Pharmacogenetics of β-blockers: CPIC Proposal for *ADRB1*, *GRK5* and *CYP2D6*

Cameron D. Thomas, Pharm.D.
Postdoctoral Fellow in Genomic Medicine

Julie A. Johnson, Pharm.D.
Dean and Distinguished Professor
Objectives

Describe pharmacogenetic factors affecting β-blocker metabolism and response

Provide insight into the robustness of the genetic associations

Discuss clinical interpretations for potential translation of variants influencing β-blocker response into practice
β-blockers

• Among most commonly used of all drugs
  • Common indications: Heart failure, ischemic heart disease, hypertension
  • Four beta-blockers in top 50 prescribed drugs in 2020 (not including combo products)
    • Metoprolol #6 – 68M
    • Carvedilol #29 – 23M
    • Atenolol #36 – 20M
    • Propranolol #41 – 18M

• Modulate sympathetic nervous system activation to produce:
  • ↓ chronotropic
  • ↓ inotropic
  • ↓ dromotropic

• Variation within genes that affect β-blocker pharmacokinetic and pharmacodynamic properties contribute to wide inter-patient variability in response

Pharmacodynamic Pathways of β1 and β2 Receptors and Resulting cAMP Generation

- **β1-AR**
  - ADRB1 Ser49Gly: increases agonist-promoted downregulation; ↓cAMP
  - ADRB1 Arg389Gly: decreases Gαs coupling; ↓cAMP
  - ADRB2 Arg16Gly: increases agonist-promoted downregulation; ↓cAMP
  - ADRB2 Gln27Glu: increases agonist-promoted responsiveness; ↑cAMP
  - GRK5 Gln41Leu: increases β-receptor desensitization; ↓cAMP

- **β2-AR**

### Phenotype and Variant Allele Frequencies

<table>
<thead>
<tr>
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<th>EUROPEAN</th>
<th>AFRICAN</th>
<th>ASIAN</th>
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<tr>
<td><strong>PHENOTYPE FREQUENCIES</strong></td>
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</tr>
<tr>
<td>CYP2D6</td>
<td></td>
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<tr>
<td>PM</td>
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<td>IM</td>
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<tr>
<td>NM</td>
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<td>44</td>
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<tr>
<td>UM</td>
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</table>

|                  |          |         |       |
| **VARIANT ALLELE FREQUENCIES** |          |         |       |
| ADRB1             |          |         |       |
| rs1801252 (Gly49) | 13       | 16      | 5     |
| rs1801253 (Gly389)| 31       | 37      | 38    |
| GRK5              |          |         |       |
| rs2230345 (Leu41) | 2        | 16      | 0     |

IM: intermediate metabolizer; NM: normal metabolizer; PM: poor metabolizer; UM: ultrarapid metabolizer. CYP2D6 phenotype frequencies from https://cpicpgx.org/. ADRB1 and GRK5 variant allele frequencies from dbGaP, with the resulting encoded variant allele amino acid in parentheses.
ADRB1
β1-adrenergic receptors are modulated by desensitization and downregulation

Major allele at both positions is predicted to be associated with greater agonist-mediated response
**ADRB1** is a determinant of antihypertensive response to β-blockers

Representative examples:

![Graph showing BP response to metoprolol by β₁-adrenergic receptor (β₁AR) haplotype pair (diplotype). Data are presented as mean reduction and SE. SR, Ser49Arg389 haplotype; SG, Ser49Gly389 haplotype; GR, Gly49Arg389 haplotype. P = .006, between groups for change in DBP from baseline to treatment.](image)

**Fig 2.** BP response to metoprolol by β₁-adrenergic receptor (β₁AR) haplotype pair (diplotype). Data are presented as mean reduction and SE. SR, Ser49Arg389 haplotype; SG, Ser49Gly389 haplotype; GR, Gly49Arg389 haplotype. P = .006, between groups for change in DBP from baseline to treatment.

![Graph showing blood pressure response to metoprolol monotherapy in patients with hypertension stratified according to β₁-adrenergic receptor Gly389Arg genotypes (Arg389Arg, n = 33; Gly389Arg, n = 19; Gly389Gly, n = 9). Data are presented as mean percentage decrease with SD. SBP, Systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure.](image)

**Fig 2.** Blood pressure response to metoprolol monotherapy in patients with hypertension stratified according to β₁-adrenergic receptor Gly389Arg genotypes (Arg389Arg, n = 33; Gly389Arg, n = 19; Gly389Gly, n = 9). Data are presented as mean percentage decrease with SD. SBP, Systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure.
ADRB1 Ser49-Arg389 carriers associated with increased risk for MACE (death, MI, stroke)

Figure 1  Associations of the ADRB1 Ser49-Arg389 haplotype with primary and secondary outcomes. Hazard ratios are based on reduced model adjusted for age, sex, and race/ethnicity. *Crude incidence per 1,000 patient years. MI, myocardial infarction.

<table>
<thead>
<tr>
<th>Event</th>
<th>No. copies Ser49-Arg389</th>
<th>Incidence*</th>
<th>Hazard ratio (95% Confidence interval)</th>
<th>P</th>
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<td>1.59 (1.12–2.27)</td>
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<td>15.6</td>
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<td>2</td>
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<td>1.09 (0.55–2.15)</td>
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<tr>
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<td>5.1</td>
<td>1.00 (reference)</td>
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<tr>
<td></td>
<td>1</td>
<td>5.1</td>
<td>0.97 (0.56–1.69)</td>
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<tr>
<td></td>
<td>2</td>
<td>5.3</td>
<td>0.99 (0.54–1.82)</td>
<td>0.97</td>
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</tbody>
</table>

Ser49-Arg389 carriers vs. non-carriers: HR, 1.51 (95% CI, 1.07-2.12); p=0.02

**ADRB1** Ser49-Arg389 is favorable response allele for β-blocker therapy in ischemic heart disease

**Figure 2** All-cause mortality and mean on-treatment blood pressure by *ADRB1* Ser49-Arg389 haplotype and atenolol/verapamil sustained-release (SR) therapy. HR, hazard ratio; 95% CI, 95% confidence interval; S49-R389, Ser49-Arg389 haplotype; AT, atenolol; VE, verapamil SR; SBP, systolic blood pressure; DBP, diastolic blood pressure.

**ADRB1** Arg389 is the favorable β-blocker response allele in heart failure

- BEST: NYHA class III-IV HFrEF
- The risks for death and hospitalization were not significantly different between bucindolol and placebo arms among Gly389 carriers
- Conclusion: benefits of bucindolol in the studied HF population were confined to those with the Arg389Arg genotype

Gly-389 carriers: HR, 0.87 (95% CI, 0.67–1.11); p=0.25
Arg389Arg: HR, 0.66 (95% CI, 0.50–0.88); p=0.004

ADRB1 Arg389Gly associated with atenolol response in children and young adults with Marfan syndrome

• Pharmacogenetic substudy of a randomized trial of atenolol vs losartan in 250 participants with Marfan syndrome

Arg389Arg: greater improvements in aortic-root z-score for atenolol-treated compared with losartan-treated participants

Positive associations identified between $ADRB1$ and hemodynamic and clinical outcomes

**Hemodynamics:** strongest data exist for an association between $ADRB1$ and DBP response to $\beta$-blockers

$\beta$-blocker therapy may offset the risk for MACE observed with the $ADRB1$ Ser49-Arg389 haplotype

Studies support greater benefits from $\beta$-blocker therapy among HFrEF patients with the Arg389Arg genotype compared to Gly389 carriers.

Associations identified between $ADRB1$ and: metoprolol, atenolol, bucindolol, carvedilol, thus implying a class effect
GRK5
G protein-coupled receptor kinases (GRKs) desensitize β-receptors

GRK5 Gln41Leu: increases β-receptor desensitization; ↓cAMP

Variant mimics β-blocker therapy; “genetic β-blockade”

β-blocker therapy mimics the survival advantage of GRK5 Leu41

HFrEF (LVEF < 40%; NYHA class II-IV); all participants of African ancestry

Comparison of GRK5 Gln41Gln subjects with and without β-blocker use.
Comparison of GRK5 Leu41 carriers with and without β-blocker use.
Comparison of GRK5 Gln41Gln subjects treated with β-blockers to GRK5 Leu41 carrier subjects without β-blocker use.

GRK5 Leu41 associated with decreased odds of adverse cardiovascular outcomes

- Hypertensive cohort with CAD
- Outcome: death, MI, or stroke
- Leu41 carriers vs. Gln41Gln; p=0.022
- Generalizability of protective role of Leu41 allele
  - Heart failure
  - Hypertension + coronary artery disease
- GRK5 Leu41 does not influence BP response to antihypertensives

CYP2D6
There is evidence CYP2D6 affects the pharmacokinetics of CYP2D6-dependent β-blockers

- **CYP2D6-dependent**
  - Metoprolol
  - Carvedilol
  - Propranolol
  - Nebivolol
  - Timolol
  - Labetalol

- **CYP2D6 independent**
  - Acebutolol
  - Atenolol
  - Betaxolol
  - Bisoprolol
  - Nadolol
CYP2D6 phenotype affects metoprolol pharmacokinetics and change in HR

Table 3  Changes from baseline in HR, SBP, and DBP in PMs, IMs, EMs, and UMs of CYP2D6 treated with metoprolol

<table>
<thead>
<tr>
<th>Parameter</th>
<th>PM</th>
<th>IM</th>
<th>EM</th>
<th>UM</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change in HR (beats/min)</td>
<td>$-16.6 \pm 6.9$</td>
<td>$-18.6 \pm 5.1$</td>
<td>$-11.4 \pm 6.6$</td>
<td>$-11.2 \pm 8.2$</td>
<td>0.0001</td>
</tr>
<tr>
<td>Change in SBP (mm Hg)</td>
<td>$-9.4 \pm 9.0$</td>
<td>$-6.5 \pm 11.1$</td>
<td>$-7.1 \pm 9.8$</td>
<td>$-9.4 \pm 5.1$</td>
<td>0.91</td>
</tr>
<tr>
<td>Change in DBP (mm Hg)</td>
<td>$-9.3 \pm 5.1$</td>
<td>$-8.3 \pm 7.5$</td>
<td>$-7.0 \pm 6.6$</td>
<td>$-7.5 \pm 4.8$</td>
<td>0.37</td>
</tr>
</tbody>
</table>

CYP2D6, cytochrome P450 2D6; DBP, diastolic blood pressure; EM, extensive metabolizer; HR, heart rate; IM, intermediate metabolizer; PM, poor metabolizer; SBP, systolic blood pressure; UM, ultrarapid metabolizer.
There is limited clinical utility for CYP2D6 and β-blocker pharmacotherapy

- CYP2D6 associated with HR response but no other response phenotypes, in part explained by usual upward titration of dose and HR being used to define target dose
- Impact of CYP2D6 on HR response is evident at lower doses while patient is still on the linear portion of the dose-response curve
- CYP2D6 not associated with:
  - BP responses
  - Adverse reactions (e.g., headache, dizziness, fatigue, dyspnea)
- PM/IM may achieve goal HR response at a lower than expected dose
- Possible clinical utility if CYP2D6 available in the electronic health record to better understand likely dose requirements for beta-blockade
Summary: *ADRB1*, *GRK5*, and *CYP2D6*

- *ADRB1* Arg389Arg, or Ser49-Arg389, associated with improved treatment outcomes with β-blocker therapy

- *GRK5*: Gln41Gln associated with ↑ risk of adverse cardiovascular outcomes, which is offset by β-blocker therapy

- *CYP2D6*
  - If available to the clinician, may provide clinical utility given PM/IM patients may achieve the target HR response at a lower doses
  - Ordering *CYP2D6* test to guide β-blocker therapy not justified
Recommending a CPIC guideline for β-blockers: Genes likely to be included in guideline are *ADRB1*, *GRK5*, and *CYP2D6*, though literature review would need to include other genes, including *ADRB2*, *GRK4* and possibly others.

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