A tailored approach to asthma management: Arg\textsuperscript{16} holds the key?
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Abstract
Asthma is heterogeneous with respect to clinical presentation, underlying disease mechanisms and response to existing drugs making tailored therapy desirable. Pharmacogenetics, the study of the influence of genetic polymorphisms on drug efficacy and/or adverse effects, is relatively advanced in asthma with replicated genetic associations identified in the main drug classes. In the present issue of *Clinical Science*, Lipworth and co-workers report a proof-of-concept study and demonstrate that, in asthmatic children carrying the \(\beta_2\)-adrenergic receptor gene Arg\textsuperscript{16} polymorphism, a combination of corticosteroid plus leukotriene receptor antagonist provides superior asthma control (e.g. quality of life scores) compared with corticosteroid plus a long-acting \(\beta_2\)-adrenergic receptor agonist as add-on therapy. The basis of these observations is well founded, as it has been demonstrated previously that the Arg\textsuperscript{16} polymorphism may confer an increased risk of exacerbation following prolonged \(\beta_2\)-adrenergic receptor agonist use. These results suggest Gly16Arg genotyping in Caucasian asthma patients may have a role in the clinical management of asthma by influencing the decision of which add-on therapy to prescribe; however, larger studies are required to provide definitive conclusions regarding the clinical utility of this approach.

**Key words:** asthma, \(\beta_2\)-adrenergic receptor, children, genotype, montelukast, salmeterol

Asthma is characterized by reversible airway obstruction, increased bronchial hyper-responsiveness and chronic inflammation. Current approaches to asthma management utilize a ‘step up/step down’ basis as outlined in the BTS (British Thoracic Society) guidelines [1]. First-line treatment is a SABA (short-acting \(\beta_2\)-adrenergic receptor agonist), for example salbutamol, as needed (Step 1); if symptoms persist, the addition of inhaled corticosteroid, for example beclomethasone, is considered (Step 2) and for further control the add-on of a LABA (long acting \(\beta_2\)-adrenergic receptor agonist), for example salmeterol, or a LTRA (leukotriene receptor antagonist), for example montelukast (Step 3). Further management includes high-dose inhaled corticosteroid or additional add-on (Step 4) and oral steroid, for example prednisolone (Step 5). This stepwise approach is prone to potential adverse effects, for example exacerbations by not tailoring the therapy closely to the individual patient, and has led to interest in the identification of both genetic and phenotypic markers that predict drug efficacy and adverse effects. Reproducible genetic associations have been identified for several genes and patient responses to the three major drug classes used in asthma: \(\beta_2\)-adrenergic receptor agonists, corticosteroids and leukotriene synthesis inhibitors/receptor antagonists; however, only a small proportion of the genetic variability has been identified to date. Similarly, careful selection of patients based on phenotype has provided important lessons, for example targeting anti-IL (interleukin)-5 therapy to patients with eosinophilic-driven asthma (reviewed in [2]).

\(\beta_2\)-Adrenergic receptor agonists are used extensively in asthma management and act by binding to the \(\beta_2\)-adrenergic receptor, a G-protein-coupled receptor encoded by the *ADRB2* gene. Agonist binding results in the activation of adenylate cyclase through stimulatory G\(\alpha_s\) that results in PKA (protein kinase A) activation. PKA phosphorylates several proteins, resulting in a decrease in intracellular calcium and airway smooth muscle relaxation. *ADRB2* is polymorphic with 49 + variants identified; however, most studies have focussed on variants that alter the protein sequence: Gly16Arg [MAF (minor allele frequency) in Caucasians = 0.38], Gln27Glu (MAF = 0.44) and Thr164Ile (MAF = 0.02) [3]. *In vitro* studies identified that codon 16 and 27 polymorphisms did not influence agonist binding or cAMP.
signalling responses; however, an enhanced agonist-mediated receptor down regulation for the Gly16 variant and a resistance to down-regulation for the Glu27 variant were observed [4].

These *in vitro* findings have led to several *in vivo* studies stratifying patient responses to both SABA and LABA based on the ADRB2 genotype to identify pharmacogenetic effects. These studies were predominantly retrospective in design and suffered from heterogeneity in the populations used, for example ethnicity, the specific ADRB2 polymorphism(s) genotyped, the power of the study and, critically, the outcome measures used, for example lung function [FEV₁ (forced expiratory volume in 1 s)] compared with measures of control, e.g. exacerbation frequency. This has led to some conflicting findings, with carriers of the ADRB2 Arg₁₆ polymorphism demonstrating: (i) a greater initial response to SABA, and (ii) a decline in asthma control and increased exacerbations following sustained SABA/LABA use [5–7]. However, these observations were not confirmed in other studies, for example in a study of 2250 asthma patients assigned (i) budesonide plus formoterol maintenance and reliever therapy, (ii) fixed dose budesonide plus formoterol or (iii) fixed dose fluticasone plus salmeterol for 6 months. No effect was observed for the Gly16Arg genotype for all clinical outcomes including exacerbations [8]. Therefore the utility of genotyping the Gly16Arg polymorphism in asthma is still debatable at this time. The potential detrimental effect of prolonged LABA use has also been identified in clinical trials; in particular, salmeterol monotherapy is associated with an increase in asthma-related exacerbations and deaths [9].

In the present issue of *Clinical Science*, Lipworth and co-workers [10] use this ADRB2 Arg₁₆ pharmacogenetic knowledge to inform decisions regarding the specific add-on therapy for asthmatic children not adequately controlled by SABA and corticosteroid alone. The hypothesis being that Arg₁₆ carriers would demonstrate greater clinical benefit by supplementing the corticosteroid fluticasone propionate with the addition of an LTRA (montelukast) compared with addition of an LABA (salmeterol). Importantly, in non-stratified trials comparing these add-on therapies, the salmeterol addition has proven to be superior to montelukast with respect to, for example, a reduction in exacerbations [11]. Arg₁₆ carriers (n = 62) were randomized to each of the active treatment arms and followed over 1 year. These two groups were well matched at baseline, for example age and sex, and, importantly, for the key outcomes under investigation.

The results are striking, with the montelukast group demonstrating a superior benefit for a wide range of measures including, school absences (primary outcome), exacerbation score, reliever (salbutamol) use, morning dyspnoea and quality-of-life scores [10]. Importantly, many of these changes were apparent after 3 months and can be considered clinically relevant. Another important observation was that these dramatic changes in objective measures were not accompanied by improvement in lung function [FEV₁ (%predicted value)]. This finding is important and provides further evidence for a relatively poor correlation between lung function and symptom-based measures.

The use of a single genetic marker to define the potentially at-risk population of asthmatic children can be considered a strength as there is a need for a simple diagnostic test if these approaches are to be implemented in practice. However, it is unclear at this time whether the use of additional markers, for examples within ADRB2 [3] or other genes, would further define the at-risk population or indeed if markers in other genes would be useful in predicting the response to the chosen add-on therapy [2]. This aside, these findings suggest Gly16Arg is a useful marker, but the underlying causative mechanisms remains to be resolved. Although the study by Lipworth et al. [10] has some limitations, for example the lack of a Gly₁₆ arm to the study to further interpret findings and that both treatment arms used SABA as reliever therapy, it is somewhat refreshing to see a relatively simple pragmatic approach to these important clinically relevant questions.

So, should the Arg₁₆ genetic test be implemented in the management of asthma? Although these results are encouraging, it is important to note that the relevance of Gly16Arg genotyping remains unclear with conflicting data observed in large prospective studies. There is a need for further validation of the present findings. In particular, larger studies with longer follow-up periods to clearly demonstrate health benefits and/or cost effectiveness compared with the existing stepwise approach is essential.

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**REFERENCES**


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