

qualitatively the same results, with the same 5 factors and similar loading of each question on each factor.

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Available online September 27, 2005.
doi:10.1016/j.jaci.2005.07.036

β₂-Adrenergic receptor polymorphism in asthma: Prospective versus retrospective perspective

To the Editor:

Contopoulos-Ioannidis et al¹ fuel the β₂-adrenergic receptor polymorphism in asthma debate further with the results of their well conducted meta-analysis. Unfortunately, the study raises more questions than it answers, because the conclusion is in stark contrast with the findings of recent data showing the *Arg16* allele to be the harbinger of poor asthma outcomes.

We suspect the wealth of conflicting data that currently exist in the literature may be attributable to the fact that the vast majority of studies of β₂-adrenergic receptor polymorphism in asthma thus far have been retrospective in nature. It may therefore come as a surprise to the reader that only 2 prospective studies have ever been conducted in this area.

In the first prospective clinical study evaluating the influence of β₂-adrenergic receptor polymorphism in asthma, it was found that cross-tolerance to albuterol after the use of long-acting β₂-agonists was independent of genotype and equally observed in both the *Arg16* and *Gly16* alleles.² In the other prospective study, presence of the *Arg16* allele resulted in poorer long-term response to albuterol use.³

We therefore disagree with Holloway and Yang⁴ that meta-analysis should form the basis and focus of future assessments of β₂-adrenergic receptor polymorphism research in asthma. Surely a well performed prospective study would be a far more enticing and convincing option?

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Available online November 8, 2005.
doi:10.1016/j.jaci.2005.08.054

Reply

To the Editor:

Lee et al¹ refer to the results of 2 prospective pharmacogenetic studies that have addressed the impact of β₂-adrenergic polymorphisms on the response to β-agonist treatment in patients with asthma. Our meta-analysis² targeted only gene-disease associations with asthma phenotypes and did not address the pharmacogenetics of response to treatment among patients with asthma. These are very different questions. In fact, there are more than 20 pharmacogenetic studies on these polymorphisms and asthma response to treatment, and we are in the process of completing a separate overview thereof. There is no reason why a polymorphism associated with nocturnal and/or severe asthma should also necessarily be associated with worse (or better) response to various bronchodilator regimens among patients with asthma. Actually, the prospective study by Israel et al³ enrolled only patients with mild asthma, and the other study by Lee et al⁴ also enrolled patients with moderate asthma severity, so nocturnal asthma and severe asthma are practically out of their scope.

Finally, we certainly welcome and strongly support prospective studies in asthma genetics and pharmacogenetics, but we should caution that pharmacogenetic studies to date have been even more limited in sample size than gene-disease association studies,⁵ and thus, their results should be viewed with great caution until they are replicated in large enough datasets.⁶ The 2 prospective studies cited here had only 78 and 20 subjects, respectively.^{3,4} While these data are useful, large-scale evidence, including meta-analysis, would be essential for making reliable progress in this field.

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