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Pharmacogenetics of asthma

John J. Lima^a, Kathryn V. Blake^a, Kelan G. Tantisira^b, and Scott T. Weiss^b

^a Centers for Pediatric Clinical Pharmacology and Pharmacogenetics, Nemours Children's Clinic, Jacksonville, Florida

^b Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts, USA

Abstract

Purpose of review—Patient response to the asthma drug classes, bronchodilators, inhaled corticosteroids and leukotriene modifiers, are characterized by a large degree of heterogeneity, which is attributable in part to genetic variation. Herein, we review and update the pharmacogenetics and pharmacogenomics of common asthma drugs.

Recent findings—Early studies suggest that bronchodilator reversibility and asthma worsening in patients on continuous short-acting and long-acting β -agonists are related to the Gly16Arg genotype for the *ADRB2*. More recent studies including genome-wide association studies implicate variants in other genes contribute to bronchodilator response heterogeneity and fail to replicate asthma worsening associated with continuous β -agonist use. Genetic determinants of the safety of long-acting β -agonist require further study. Variants in *CRHR1*, *TBX21*, and *FCER2* contribute to variability in response for lung function, airways responsiveness, and exacerbations in patients taking inhaled corticosteroids. Variants in *ALOX5*, *LTA4H*, *LTC4S*, *ABCC1*, *CYSLTR2*, and *SLCO2B1* contribute to variability in response to leukotriene modifiers.

Summary—Identification of novel variants that contribute to response heterogeneity supports future studies of single nucleotide polymorphism discovery and include gene expression and genome-wide association studies. Statistical models that predict the genomics of response to asthma drugs will complement single nucleotide polymorphism discovery in moving toward personalized medicine.

Keywords

asthma; genes; personalized medicine; polymorphisms; response heterogeneity

Introduction

Asthma imposes a serious burden on our society with respect to mortality, morbidity, and healthcare costs. The long-range goal of asthma pharmacogenetics and pharmacogenomics is to personalize asthma pharmacotherapy using genetic information, which is expected to reduce the asthma burden. Novel sequence variants have been recently identified that associate with response to commonly used asthma drug classes [bronchodilators, inhaled corticosteroid (ICS), and leukotriene modifiers) and that support continuing research in asthma pharmacogenetics and pharmacogenomics. Herein, we review the pharmacogenetics and pharmacogenomics of bronchodilators, ICSs, and leukotriene modifiers focusing on recently published work.

Bronchodilators

β -agonists are the most commonly used bronchodilators in the treatment of asthma. Short-acting β -agonists (SABAs) are used by virtually all patients with asthma as rescue bronchodilator medications to treat acute bronchoconstrictive symptoms, whereas long-acting β -agonists (LABAs) are used in combination with ICSs to provide prolonged bronchodilation and control asthma symptoms. The bronchodilator response to SABA, that is, bronchodilator reversibility, is highly variable [1] (Fig. 1). The majority of asthma pharmacogenetic and pharmacogenomic studies have focused mainly on SABA and LABA, particularly on genetic determinants of bronchodilator reversibility and on asthma worsening related to continuous use of SABA or LABA.

The safety of pressurized β_2 -agonist aerosols has been controversial since their introduction in the 1950s. Two epidemics of asthma mortality occurring in the 1960s and 1970s coincided with increased use of isoproterenol and fenoterol [2–5]. Subsequently, with the discovery and sequencing of the β_2 -adrenergic receptor gene (*ADRB2*), interest has focused on pharmacogenetics to explain both the widespread variability in bronchodilator response observed between patients and the occurrence of worsening asthma control noted in small numbers of asthmatics treated with inhaled β_2 -agonists.

The *ADRB2* is a small, intronless gene, which has been recently resequenced in multiple ethnic populations to determine polymorphic variability and haplotype structure [6,7]. Of 80 polymorphisms identified, 45 single nucleotide polymorphisms (SNPs) and two insertion/deletion variants have been validated. Two common nonsynonymous variants at amino acid positions 16 (Gly16Arg) and 27 (Gln27Glu) have functional relevance *in vitro* [8,9], and most clinical studies have focused on outcomes resulting from the Gly16Arg polymorphism.

Initial studies exploring associations between bronchodilator response to SABA and the Gly16Arg polymorphism in outpatients found that Arg16 homozygotes had a greater bronchodilator response than Gly16 homozygotes [10–12]. Subsequent studies found opposite results or no association [6,13–17]. More recently, no association was found between bronchodilator response and *ADRB2* haplotype tagging SNPs in over 500 asthmatic patients [18]. Additionally, both a candidate gene and genome-wide association analysis failed to associate any polymorphism in *ADRB2* with bronchodilator response but did identify associations with SNPs in novel genes (*ARG1* and *ABLM2*) [19,20]. Association studies between *ADRB2* polymorphisms and bronchodilator response to high-dose SABA during treatment of severe acute asthma have only begun to be reported [21,22].

In the early 1990s, regularly scheduled fenoterol use was found to worsen asthma control [23], but a similar study with albuterol in mild asthmatic patients [the Beta-Agonist in Mild Asthma (BAGS) Trial] found no harmful effects [24]. However, when the BAGS trial was analyzed by genotype, Arg16 homozygotes had worse asthma control on regularly scheduled albuterol than Gly16 homozygotes on regularly scheduled albuterol and Arg16 homozygotes treated as needed with albuterol [25]. Prospective [Beta-Adrenergic Response by Genotype (BARGE) Study] and retrospective studies have been consistent with these findings [26–28].

The effect of LABA therapy on asthma control by *ADRB2* genotype has generated significant interest. The safety of LABAs has been hotly debated [29–31]. A review of 26 trials with over 60,000 patients found that salmeterol (with and without ICSs) was associated with slight but significantly worse asthma control compared with placebo [32••]. The first published pharmacogenetic association analyses of LABA (salmeterol) on asthma control were consistent with studies of SABA [33,34]. However, numerous retrospective pharmacogenetic analyses in all racial groups and in both children and adults have failed to find any association between the Gly16Arg genotype and asthma control in patients treated with salmeterol or formoterol

[35–39]. A prospective clinical trial by the Asthma Clinical Research Network is currently underway. This randomized, double-blind, crossover, placebo-controlled trial will examine the effects of regularly scheduled long-acting β -agonist in a group of asthmatic patients harboring the Arg16 homozygous genotype and in a separate group matched for forced expiratory volume in 1s (FEV₁) and matched and race-matched (whites versus nonwhites) patients harboring the Gly16 homozygous genotype at the β_2 -adrenergic receptor. Both groups will receive concurrent ICSs (website: www.acrn.org).

The discrepant findings of coding block polymorphisms on β_2 -agonist response have prompted investigation into effects of *ADRB2* regulatory regions on receptor function. Early study of a variant in the in the *ADRB2* promoter region affected receptor translation and density but not transcription [40]. A variable-length poly-C tract polymorphism in the 3'UTR has been found to influence β_2 -adrenergic receptor expression, mRNA expression, mRNA degradation, and agonist-induced receptor downregulation *in vitro* [41•]. However, this polymorphism was not found to associate with effects of salmeterol on asthma control [39]. Clearly, coding block variants in *ADRB2* do not reliably predict the response to SABA and LABA as was initially expected. Meticulously designed large prospective studies of asthmatic patients with homogenous phenotypes, carefully controlled environmental influences, and analysis of gene–gene interactions are clearly needed to move forward toward personalizing SABA and LABA therapy.

Corticosteroids

ICSs are the most effective and commonly used drugs for the chronic treatment of asthma but may result in serious adverse effects [42]. There is substantial interindividual variability in the response to ICSs [43,44] (Fig. 2), and the intraindividual response to ICSs in patients with asthma is highly repeatable [45]. The combination of wide interindividual variability and high intraindividual repeatability supports a genetic difference for the response to ICSs in asthma [45].

In a study of 14 candidate genes selected for their biologic relevance to the corticosteroid pathway, a significant association between 8-week FEV₁ response to ICSs and SNPs from the corticotropin-releasing hormone receptor 1 (*CRHR1*) gene in both adult and pediatric asthmatic patients was noted [46]. Rs242941 (minor allele frequency ~30%) was associated with about 2½ times the improvement in FEV₁ in both the Adult Study and Childhood Asthma Management Program (CAMP) populations ($P=0.025$ and 0.006 , respectively). In CAMP, although ICS usage was associated with improved FEV₁, evaluation of the placebo arm revealed no association with change in lung function (interaction $P=0.02$). One *CRHR1* haplotype had even larger improvements in FEV₁ on inhaled steroids. However, the overall explained phenotypic variance was small (<5% in both populations). Moreover, the same *CRHR1* variants were not associated with protection against lung function decline in a cohort of adult asthmatic patients taking ICSs [47]. Although differences in the studies may be related to the much smaller sample size in the lung function decline cohort, additional factors (including other genetic loci) clearly contribute to FEV₁ response variability to ICSs. Interestingly, the initial association may be related to a large structural inversion, rather than to an effect within the *CRHR1* gene itself [48••].

TBX21 encodes for T-bet, a transcription factor crucial for naive T-lymphocyte production. The T-bet knockout mouse spontaneously develops airways inflammation and hyperresponsiveness suggestive of asthma [49]. One common nonsynonymous SNP has been identified in the *TBX21* gene, encoding for a replacement of histidine by glutamine at amino acid position 33 (H33Q). Four and a half percent of CAMP children are heterozygous for this variant. Each H33Q white individual on ICSs demonstrated a marked improvement in airways

responsiveness, as measured by PC₂₀, when compared with either H33H homozygotes or individuals not taking inhaled steroids (interaction $P=0.0002$) [50]. The average improvement in the level of PC₂₀ in those H33Q individuals taking ICSs was similar to that associated with nonasthmatic individuals.

A novel variant in *FCER2* (which encodes for the low-affinity IgE receptor) has recently been associated with asthma exacerbations while on ICSs [51••]. The SNP, rs28364072, was associated with increased risk of exacerbations in asthmatic children taking ICSs despite generally protective effects of this medication class. Relative risk, expressed as hazard ratios, for exacerbations in those homozygous for the variant allele was 3.95 [95% confidence interval (CI), 1.64–9.51] for white children and 3.08 (95% CI, 1.00–9.47) for African-American children. Of interest, this novel variant was also associated with both higher IgE levels and with differential expression of the *FCER2* gene, supporting the contention that variation in *FCER2* can adversely affect normal negative feedback in the control of IgE synthesis and action.

In addition to studies evaluating genetic associations, genomic association studies, focusing on differential expression of genes influencing treatment response, have commenced. Hakonarson *et al.* [52] evaluated glucocorticoid-sensitive and resistant asthmatic patients. Using oligonucleotide microarrays (11 812 genes), expression was measured in blood mononuclear cells at baseline and following stimulation with IL-1 β /TNF- α with or without dexamethasone. Fifteen genes predicted glucocorticoid response category with a reported accuracy of 84%. This study focused only on phenotypic extremes; additional studies of this type are warranted. Nonetheless, the promise of rapidly identifying a small subset of candidate genes by expression profiling in this manner is clearly appealing.

In summary, pharmacogenetic studies of ICS response in asthma have shown significant associations with lung function, airways responsiveness, and exacerbations. Future studies are needed to identify novel loci that contribute to response heterogeneity and will achieve the goal of personalizing ICS therapy.

Leukotriene modifiers

Leukotriene modifiers act by inhibiting the action of leukotrienes, which are a family of products generated from the metabolism of arachidonic acid in leukocytes [53]. Leukotrienes can be produced in other cells that lack the complete cassette of enzymes required for this production through the process of transcellular biosynthesis [54]. Two classes of leukotriene modifiers are available for use in the treatment of asthma: 5-lipoxygenase (5-LO) inhibitors (zileuton) and leukotriene receptor antagonists (LTRAs), montelukast, zafirlukast and pranlukast. There is little question that leukotriene modifiers are an important addition to asthma controller therapy owing to their unique mechanism of action, safety (especially LTRAs) and efficacy, and convenient once-daily (for LTRAs) oral dosing. However, heterogeneity in response to leukotriene modifiers seriously detracts from their advantages [43,55] (Fig. 2).

An important question is which polymorphisms contribute to the heterogeneity in response to leukotriene modifiers? The addition/deletion variant in the promoter of *ALOX5* reported by Drazen *et al.* [56] for ABT-761, a 5-LO inhibitor similar to zileuton, has not been replicated in asthma. Recently, we [57] reported that montelukast but not placebo was associated with a 73% reduced risk of an asthma exacerbation in carriers of the mutant allele (number of repeats, five) as compared with homozygous wildtype (five repeats on each allele), which was not consistent with the findings of Drazen *et al.* [56]. Consistent with the study by Drazen *et al.* [56], Telleria *et al.* [58] reported that montelukast treatment decreased the number of asthma exacerbations, improved FEV₁, and decreased the use of inhaled β_2 -agonists in patients with

5/5 or 4/5 repeats but not in participants carrying 4/4 homozygotes. However, both reports [57,58] of montelukast studied a small number of white participants ($n=61$), and the Telleria study was not blinded. Clearly, associations between this polymorphism and response to LTRAs should be studied in larger and more diverse populations with asthma.

Early reports suggested an association between the response to LTRAs and the C allele of the LTC₄ synthase gene promoter (A-444C) polymorphism [59–61]. We replicated this association and also identified three novel SNPs in the *ALOX5* (rs2115819), *ABCC1* (rs119774), and *LTA4H* (rs2660845) genes for changes in FEV₁ or exacerbation rates [57]. Klotzman *et al.* [62] also identified novel SNPs in *ALOX5* and *CYSLTR2* that was associated with response to montelukast in asthma.

Montelukast (and probably other LTRAs) undergoes transport-mediated absorption by OATP2B1 and likely other transporters [63]. A nonsynonymous G1199A (rs12422149; R312G) in *SLCO2B1* gene associates with the asthma symptom utility index (ASUI) [64], which is a validated tool that assesses patient preferences of asthma-related symptoms and drug effects on a scale from worse (0) to best possible state (1) and with plasma levels of montelukast obtained from individuals who participated in a large asthma clinical trial [65]. Plasma concentrations of montelukast and ASUI were significantly higher in R312 homozygotes [66] than in heterozygotes. Thus, SNPs in transporters expressed in the gut may have an important influence on the pharmacokinetics of montelukast and other LTRAs, which in turn could influence the patient response to these drugs. However, these associations require replication.

Conclusion

During the past 2 years, significant progress has been made toward identifying novel sequence variants that contribute to the heterogeneity in response to drugs commonly used to treat asthma. In order to move forward toward achieving the goal of personalizing asthma pharmacotherapy, we need to continue to identify novel polymorphisms that associate with response focusing on relevant phenotypes, including bronchodilator reversibility and indices of asthma control in large pharmacogenomic studies. Gene expression studies and studies utilizing genome-wide association methods promise to identify novel loci that contribute to heterogeneity in response to asthma pharmacotherapy. Additionally, the development of statistical models that predict the genomics of response to asthma drugs will complement SNP discovery in moving toward personalized medicine. Currently, we are using Bayes Networks to develop multi-SNP predictions of asthma exacerbations and bronchodilator reversibility. This method is promising for performing multi-SNP, multi-gene prediction of drug response.

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References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

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- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 000–000).

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Figure 1.

Fitted dose-response after cumulative doses of albuterol (solid line) gr1

Open circles represent individual patient responses. Response is percentage predicted FEV₁.

The cumulative doses of albuterol administered from the metered dose inhaler (MDI) were 180, 270, 360, 450, and 540 μ g, and the cumulative doses from the MDI and nebulizer were 2770 μ g (270 μ g MDI + 2500 μ g nebulized), 2860 μ g (360 μ g MDI + 2500 μ g nebulized), 2950 μ g (450 μ g MDI + 2500 μ g nebulized), and 3040 μ g (540 μ g MDI + 2500 μ g nebulized).

A population-based pharmacodynamic model was fitted to the data and predicted maximal bronchodilator effect of 24% (E_{max}) above baseline (average of percentage predictive FEV₁, 62%) with an EC_{50} (dose of albuterol achieving 50% of E_{max}) of 141 μ g. The baseline ranged between 40 and 80%, whereas the E_{max} ranged between 50 and 140% predicted. Adapted from [1].

Figure 2.

Distribution of treatment responses for FEV₁ gr2

The response distributions are shown as histograms for predefined intervals of percentage change in FEV₁. Striped bars represent patients receiving monelukast, 10 mg once daily; white bars represent patients receiving inhaled beclomethasone, 200 mg twice daily, Adapted from [43].