞C	Chinese population	Metoprolol	/	Patients with the ADRB1 389 CC genotype have higher drug sensitivity and better efficacy to metoprolol.
Shen Juanqin et al. [43]	2023	ADRB1 1165G＞C	Chinese population	Metoprolol	41	Carriers of the ADRB1 1165 CC genotype had the most significant effects of metoprolol sustained-release tablets on lowering blood pressure and slowing heart rate.
Chen et al. [44]	2018	ADRB1 Gly389Arg (1165G＞C)	Chinese population	Metoprolol	522	Compared with patients with other genotypes, hypertensive patients carrying the ADRB1 Gly389Gly genotype had significantly improved antihypertensive efficacy when treated with metoprolol.
Petersen et al. [45]	2012	ADRB1 Gly389Arg (1165G＞C)	Caucasian population	Metoprolol	29	Compared with the Arg389Arg genotype, the Gly389Gly genotype was associated with reduced plasma renin activity and decreased resting and exercise-induced heart rate responses during metoprolol treatment.
Castaño-Amores et al. [46]	2021	ADRB1 Gly389Arg (1165G＞C)	General population	Bisoprolol	/	The ADRB1 Gly389Arg polymorphism had no significant impact on the blood pressure-lowering effect of bisoprolol in cardiovascular patients.
Zhang Tianqi et al. [47]	2024	ADRB1 Gly389Arg (1165G＞C)	Caucasian and Chinese populations	Bisoprolol	1339	The ADRB1 Arg389Gly polymorphism had no significant effect on the improvement of diastolic blood pressure, systolic blood

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						pressure, or left ventricular ejection fraction by bisoprolol.
Zeng et al. [48]	2022	ADRB1 Ser49Gly, Gly389Arg	Chinese population	Bisoprolol	99	The two common polymorphisms of the ADRB1 gene were not significantly correlated with blood pressure and heart rate responses to bisoprolol in hypertensive patients.
Si et al. [49]	2014	ADRB1 Ser49Gly, Gly389Arg	Chinese population	Carvedilol	87	The reduction degree of diastolic blood pressure in patients with the ADRB1 Arg389 homozygous genotype was approximately 4 times that of patients with the ADRB1 Gly389 homozygous genotype.
Sehrt et al. [50]	2011	ADRB1 Ser49Gly	/	Carvedilol	110	The ADRB1 Gly49 genotype was significantly associated with a higher baseline heart rate in healthy volunteers and the effect of carvedilol on exercise-induced heart rate.

5. Conclusions and Prospects

With the in-depth development of the concept of precision medicine, the role of genetic factors in hypertension treatment has received increasing attention. Phase data results show that individualized treatment based on pharmacogenomics can significantly improve the hypertension control rate and effectively reduce the incidence of cardiovascular and cerebrovascular events caused by hypertension. CYP2D6 and ADRB1 gene polymorphisms are important factors affecting the efficacy of β-blockers in hypertension treatment. Understanding the patient's genotype is helpful for selecting appropriate drugs and dosages to improve treatment outcomes. In the future, research should further explore the specific mechanisms by which CYP2D6 and ADRB1 gene polymorphisms affect the efficacy of β-blockers, providing a more accurate theoretical basis for the precision treatment of hypertension.

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