

Beta-2-Adrenergic Receptor (ADRB2) Haplotyping

TO IDENTIFY ADRB2 GENE HAPLOTYPES AFFECTING ASTHMA SEVERITY AND RESPONSE TO BETA-AGONISTS

Disease Overview

- *ADRB2* encodes the beta-2 adrenergic receptor that is expressed on cells of numerous tissues, including respiratory, vascular, immune, and fat.
- By binding endogenous catecholamine, the receptor plays an essential role in the regulation of respiratory, cardiac, and metabolic functions.
- *ADRB2* serves as the target for beta-agonist drugs.
- Polymorphisms in the receptor have been associated with asthma severity and individual response to beta agonists.
- Asthma, the most common inflammatory disease of the airways, is known to have a genetic and an environmental component.
- Severe asthma is often nocturnal and persists after puberty.

Epidemiology

- Asthma is the most common chronic childhood disease.
- Approximately 30 million Americans are affected by asthma.
- Asthma is more prevalent in African-Americans and those of lower income.

Genetics

- Two *ADRB2* polymorphisms, c.46A>G (p.R16G) and c.79C>G (p.Q27E), result in three common haplotypes: Arg16-Gln27, Gly16-Gln27, and Gly16-Glu27.
- The frequency of the three haplotypes varies depending on ethnicity.
- The two polymorphisms and resulting haplotypes are associated with differences in receptor expression and regulatory response to endogenous catecholamine and beta-agonists.
- Receptors with Gly16 are sensitive to down-regulation by agonists; thus, the pharmacodynamic response to beta-agonists is predicted to wane over time in patients with this variant.

Indications for Ordering

- To predict asthma severity.
- To predict the long-term effect of beta-agonist therapy.

Contraindications

To predict the clinical severity of disease or effect of beta-agonist therapy on congestive heart failure, hypertension, obesity, and rheumatoid arthritis.

Research Testing Only

Contact ARUP Laboratories at (800) 242-2787, extension 2546, to arrange research collaboration for:

- Correlating *ADRB2* haplotypes with asthma, congestive heart failure, hypertension, or obesity.
- Determining the *ADRB2* pharmacogenetics response to beta-blockers.

Interpretation

- The Gly16 - Gln27 haplotype has been associated with nocturnal asthma and asthma that persists into adulthood. Gly16 also imparts an accelerated agonist-promoted down-regulation of the *ADRB2* receptor.
- The Arg16 - Gln27 haplotype may be associated with decreased lung function after long-term use of beta-agonist therapy, but Arg16 is not associated with nocturnal asthma.
- In the Gly16 - Glu27 haplotype, Gly16 imparts an accelerated agonist-promoted down-regulation of the *ADRB2* receptor.

Methodology

- Polymerase chain reaction (PCR) followed by melting-curve analysis, simultaneously interrogating the *ADRB2* polymorphisms c.46A>G (p.R16G) and c.79C>G (p.Q27E).
- Analytic sensitivity and specificity is 99 percent.

Limitations

- Only the *ADRB2* haplotypes Arg16-Gln27, Gly16-Gln27, and Gly16-Glu27 are identified.
- Rare diagnostic errors may occur due to primer-site mutations.

References

1. Wechler et al, β -Adrenergic Receptor Polymorphisms and Response to Salmeterol. *Am J Respi Crit Care Med* 2006; 173:519–26.
2. Contopoulos-Ioannidis et al. Meta-analysis of the association of β 2-adrenergic receptor polymorphisms with asthma phenotypes. *J Allergy Clin Immunol* 2005; 115:963–72.
3. Drysdale CM, et al. Complex promoter and coding region beta 2-adrenergic receptor haplotypes alter receptor expression and predict in vivo responsiveness. *Proc Natl Acad Sci* 2000; 97:10483–8.
4. Pont-Kingdon G, Lyon E. Direct molecular haplotyping by melting curve analysis of hybridization probes: beta 2-adrenergic receptor haplotypes as an example. *Nucleic Acids Res* 2005; 33:e89.

Test Information

0051288 **Beta-2-Adrenergic Receptor Haplotyping**

For specific collection, transport, and testing information, refer to the ARUP Web site at www.aruplab.com.

For information on test selection, ordering, and interpretation, refer to ARUP Consult® at www.arupconsult.com.