

# **Influence of the ADRB2 gene polymorphisms on the response to $\beta$ 2-agonists in airway diseases: a HuGE review and meta-analysis**

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## Background

Inhaled beta-2 agonists are commonly and successfully used, as bronchodilators, in the management of asthma and other airway diseases. However, response to both short- and long-acting beta-2 agonists (SABA and LABA) is heterogeneous among patients, and genetic polymorphisms in beta-2 agonist metabolic enzymes, receptors, signalling pathways, as well as disease patterns are believed to be responsible for this variability (Bhatnagar 2006). To date, gene-treatment interactions (pharmacogenetic effects) have been mainly confined to studies of genetic variation in the  $\beta$ 2-adrenergic receptor (*ADRB2*) with most pharmacogenetic researches having focused on the polymorphisms causing amino acid substitutions at positions 16 and 27 (Gly16Arg and Gln27Glu).

While the evidence from *in vitro* studies strongly suggests a pharmacogenetic effect of the *ADRB2* gene polymorphisms on the response to  $\beta$ 2-agonists, the results of clinical studies are conflicting (Lipworth 2000; Israel 2004; Tan 1997; Bleecker 2006). Moreover studies which include the haplotype-based analyses could not replicate results emerging from those focusing on single nucleotide polymorphisms – SNPs (Van Veen 2006). In fact, at present, 49 polymorphisms have been described for the *ADRB2* gene and promoter region, all potentially playing a role. However, most of these studies were underpowered to detect a pharmacogenetic effect, which requires much larger sample sizes than those needed to assess main treatment effects. Moreover, some studies have investigated the acute or chronic effects of SABA and other the effects of LABA, and there is a possibility that the pharmacogenetic effects might vary between the two groups of drugs.

A systematic review of the literature on the pharmacogenetics of the response to beta-2 agonists has been published last year (Contopoulos-Ioannidis 2007). The authors did not perform a meta-analysis due to the heterogeneity of the studies, mainly in terms of disease outcomes measured, and they concluded that further research was needed to provide a conclusive answer. Indeed, further pharmacogenetic studies have been published in the meanwhile, including the report of two large randomised clinical trials where LABA were used in association with corticosteroids and which showed no pharmacogenetic effect (Bleecker 2007). However, the concomitant use of corticosteroids might have masked pharmacogenetic effects, as acknowledged by the authors of the studies.

## Aims

We undertake a systematic review and meta-analysis with the primary aim of providing conclusive evidence on the role of *ADRB2* gene variants in modulating the effectiveness of short-acting (single use or regular use) and long-acting  $\beta$ 2-agonists, in patients with airway disease. The secondary aim is to assess whether the concomitant use of inhaled steroids might modify the pharmacogenetic effect of *ADRB2* gene on the response to  $\beta$ 2-agonists.

## Methods

### **Criteria for study inclusion**

#### *Types of studies*

All study designs (interventional and observational studies), performed in vivo in humans, which assess the modulating effect of *ADRB2* gene on therapeutic response to beta-2 agonists in patients with airways disease.

#### *Polymorphisms*

Any *ADRB2* gene variant.

#### *Treatments*

Any SABA and LABA, used either in single dose or regularly. Subgroup analyses will be performed to explore differences between SABA and LABA, and, within the two groups, between different drugs.

#### *Outcomes*

Primary outcomes will be FEV1 and asthma exacerbations. Secondary outcomes will include: other spirometric measures, airways hyperreactivity, asthma symptom score, use of rescue medications and quality of life, as well as development of tolerance to  $\beta$ 2-agonists. Potential side effects related to the administration of beta-2 agonists will be also reviewed.

### **Search methods**

- Electronic search of: MEDLINE, EMBASE, ISI Web of Science, HuGENet Cochrane Library and DARE
- Cross-checking of reference lists
- Contact with authors of studies eligible for inclusion, but for which complete data were not available from the published report
- Contact with major pharmaceutical companies marketing beta-2 agonists to identify unpublished studies

### **Data extraction**

Two reviewers (MB and CM) will independently extract the data using a pre-piloted form. A third reviewer (JT) will be available for arbitration.

### **Quality assessment**

Quality assessment will be based on the HuGENet guidelines for the reporting of genetic association studies (HuGE Review Handbook). Due to the peculiarities of the field of pharmacogenetics, this will be complemented by the assessment of additional specific issues, as highlighted by recent work on this topic (Jorgensen, in press). Sensitivity analyses will be performed to assess the possible influence of quality on the pooled results.

## Data synthesis

The data will be pooled with random effects models, using per-genotype odds ratios. For all polymorphisms considered, the pharmacogenetic effect will be evaluated as the probability of response to  $\beta$ 2-agonists for mutant homozygotes and heterozygotes compared with that of wild homozygotes.

Between-study heterogeneity will be investigated using the  $Q$  test and the  $I^2$  statistic. The possible presence of publication bias will be assessed graphically using funnel plots, and its asymmetry will be formally evaluated using Begg's and Egger's tests.

Deviations from Hardy-Weinberg equilibrium (HWE) will be tested in non-diseased subjects using the exact test, and the magnitude of the departure will be evaluated using the inbreeding coefficient. Studies with statically significant and/or large deviations from HWE will be further investigated for methodological problems, including population stratification and genotyping errors. However, they will be excluded from the analysis only if there is evidence of such problems (Minelli *et al.*, 2007).

## Potential conflict of interest

Peter Burney has provided consultancy to GSK and received lecture fees from Astra-Zeneca; both pieces of work were unrelated to this proposal. There are no conflicts of interest for the other authors.

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