SMART Approach

Pharmacogenetic Considerations in Beta-Blocker Therapy

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Overview

Pharmacogenetic testing offers a promising approach to personalizing beta-blocker therapy which is used for a variety of diseases, such as heart failure, myocardial infarction and migraine prophylaxis. The genetic variability in the metabolism and response to beta-blockers such as metoprolol can significantly influence treatment outcomes. Understanding these genetic differences can help optimize therapy and minimize adverse effects. A brief summary of the current guidelines and recommendations:

- Approximately 0.3-6.5% (depending on their ancestry) of patients are CYP2D6 poor metabolizers.
- CYP2D6 Poor Metabolizers have significantly decreased metabolism of metoprolol, leading to increased drug concentration and a higher risk of adverse effects.
- The highest dose of metoprolol that patients can tolerate may be lower in CYP2D6 poor metabolizers compared to those that are non-poor CYP2D6 metabolizers.
- Current evidence is insufficient to support routine clinical testing or therapeutic adjustments for other genes affecting beta-blocker pharmacodynamics, such as *ADRB1*, *ADRB2*, *ADRA2C*, and *GRK5*.
- Future research should consider the combined effects of multiple genetic variants (e.g., polygenic risk scores) rather than focusing solely on single-gene associations.

Pharmacogenetics of Beta-Blockers

Beta-blockers are a widely used class of medications to treat various cardiovascular (e.g., angina, heart failure) and non-cardiovascular (e.g., anxiety disorder, glaucoma) conditions. Genetic variations affecting beta-blocker pharmacokinetic and pharmacodynamic properties contribute to inter-individual variability in beta-blocker treatment responses.

Most recently, the Clinical Pharmacogenetics Implementation Consortium (CPIC) published a new guideline for genes *CYP2D6, ADRB1*, *ADRB2*, *ADRA2C*, *GRK4* and *GRK5*. They included detailed evidence of each gene, providing valuable insights for clinicians to personalize beta-blocker therapy based on genetic makeup. The U.S. FDA also includes some information about beta-blocker pharmacogenetics on two of their websites,[1, 2] but the information is not consistent, and thus health systems that are implementing pharmacogenetic testing are prioritizing CPIC guidelines.[3]

In summary, if it is known that the patient is a CYP2D6 poor metabolizer, then CPIC recommends that pharmacogenetics should be considered when prescribing metoprolol. CYP2D6 poor metabolizers have significantly decreased metabolism of metoprolol, leading to increased drug concentration, and also higher risk of adverse effects. Notably, however, current evidence is insufficient to support therapeutic adjustments for CYP2D6 and other beta-blockers, and for other pharmacodynamic genes. No clinical recommendation has been made for them by CPIC.[4]

This article summarizes pharmacogenetic factors affecting beta-blocker metabolism and response, focusing on the pharmacodynamic genes *ADRB1*, *ADRB2*, *ADRA2C*, *GRK5*, and the pharmacokinetic gene *CYP2D6*, providing insights for clinicians.

ADRB1 variants

The *ADRB1* gene encodes the beta-1 adrenergic receptor, crucial for the heart's response to sympathetic nervous stimulation. Two common variants in this gene, rs1801252 (c.145A>G; p. Ser49Gly); hereafter referred to as "Ser49Gly"]. and rs1801253 (c.1165C>G; p. Arg389Gly; hereafter referred to as "Arg389Gly"), have been extensively studied and significantly affect beta-1 adrenergic receptor function.[5]. Some found with the Arg389Arg genotype, patients had a better response to beta-blockers including significant improvement in left ventricular ejection fraction (LVEF), increasing from 23±5% to 29±10% compared to those with the Gly389 allele in a prospective study; a substantially greater improvement in LVEF (8.7 ± 1.1%) compared to Gly389 homozygous patients (0.93 ± 1.7%) in a study involving 224 heart failure patients treated with

Abbreviations used in this paper. CPIC , Clinical Pharmacogenetics Implementation Consortium;
poor metabolizers (PM), intermediate metabolizers (IM), extensive metabolizers (EM), and ultrarapid metabolizers (UM). left ventricular ejection fraction (LVEF),

ISSN 2997-2876 (online)
ISSN 2997-2868 (print)
DOI: https://doi.org/10.69734/hpaezm84
Website: www.SMART-MD.org

carvedilol.[6, 7] However, other studies found no such association.[8, 9]

ADRB2 variants

The *ADRB2* gene encodes the beta-2 adrenergic receptor, which regulates vascular and bronchial smooth muscle tone. Key genetic variants include rs1042713 (c. 46A>G; p. Arg16Gly; hereafter referred to as "Arg16Gly")and rs1042714 (c.79C>G; p.Gln27Glu; hereafter referred to as "Gln27Glu") and also significantly affect receptor function(10). However, mixed results regarding their impact on LVEF response to beta-blockers were reported. Gln27 homozygotes have been associated with lower response rates, defined as LVEF improvement by 10%, compared to Glu27 carriers, though this finding is not consistently replicated.[11] The association between *ADRB2* variants and clinical outcomes in response to beta-blockers has been inconsistent, reflecting no clear clinical significance.[11]

ADRA2C variants

The *ADRA2C* gene encodes the α2c-adrenergic receptor, which regulates presynaptic norepinephrine release.[12] An insertion/deletion polymorphism in this gene, in combination with the *ADRB1* Arg389Gly polymorphism, has been shown to increase the risk of heart failure in African Americans.[13] However, larger studies are needed to confirm these findings.

GRK5:

G protein–coupled receptor kinases (GRKs) are involved in the desensitization of adrenergic receptors. A nonsynonymous polymorphism in rs17098707 (c. 122T>A; p. Leu41Gln; hereafter referred to as "Leu41Gln"), common in African Americans has been identified, with minor allele frequency of 32.6% in African Americans.[14] GRK5-Leu41 variant has been found to have a protective effect in heart failure patients. In human studies, the presence of the variant was associated with decreased mortality in African Americans with heart failure or cardiac ischemia. A prospective study of 375 African American subjects with heart failure also demonstrated protective effects against death. Carriers of one allele had a 72% lower risk of death (RR = 0.28), while carriers of both alleles had a 92% lower risk of death (RR = 0.08).[15] But still, continued research and validation are essential to fully integrate these findings into clinical practice.

Pharmacokinetic genes

Pharmacokinetic pathways among the different beta-blockers vary, with a variety of metabolic enzymes and contributions by the liver or kidneys (**Table 1**). For beta-blockers metabolized by CYP450 enzymes in the liver, CYP2D6 is particularly important. Metoprolol, for instance, is highly dependent on CYP2D6, with 60–70% of its metabolism occurring via this pathway.[16] Genetic variants of CYP2D6 result in different metabolizer phenotypes: poor metabolizers (PM), intermediate metabolizers (IM), extensive metabolizers (EM), and ultrarapid metabolizers (UM). CYP2D6 PMs have significantly decreased metabolism of metoprolol, leading to markedly increased drug concentrations (5-fold difference in area-under the plasma concentration-time curve) and potential reductions in heart rate (mean difference = 3.16 bpm in CYP2D6 PM vs. non-CYP2D6 PM) and blood pressure with average decreases both greater than non-CYP2D6 PM by about 3 mmHg.[4, 17-19] Approximately 6.5% of patients with European ancestry and 2.3% with African ancestry are CYP2D6 PMs. The CPIC recommends initiating therapy with the lowest recommended starting dose for CYP2D6 PMs and carefully titrating the dose upward while monitoring closely for bradycardia.[4] or using an alternative beta-blocker than metoprolol.

There have been a few pharmacogenetic studies of the effects of variants in other pharmacokinetic genes and on beta-blockers other than metoprolol, but the CPIC author group did not conclude that there was sufficient evidence to justify any changes to beta-blocker therapy at this time.

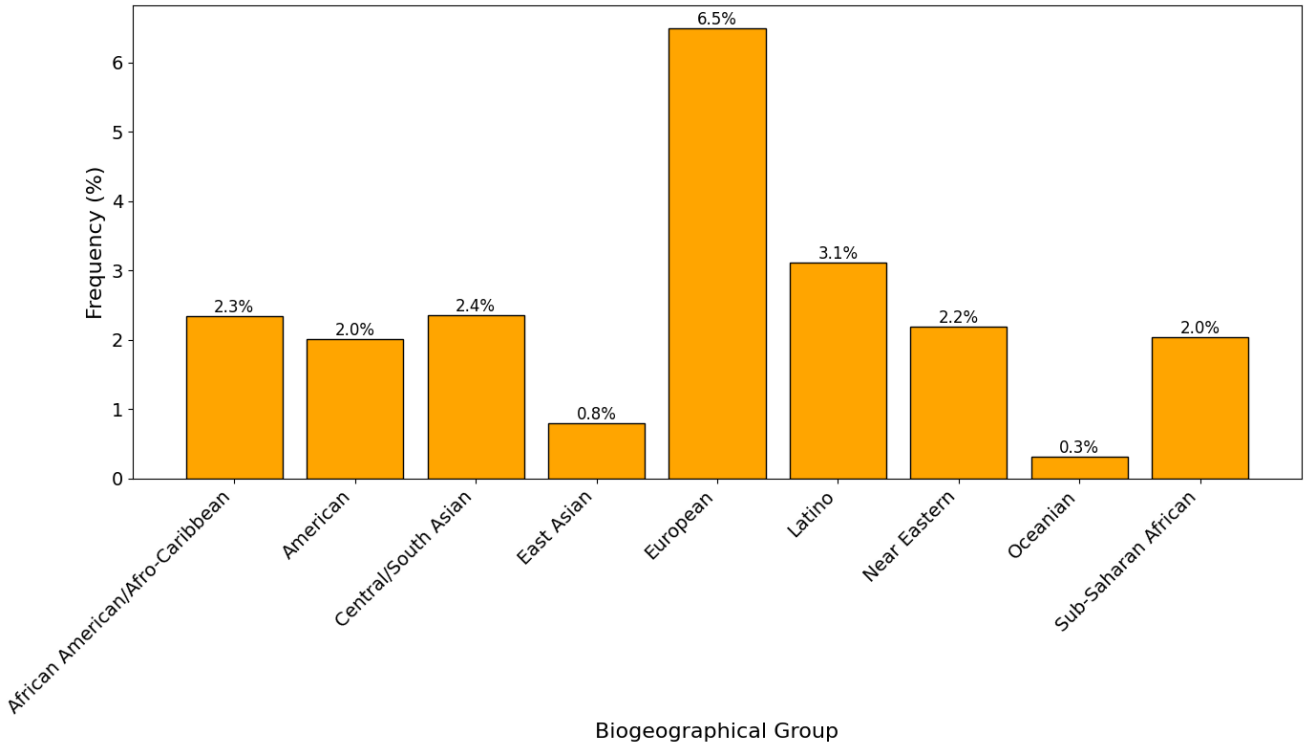
Current Issues to Consider

- Population frequencies of CYP2D6 PMs in different biogeographical groups is shown in the **Figure 1**.[20] The frequencies vary significantly across ancestries, e.g. 6.5% in Europeans followed by Latinos at 3.1%. These variations highlight the need for personalized medicine, particularly for medications metabolized by CYP2D6, to ensure efficacy and minimize adverse effects across different populations.
- Phenoconversion is recognized as an important factor in CYP2D6 metabolism. Even though pharmacogenomic tests may identify a patient as a normal CYP2D6 metabolizer, drug-drug interactions can convert the metabolism status to a PM. In clinical settings where CYP2D6 genotypes may be used, approximately 20%-30% of individuals are also taking enzyme inhibitors, resulting in phenoconversion.[21]
- Most studies to date have assessed the effects of individual genetic variants on beta-blocker response. For the pharmacodynamic genes described above, the evidence has generally been weak when examined individually. By considering the cumulative effects of multiple genetic variants, polygenic risk scores may offer better predictive power for beta-blocker response than single-gene approaches.[22, 23]

Table 1. Metabolic pathways of beta-blockers.

Beta-blocker	Primary metabolic pathway	Key metabolizing enzyme	PGx considerations
Atenolol	Renal	/	/
Bisoprolol	Hepatic	CYP3A4, CYP2D6 (minor)	**CYP3A4**: Variants may lead to increased plasma concentrations and risk of adverse effects, but the influence has not been demonstrated(24). **CYP2D6**: Poor metabolizers may have slightly higher drug levels, but as it's a minor pathway, the impact is limited(25).
Carvedilol	Hepatic	CYP2D6, CYP2C9	**CYP2D6**: Poor metabolizers may have increased plasma levels, leading to enhanced efficacy, potentially lower blood pressure and increased toxicity(26). **CYP2C9**: Variants may alter metabolism, affecting drug levels and response. Dose adjustment could be considered(27).
Labetalol	Hepatic	UGT, CYP2D6	**UGT**: The major metabolic pathway involves the enzyme UGT, which facilitate the glucuronidation process. Variants may also influence metabolism, affecting drug levels(28). **CYP2D6**: CYP2D6 is involved in the minor metabolic pathways of labetalol, influencing its metabolism to a lesser extent(16).
Metoprolol	Hepatic	CYP2D6	**CYP2D6**: Poor metabolizers have significantly higher plasma concentrations, leading to increased efficacy but also higher risk of adverse effects like bradycardia and hypotension(18, 29).
Nebivolol	Hepatic	CYP2D6	**CYP2D6**: Poor metabolizers have increased plasma concentrations, potentially leading to increased toxicity(30).
Propranolol	Hepatic	CYP2D6, CYP1A2	**CYP2D6**: Individuals with different CYP2D6 genotypes may metabolize propranolol at different rates. It could potentially affect plasma concentrations, therapeutic effects and the risk of adverse reactions(31). **CYP1A2**: Variants may alter metabolism(27).
Sotalol	Renal	/	/

Figure 1. Frequencies of CYP2D6 PMs in Biogeographical Groups



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Contributions:

Benyu Yang conducted the literature search, compiled the relevant studies, and drafting the manuscript. Dr. Jasmine Luzum supervised the project, provided guidance and critically revised the manuscript. Both authors read and approved the final manuscript.

Conflicts of interest:

The authors declare no conflict of interest.

Funding

N/A