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PharmGKB Submission Update: IX. ADRB1 Gene Summary

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Gene HGNC Name: ADRB1

Gene Common Name: β_1 Adrenergic Receptor (β_1AR)

Introductory Information: The β_1-adrenergic receptor (β_1AR) is a G-protein-coupled receptor that was first characterized by its pharmacological specificity. The gene for this receptor (ADRB1) was cloned in 1987 from a placental cDNA library and subsequently mapped to chromosome 10q24-q26 (10q25.3). The intronless gene consists of 1,714 bp and codes for a 51.3 kDa protein consisting of 477 amino acid residues. β_1ARs are the predominant βAR subtype expressed in cardiac tissue, where they mediate the heart rate and contractility. β_1AR expression in renal, vascular, and adipose tissues is also physiologically important.

The A145G (Ser49Gly) and C1165G (Arg389Gly) variants are the most common and well studied in the β_1AR gene. The variant at codon 49 results in increased agonist-promoted desensitization, whereas the codon 389 polymorphism alters G-protein coupling and adenylyl cyclase activity. The impact of these polymorphisms on cardiovascular disease and drug response has been the subject of numerous investigations, which were recently reviewed in detail. Three other validated SNPs are currently documented in dbSNP, two of which have been confirmed by SeattleSNPs. Several other SNPs have been reported but not validated. The functional consequences of these other polymorphisms are unknown.

Key PubMed IDs: 2825170, 2154750, 11102996, 10794544, 16120061

Important Variant Information for ADRB1: 49 Ser>Gly (rs1801252)

Genomic Variant and GenBank ID: 34552562 A>G on NT_030059

MRNA Variant and GenBank ID: 145 A>G on AF169007

Protein Variant and GenBank ID: 49 SerGly on NP_000675

dbSNP RS Number: rs1801252

Goldenpath Position: chr10:115794026

Variant Summary: The Ser49Gly polymorphism is located in the extracellular portion of the protein near the amino-terminus. In vitro site-directed mutagenesis studies are not consistent with regard to the effect of this variant on adenylyl cyclase activity or cAMP accumulation in the presence of agonists or antagonists. Greater agonist-promoted downregulation in cells expressing the Gly49 allele is well characterized. Cardiac inotropy and lusitropy, however, did not differ by codon 49 genotype in atrial isolates treated with norepinephrine ex vivo, with or without consideration given to previous β-blocker use by the donor patient.

The estimated minor allele frequencies/heterozygosity of Ser49Gly (A145G) among different racial/ethnic groups based on the literature to date are as follows: white 12–16%/21–28%, black 23–28%/36%, Hispanic 20–21%/33%, and Asian 14%/23%.

This variant is commonly referred to as 145 A>G on the mRNA sequence. This positional numbering is relative to the start of the coding sequence.

Hypertension: The Ser49Gly polymorphism does not appear to be associated with hypertension, although the Gly49 genotype was associated with lower resting heart rate in hypertensive patients, independent of ß-blocker therapy. In a small study, blood pressure responses to metoprolol did not differ significantly as a function of the Ser49Gly polymorphism alone. When considered in a multivariate analysis with the codon 389 genotype, however, Ser49 homozygosity predicted greater blood pressure reduction. Haplotype analysis of the variants at codons 49 and 389 in the same study revealed that those with the Gly49Arg389/Ser49Gly389 diplotype were virtually unresponsive to metoprolol, whereas the greatest response (almost 15 mmHg reduction in systolic blood pressure) was observed in subjects with the Ser49Arg389/Ser49Arg389 diplotype (other diplotypes were intermediate). The negative chronotropic response

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to metoprolol was not influenced by the Gly49 variant in untreated hypertensive patients after adjustment for plasma S-metoprolol concentrations.

Coronary Artery Disease: The Gly49 allele was nonsignificantly associated with lower resting heart rate in patients undergoing cardiac stress testing, but did not influence exercise-induced changes in hemodynamic parameters. The Ser49Gly polymorphism did not alter the risk of mortality in patients followed for three years after myocardial infarction, regardless of β-blockade.

Heart Failure: The codon 49 polymorphism does not appear to be a risk factor for developing heart failure. The Ser49 allele was associated with a relatively greater need for adjustment of concomitant heart failure medications during the initial titration phase of metoprolol succinate, but variation at this locus did not influence drug tolerability, the dose of metoprolol achieved, changes in the 6-minute walk, or quality of life. Left ventricular end diastolic diameter reduction was significantly greater in Gly49 carriers at similar heart rates and doses of metoprolol; however, no influence of the polymorphism on the change in ejection fraction following the initiation of a β-blocker (metoprolol, carvedilol or bisoprolol) has been observed. The Ser49 allele was associated with poorer clinical outcomes in heart failure patients. Hospitalization or death rates at five years were significantly lower for patients carrying the variant allele, particularly those treated with β-blockers, when compared to patients with the wild-type allele not receiving β-blockers, who had the least favorable prognosis. Consistent with this, variant carriers that were not treated with β-blockers had a similar prognosis as Ser49 homozygotes that did receive these drugs. The variant allele was also associated with improved survival at five years in idiopathic dilated cardiomyopathy patients receiving lower β-blocker doses; at higher doses the gene effect disappeared, suggesting that patients with the wild-type allele may require higher doses to derive any survival benefit. Ser49 homozygotes also tended to require higher β-blocker doses than variant carriers to achieve similar heart rates.

Metabolic: The Gly49 allele was associated with greater increases in body mass in women 15 years postpartum. Conversely, the variant at codon 49 was not associated with body mass index, obesity, waist-to-hip ratio, or waist circumference.

Miscellaneous: The codon 49 polymorphism was not associated with acquired long QT syndrome or Torsades de Pointes in patients treated with QT-prolonging drugs. Variation at codon 49 was associated with low extraversion.

Drugs/Substrates: Beta adrenergic antagonists, Metoprolol, Carvedilol, Bisoprolol, Xenobiotics

Important Variant Information for ADRB1: 389 Arg>Gly (rs1801253)

Genomic Variant and GenBank ID: 34553582 C>G on NT_030059

MRNA Variant and GenBank ID: 165 C>G on AF169007

Protein Variant and GenBank ID: 389 Arg>Gly on NP_000675

dbSNP RS Number: rs1801253

Goldenpath Position: chr10:115795046

Variant Summary: The Arg389Gly polymorphism is located in the cytoplasmic tail in the G-protein coupling domain. Site-directed mutagenesis studies of the codon 389 variant indicate that basal and agonist-simulated adenylyl cyclase activity is higher with the Arg389 allele as a result of enhanced coupling to $G_{\alpha s}$; a higher level of activity relative to the Gly389 allele is maintained even in the face of agonist-promoted desensitization. A later study did not confirm the differential effect of this polymorphism on basal adenylyl cyclase activity. Cardiac inotropy and lusitropy also did not differ consistently by codon 389 genotype in atrial isolates treated with norepinephrine ex vivo, with or without consideration given to previous β-blocker use by the donor patient.

The estimated minor allele frequencies/heterozygosity of Arg389Gly (C1165G) among different racial/ ethnic groups, based on the literature to date, are as follows: white 24–34%/35–42%, black 39–46%/44–53%, Hispanic 31–33%/41–42%, and Asian 20–30%/30–39%.

This variant is commonly referred to as 1165 C>G on the mRNA sequence. This positional numbering is relative to the start of the coding sequence.

Hypertension: The Arg389 allele was associated with hypertension in case-control studies, and it was observed in a discordant sib-pair study that diastolic blood pressures and heart rates were significantly higher among Arg389 homozygotes. The association with resting heart rate was not reproduced in treated or untreated hypertensives. Three studies demonstrated a significant effect of this polymorphism on the blood pressure response to β-blockade; one study could not confirm this effect. Blood pressure responses to metoprolol and atenolol were significantly greater among Arg 389 homozygotes when compared to variant carriers, with a three-fold difference described in one study. Haplotype analysis of the variants at codons 49 and 389 revealed that virtually no response was apparent in those with the Gly49Arg389/Ser49-Gly389 diplotype, whereas the greatest response (almost 15 mmHg reduction in systolic blood pressure) was observed in subjects with the Ser49Arg389/Ser49Arg389 diplotype (other diplotypes were intermediate). The negative chronotropic response to metoprolol was not influenced by the Gly389 variant in untreated hypertensive patients after adjustment for plasma S-metoprolol concentrations. The extent to which β-blockers blunt exercise-induced changes in hemodynamic parameters may also differ based on genotype. The influence of this polymorphism on the antihypertensive response to hydrochlorothiazide has also been studied with no demonstrable effect, but increases in total cholesterol subsequent to administration of hy-

drochlorothiazide were predicted by heterozygosity at codon 389 (relative to Arg389 homozygotes).

Coronary Artery Disease: Resting heart rate and blood pressure appeared to be higher in Arg389 carriers undergoing stress testing, while the change in systolic blood pressure during exercise was greater for Gly389 carriers. Carriers of the variant were also less likely to have extrasystoles compared to noncarriers during stress testing. A case-control study of patients with dyslipidemia did not identify any significant genotype effect for cardiovascular events at five years. The codon 389 polymorphism did not alter the risk of mortality in patients followed for three years after myocardial infarction, regardless of β-blocker therapy.

Heart Failure: The Arg389 genotype alone was not associated with heart failure, although when considered in the presence of another polymorphism in the α_{2C} adrenergic receptor (ADRA2C), a multiplicative association was identified. This effect was ascertained reliably only in black patients due to the limited number of white patients that were polymorphic at both loci. The Gly389 allele was associated with lower resting systolic blood pressure and diminished exercise capacity. In patients initiated on carvedilol or bisoprolol, neither heart rate or systolic blood pressure responses, nor improvement in left ventricular ejection fraction was influenced by the Arg389Gly polymorphism. This is in contrast to other studies demonstrating significantly greater improvements in left ventricular ejection fraction in patients treated with carvedilol that were homozygous for the Arg389 allele compared with variant homozygotes. In addition to favorable changes in ejection fraction, left ventricular end systolic and diastolic diameters improved to a greater extent among Arg389 homozygotes treated with metoprolol succinate as compared to variant carriers, in whom no change or an increase was observed. The codon 389 genotype did not influence the tolerability of metoprolol succinate during the initial titration phase, though patients with the Arg389 genotype experienced a higher rate of decompensation, as indicated by the need for adjustment of concomitant heart failure medications. β-blocker induced changes in the 6-minute walk, quality of life, or the dose of metoprolol achieved did not differ between genotypes. Polymorphism at codon 389 did not appear to influence baseline hemodynamic parameters or clinical outcomes (death or hospitalization) in heart failure patients treated with extended-release metoprolol. However, a significant survival advantage was observed in heart failure patients that were homozygous for Arg389 receiving bucindolol. The mortality and hospitalization rates of these patients were significantly better than Gly389 carriers receiving bucindolol, and all patients receiving placebo. This polymorphism was not associated with idiopathic dilated cardiomyopathy, disease severity, or the development of heart failure. The effect of the Arg389 variant on five-year mortality in idiopathic dilated cardiomyopathy patients was not significant, however, a modest but significant increase in mortality risk was observed in Gly389 carriers receiving lower dose β-blocker therapy. A lower odds of ventricular tachycardia was observed in variant carriers with idiopathic dilated cardiomyopathy.

Miscellaneous Cardiovascular: No difference in cardiovascular response to exercise between codon 389 genotypes in healthy subjects has been described, with or without β-blocker administration. 389 homozygotes with renal failure were found to have significantly higher left ventricular mass. Plasma renin activity, heart rate, and contractility increased in response to dobutamine infusion to a significantly greater extent in Arg389 homozygotes than Gly389 homozygotes; the attenuation of these effects by bisoprolol was significantly greater among Arg389 homozygotes, while systolic and diastolic blood pressure responses were not significantly different. Another study demonstrated that the inotropic actions of dobutamine (fractional shortening) were significantly enhanced in healthy individuals not carrying the Gly389 polymorphism, as was the systolic blood pressure response, while no difference in heart rate responses was observed. The codon 389 polymorphism was not associated with acquired long QT syndrome or Torsades de Pointes in patients treated with QT-prolonging drugs. In patients with obstructive sleep apnea, the polymorphism was not associated with any hemodynamic variable at baseline, however, after initiation of continuous positive airway pressure therapy, the heart rate decreased to a significantly greater extent in patients with Arg389 genotype compared with the other genotypes.

Metabolic: The codon 389 variant was not associated with body mass index (BMI), longitudinal changes in body mass index, obesity, waist-to-hip ratio, or waist circumference. An earlier study suggested that this variant might be associated with weight and fat mass. Polymorphisms in ADRB2 and ADRB3 may interact with the codon 389 variant as described in one study evaluating longitudinal changes in body mass index. No difference in allele frequencies between lean and obese children has been documented. The codon 389 genotype did not affect dobutamine- stimulated lipolysis.

Neurologic/Psychiatric: Susceptibility to Alzheimer's disease was greater in Arg389 homozygotes that were also variant homozygotes at position 825 of GNB3. Variation at codon 389 was not associated with extraverted behavior, unlike the codon 49 variant. Antidepressant responses in the context of the codon 389 polymorphism suggested less improvement in Gly389 carriers, although this finding was not significant after correction for multiple comparisons.

Drugs/Substrates: Beta adrenergic antagonists, tremolo, metoprolol, hydrochlorothiazide, carvedilol, bisoprolol, xenobiotics, beta adrenergic agonists, dobutamine, antidepressants.