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Pharmacogenetics and the Development of Personalized Approaches for Combination Therapy in Asthma

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Abstract

Asthma is a common, chronic disease of the airways that is treated with a combination of different therapies. The combination of LABA and ICS therapy results in a synergistic interaction that is efficacious in improving asthma symptom control; however, genetic variation has the potential to alter therapeutic efficacy. Both agents mediate complex molecular pathways consisting of gene variation that has been investigated with the analysis of candidate genes in the β_2 -adrenergic receptor and glucocorticoid pathway. These pharmacogenetic studies have been limited to retrospective analyses of clinical trial cohorts and a small number of prospective, genotype-stratified trials. More recently, genome-wide association studies in combination with replication in additional cohorts and in vitro cell-based models have been used to identify novel pathway-related pharmacogenetic variations. This review of the pharmacogenetics of the β_2 -adrenergic receptor and glucocorticoid pathways highlights the genotypic effects of variation in multiple genes from interacting pathways which may contribute to differential responses to inhaled beta agonists and glucocorticoids. As our understanding of these genetic mechanisms improves, panels of biomarkers may be developed to determine which combination therapies are the most effective with the least risk to an individual asthma patient. Before we can usher in an era of personalized medicine for asthma, it is first important to improve our ability to analyze large volumes of genetic data in large clinical trial cohorts using a combination of study designs, analytical methods, and in vitro functional studies.

Keywords

Pharmacogenetics; Genes; Asthma; Response heterogeneity; SNP; Combination therapy; Glucocorticoid pathway

Introduction

Asthma is a common, chronic disease of the airways affecting more than 300 million worldwide characterized by airway inflammation and variable degrees of airflow obstruction [1]. Asthma is a markedly heterogeneous disease that is caused by the interaction of multiple biologic pathways. Interindividual genetic variability and the effects of environmental

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factors are key components in how these pathways function and interact [2]. Therapeutic options for treating asthma include inhaled beta₂ (β₂)-adrenergic receptor agonists (beta agonists), inhaled and systemic corticosteroids, leukotriene modifiers, inhaled anticholinergics, and theophylline. Despite the availability of different single and combination therapeutic options, two issues continue to affect the efficacy of these therapies: First, some asthma therapies, particularly inhaled beta agonists, are known to be associated with adverse effects sometimes leading to rare adverse life-threatening events [3–5]. Second, a small subset of asthmatics are refractory to high doses of inhaled corticosteroids in combination with other anti-asthma therapies, resulting in significant morbidity and a financial burden over six times greater than those with less severe asthma. [6–8].

Pharmacogenetics is the study of how genetic variability determines interindividual responses to pharmacological therapies and the effects of this gene-by-environment interaction (Fig. 1). High interindividual variability and low intraindividual variability in clinical responses to anti-asthma therapies suggests that heritable factors are important in determining drug response, providing the rationale for pharmacogenetics research [9–11]. Gene variation determines drug response through different mechanisms that include pharmacodynamic mechanisms which result from activation of a receptor pathway and pharmacokinetic mechanisms which determines drug metabolism.

The majority of pharmacogenetic studies in asthma have been limited to retrospective study designs; therefore, the phenotype of interest in these studies has been pharmacodynamic endpoints such as forced expiratory volume in 1 s (FEV₁), peak expiratory flow rates (PEFR), and asthma exacerbations. In these retrospective studies, genetic analysis was performed after completion of the study to determine the effect of genetic variation on clinical endpoints. This type of analysis may involve the use of genome-wide association studies (GWAS) and is important in that unknown genetic effects can be identified without prior hypotheses. In contrast, a small number of studies have employed a prospective, genome-stratified study design where pre-selected genotypes are obtained prior to randomization. A prospective, genotype-stratified strategy provides the advantage of sufficiently powering the analysis for less common genetic variants by allowing recruitment of an adequate sample size containing the risk genotype.

Combination Therapy in Asthma and the Need for a Personalized Approach

Asthma pharmacogenetic studies have primarily focused on the role of gene variation as a determinant for therapeutic response to three major drug classes: β₂-adrenergic receptor agonists (beta agonists), glucocorticoids, and leukotriene modifiers. Since few recent pharmacogenetic studies of leukotriene modifiers have been published, we will focus on the most studied and efficacious combination therapy of a long-acting beta agonist (LABA) and an inhaled corticosteroid (ICS) [12–14].

Multiple clinical trials have demonstrated the synergy between LABA and ICS therapies resulting in effective symptom control and the prevention of asthma exacerbations [15–17]. In vitro studies have provided additional support for this synergistic effect. In sputum cells from asthmatics, treatment with a LABA or SABA in combination with ICS resulted in enhanced translocation of the glucocorticoid receptor into the nucleus, the intracellular location where steroids exert their anti-inflammatory activity [18]. In addition, treatment of sputum cells with corticosteroids results in a significant increase in β₂-adrenergic receptor gene expression [19]. This synergistic interaction thus provides a rationale as to why the combination of a LABA and ICS is efficacious in improving asthma symptom control with lower ICS doses; however, gene variation has the potential to alter this relationship resulting

in alterations in therapeutic efficacy. Below, we will highlight how the pharmacogenetics of two major therapeutic pathways has identified genetic biomarkers which may eventually be used to predict therapeutic responses to different combination therapies for the personalized management of persistent asthma.

Beta2-Adrenergic Receptor Pathway

Inhaled beta agonists are the most commonly prescribed medications for the treatment of asthma, and include both short-acting beta agonists (SABA: fenoterol, isoproterenol, pirbuterol, levalbuterol, and albuterol) and LABAs (salmeterol and formoterol). LABAs are administered as a maintenance controller therapy in combination with ICS, while SABAs are prescribed for the as-needed use in acute symptom relief [14]. Beta agonists allow for airway smooth muscle relaxation by the activation of a G-protein coupled receptor pathway via adenylyl cyclase type 9 [20].

There have been concerns related to the safety of inhaled beta agonists as far back as the 1960s. During this time, asthma mortality epidemics were associated with the use of SABAs in high-dose preparations (isoproterenol) or with less selective β_2 -adrenergic receptor activity (fenoterol) resulting in the withdrawal of these agents from the market [21–25]. More recently, surveillance trials, where subjects were randomized to LABA without an ICS, and meta-analyses have suggested an association between LABA therapy and the risk for life-threatening asthma exacerbations and death [3–5, 26]. Based on these observations, the United States Food and Drug Administration (FDA) has held two advisory panel meetings and have issued public health advisories regarding the risk for life-threatening exacerbations associated with LABA use and a boxed warning for all LABA-containing inhalers including combination preparations [27]. Subsequent clinical trials, large meta-analyses, and case–control trials have shown that the use of a LABA in combination with an ICS results in beneficial effects on asthma exacerbation rates and overall symptom control without an increased risk for life-threatening adverse events [28–31]. This LABA safety controversy is currently being evaluated in an FDA-mandated international study of over 40,000 asthma subjects [27, 32]. Pharmacogenetic studies of candidate genes related to the β_2 -adrenergic receptor pathway and a recent genome-wide association study (GWAS) have attempted to identify gene variants that determine response to inhaled beta agonists (Table 1).

Pharmacogenetic studies of the β_2 -adrenergic receptor pathway have primarily focused on the gene encoding for the β_2 -adrenergic receptor. *ADRB2* is an intronless gene with nearly 49 validated genetic polymorphisms in asthma subjects [33, 34]. The most studied *ADRB2* polymorphism is a common coding variant which codes for either a glycine or an arginine in the 16th amino acid position, Gly¹⁶Arg [33, 35]. In vitro, the Gly¹⁶ variant results in increased receptor downregulation in response to beta agonist, compared to the Arg¹⁶ allele [36, 37].

In two early pharmacogenetic studies, asthmatic children homozygous for Arg¹⁶ consistently demonstrated a greater post-bronchodilator FEV1 response to a one-time dose of al-buterol compared to the Gly¹⁶ homozygotes [38, 39]. These results have been replicated in smaller asthma populations, including ethnic groups such as Puerto Ricans [40–42]. Two retrospective pharmacogenetic studies, the NIH National Heart Lung and Blood Institutes Asthma Clinical Research Network (NHLBI ACRN) Beta Agonist Study (BAGS) trial and a crossover trial by Taylor and coworkers, further evaluated *ADRB2* genotypes and the response to long-term regular therapy with albuterol. These studies showed that during regular SABA treatment Arg¹⁶ homozygotes experienced a decline in peak flow rate (PEFR), an effect that was not seen in Gly¹⁶ homozygotes [43, 44].

The ACRN Beta Agonist Response by Genotype (BARGE) trial was a genotype-stratified, cross-over trial that prospectively randomized 37 Arg¹⁶ homozygotes and 41 Gly¹⁶ homozygotes to regular albuterol or placebo for 16 weeks with ipratropium as a rescue inhaler to minimize beta agonist use. In this study, Arg¹⁶ homozygotes did not experience a change in PEFR during treatment with albuterol while PEFR improved during placebo treatment. In contrast, the Gly¹⁶ homozygotes experienced an improvement in PEFR during regular albuterol treatment (Fig. 2). Secondary endpoints such as asthma symptom score and rescue inhaler use improved in Gly¹⁶ homozygotes and deteriorated in Arg¹⁶ homozygotes during regular albuterol treatment [45]. The contrasting genotypic effects of Gly¹⁶Arg during acute versus chronic SABA exposure is possibly related to receptor kinetics or pro-inflammatory effects and provides the rationale for pharmacogenetic studies evaluating effects of Gly¹⁶Arg genotypes during long-term LABA therapy.

Two small retrospective pharmacogenetic studies initially evaluated the genotypic effects of Gly¹⁶Arg on long-term treatment with LABA therapy. The first was the previously mentioned cross-over trial by Taylor and coworkers which did not show significant differences in PEFR or exacerbation frequency responses during salmeterol therapy between Gly¹⁶Arg genotypes [43]. The second study was an analysis of two ACRN trials which showed that Arg¹⁶ homozygotes experienced worsening of PEFR, asthma symptoms scores, and rescue inhaler use during salmeterol treatment compared to Gly¹⁶ homozygotes [46]. Bleecker and colleagues subsequently performed retrospective analyses in three larger trial cohorts genotyped for *ADRB2* single nucleotide polymorphisms (SNPs) and showed that there was no significant differences in exacerbations, PEFR, or rescue inhaler use between Gly¹⁶Arg genotypes during treatment with LABA therapy [47, 48].

Subsequently, two prospective, genotype-stratified clinical trials investigated whether Gly¹⁶Arg genotypes determined the response to LABA therapy. The ACRN Long-Acting Beta Agonist Response by Genotype (LARGE) trial randomized 42 Arg¹⁶ homozygotes and 45 Gly¹⁶ homozygotes to salmeterol or placebo in combination with ICS therapy and ipratropium rescue therapy for 18 weeks, followed by crossover to the alternative treatment arm (placebo or salmeterol). In the LARGE trial, both genotypes experienced improvements in PEFR during LABA and ICS treatment; however, Gly¹⁶ homozygotes experienced an increase in methacholine bronchial reactivity, a bronchoprotective effect not observed in Arg¹⁶ homozygotes [49]. This bronchoprotective effect of Gly¹⁶Arg genotypes during LABA treatment was previously observed in 152 asthma subjects and warrants further investigation [50]. A second genotype-stratified trial by Bleecker and colleagues randomized 179 Arg¹⁶ homozygotes, 182 Gly¹⁶ Arg heterozygotes, and 183 Gly¹⁶ homozygotes to salmeterol monotherapy or salmeterol in combination with an ICS for 16 weeks. In this cohort, similar improvements in PEFR were observed between Gly¹⁶Arg genotypes independent of whether LABA was given as a monotherapy or in combination with an ICS [51].

Although evidence suggests that genetic variation in *ADRB2* affects response to acute and chronic SABA therapy, similar effects have not been observed with LABA therapy. A genotype-stratified study of 62 Arg¹⁶ homozygotes demonstrated improved symptom control in those treated with the addition of montelukast rather than the addition of a LABA to ICS therapy [52]. This study was limited by the absence of a comparison group with the alternative genotype (i.e. Gly¹⁶ homozygotes), but suggests that gene variation at the Gly¹⁶Arg locus might determine the appropriate combination therapy for a subset of asthma subjects.

Since adverse responses to LABA appear to be uncommon and severe (i.e. life-threatening events), it is possible that rare gene variants with strong effects on phenotypes determine

adverse responses to beta agonists. For example, a rare variant within *ADRB2*, Thr¹⁶⁴Ile, has been associated with decreased receptor coupling to G_s protein, receptor ligand binding, and receptor sequestration in response to SABAs such as isoproterenol and albuterol [53, 54]. This rare variant has been associated with similar in vitro effects in response to LABAs and alters binding of salmeterol to its “exosite” on the β_2 -adrenergic receptor [54]. In addition, a variable length polynucleotide cytosine repeat variant (poly-C) in the 3′ untranslated region of *ADRB2* was not associated with response to LABA and ICS combination therapy in 2,192 subjects; however, over half of the 13 possible poly-C alleles had allele frequencies of less than five percent indicating that these alleles were rare [55]. The impact of rare variants in *ADRB2*, such as Thr¹⁶⁴Ile, on therapeutic responses to beta agonist remains to be studied in an asthma trial cohort; however, the rare Ile¹⁶⁴ allele has been associated with reduced lung function and the risk for airflow obstruction in a population-based analysis of over 60,000 subjects [56].

Candidate gene analyses of the β_2 -adrenergic receptor pathway have identified other genes with the potential to alter beta agonist response. A canonical β_2 -adrenergic receptor pathway gene, adenylyl cyclase type 9 (*ADCY9*), contains a common coding polymorphism, Ile⁷⁷²Met, that has been associated with FEV1 change in response to a one-time dose of albuterol during ICS treatment in 436 children from the CAMP cohort [20]. In vitro, this variant has been shown to alter albuterol-stimulated adenylyl cyclase activation in the presence of dexamethasone, demonstrating an important interaction between the β_2 -adrenergic receptor and glucocorticoid pathways [20, 57]. Another pathway-related gene encoding for corticotropin-releasing hormone receptor-2 (*CRHR2*) is a G-coupled protein receptor that mediates airway smooth muscle relaxation via the activation of adenylyl cyclase and protein kinase A, similar to β_2 -adrenergic receptors. A candidate gene analysis of *CRHR2* in 607 children from CAMP, 427 asthma subjects from a trial conducted by Sepracor Inc., and 152 subjects from the Effectiveness of Low-Dose Theophylline as Add-on Treatment in Asthma (LODO) Trial identified five SNPs in *CRHR2* significantly associated with acute bronchodilator response to SABA [58].

A retrospective analysis of 111 candidate genes within the glucocorticoid and β_2 -adrenergic receptor pathways was performed in 209 probands from the Childhood Asthma Management Program (CAMP) with subsequent replication in 864 asthma subjects from three additional trial cohorts. This hierarchical approach identified a SNP in the arginase 1 gene (*ARG1*), rs2781659, associated with FEV1 percent change with acute albuterol bronchodilation [59]. Subsequently, SNPs in *ARG1* (rs2781667) and *ARG2* (rs7140310 and rs10483801) have been associated with acute bronchodilator response to SABA in 200 asthma subjects from a Dutch longitudinal study [60]. Arginase 1 and 2 metabolize L-arginine, a natural substrate for nitric oxide synthase which produces nitric oxide, an endogenous bronchodilator. Thus, genetic variants in *ARG1* and *ARG2* may determine airway smooth muscle relaxation in response to an inhaled beta agonist [61]. In addition, the gene for endothelial nitric oxide synthase (*NOS3*) contains a coding SNP, Asp²⁹⁸Glu, that has been associated with lung function response to LABA and ICS combination therapy in recent preliminary study of 81 asthmatic children [62].

A recent GWAS has identified a novel genetic locus association with beta agonist response. Himes and colleagues analyzed 1,644 non-Hispanic White asthma subjects from six trial cohorts for associations with percent change in FEV1 after acute SABA administration in a primary GWAS. Significant associations from the primary GWAS were analyzed for replication in two cohorts: 501 subjects from the NIH NHLBI Severe Asthma Research Program (SARP) and 550 subjects from a Dutch asthma cohort. A SNP in the 5′ promoter region of the spermatogenesis-associated, serine-rich 2-like gene (*SPATS2L*), rs295137, was associated with bronchodilator response in the primary GWAS and SARP, with a pooled *p*

value of 7.7×10^{-7} . The investigators further validated the functional, in vitro function of *SPATS2L* in the β_2 -adrenergic receptor pathway with an miRNA knockdown of *SPATS2L* in human airway smooth muscle cells. This in vitro study showed that *SPATS2L* increased β_2 -adrenergic receptor expression [63••]. The investigators also identified significant associations with SNPs from three bronchodilator candidate genes, *ADCY9*, *CRHR2*, and *ARG1*, replicating prior pharmacogenetic candidate gene analyses [20, 58, 59, 63••]. These findings reinforce the role of pathway-related gene variation as a pharmacogenetic determinant of beta agonist response that warrants further investigation in asthma trial cohorts where subjects are treated with the combination of LABA and ICS therapy.

Pharmacogenetics of the Glucocorticoid Pathway

Glucocorticoids are the principal anti-inflammatory medication for the treatment of asthma and have greater beneficial effects on asthma symptom control and lung function compared to other recommended controller therapies such as leukotriene receptor antagonists (LTRA) [13, 64, 65]. The glucocorticoid pathway consists of biosynthetic hormones and the chaperone–receptor heterocomplex which orchestrates the binding of glucocorticoids to the cytosolic receptor and translocation of the activated complex into the nucleus to exert anti-inflammatory effects [66].

Since clinical trial findings are reported as mean responses in asthma trial cohorts, they do not account for interindividual variability and may not identify a subset of patients who might benefit from alternative therapies. The majority of asthma subjects randomized to an ICS or the LTRA, montelukast, experience an improvement in FEV1 in response to either therapy; however, a subset experienced no response or a negative response to either treatment [64, 67]. This phenomenon contributes to the pathophysiology of refractory asthma and provides an important rationale for pharmacogenetic research to identify those asthma subjects in whom ICS therapy is efficacious, ineffective, or harmful.

Among the earliest pharmacogenetic studies of the glucocorticoid pathway was a retrospective candidate gene analysis of the corticotropin-releasing hormone receptor-1 (*CRHR1*) gene in three clinical trial cohorts randomized to ICS treatment: 336 adults from the ACRN, 470 adult asthmatic from the “Adult Study,” and 211 children from the Childhood Asthma Management Program (CAMP). Two *CRHR1* SNP’s were associated with lung function response to ICS in these cohorts: rs1876828 in ACRN and rs242941 in the Adult Study and CAMP [68]. Hawkins and coworkers also analyzed candidate genes encoding the chaperone heterocomplex in the Adult Study cohort and identified three SNPs within the heat shock organizing protein gene (*STIP1*) associated with FEV1 response to the ICS flunisolide: rs6591838, rs2236647, and rs1011219 [69].

The interaction of the glucocorticoid pathway with other gene pathways is demonstrated through the pharmacogenetics of ICS response in relation to the *TBX21* gene, *ADCY9*, and *ORDML3*. *TBX21* encodes the T-box expressed in T-cells transcription factor which influences naïve T-lymphocyte development. *TBX21* contains a nonsynonymous SNP, His³³Glu, associated with improvements in bronchial hyperresponsiveness in response to ICS in subjects from CAMP cohort as well as an independent Korean population [70, 71]. A nonsynonymous SNP in the canonical β_2 -adrenergic receptor pathway gene *ADCY9*, Met⁷⁷²Ile, was associated with bronchodilator response to albuterol only in those treated with ICS, a pathway interaction reproduced in a Korean population treated with ICS in combination with formoterol [20, 72]. In addition, a SNP from an asthma susceptibility gene, rs2872507 in *ORDML3*, has been associated with lung function response to ICS in a recent pharmacogenetic study of asthmatic children from a European White population [73].

The complexity of the corticosteroid pathway is illustrated through two recent GWAS that have identified novel pharmacogenetic loci for ICS response. Tantisira and colleagues performed a family-based genome-wide association study in 118 probands from the CAMP study with replication in four cohorts consisting of 935 asthma subjects. A SNP in the promoter of the glucocorticoid-induced transcript 1 gene (*GLCCI1*), rs37972, was associated with lung function response to ICS treatment (pooled p value=0.0007). In addition, a complementary in vitro study of a SNP strongly correlated (in linkage disequilibrium) with rs37972 in the *GLCCI1* promoter region, rs37973, was associated with reduced gene transcription in cells transfected with the minor, variant allele [74••]. A second GWAS of 408 asthma subjects from the ACRN, CAMP, and Childhood Asthma Research and Education (CARE) network also identified two SNPs in the *T* gene (rs3127412 and rs6456042) associated with lung function response to ICS after replication in an additional 407 ICS-treated asthma subjects [75••].

Few pharmacogenetic studies have evaluated the association between gene variation and drug metabolism (i.e. pharmacokinetics) in asthma. A recent retrospective analysis of 413 asthmatic children treated with an ICS demonstrated that children with the *CYP3A4**22 allele had significant improvements in symptom control compared to those without this allele; however, this finding was limited to a small subset of children treated with inhaled fluticasone who inherited this beneficial allele ($n=20$) [76]. Pharmacogenetic loci in the canonical glucocorticoid pathway such as *GLCCI1*, *CRHR1*, *STIP1*, and the *T* gene likely account for a small proportion of the interindividual variability in ICS responses among asthmatics, while genetic loci in other pathways that determine airways inflammation (*TBX21*), drug metabolism (*CYP3A4**22), beta agonist response (*ADRB2*, *ADCY9*, *CRHR2*), and disease susceptibility (*ORDML3*) may also contribute to this variability (Table 2). These pharmacogenetic findings will require either genotype-stratified pharmacogenetic studies powered for risk genotypes or replication in larger trial cohorts to determine whether these gene variants impose additive effects or are independent predictors of ICS response as a monotherapy and in combination with a LABA.

Pharmacogenetics and Personalized Approaches for Combination Therapy

Our review of the pharmacogenetics of the β_2 -adrenergic receptor and glucocorticoid pathways in asthma demonstrates that variation in multiple genes from interacting pathways may contribute to the differential responses to inhaled beta agonists and glucocorticoids. Although some gene variants may have significant effects on the pharmacologic response to a specific therapy, other sources of variability that may result in false positives or obscure true associations in future studies need to be considered. Co-inheritance of genetic variants in two or more loci may occur within the same gene in form of a haplotype or between different genes resulting in gene–gene interactions that could be detected with haplotype or gene pathway analyses.

When LABA and ICS are used in combination, it is possible that gene variants in the glucocorticoid pathway might result in a beneficial response to ICS but interact with gene variation within the same pathway or another pathway, such as the β_2 -adrenergic receptor pathway during concomitant treatment with a LABA. In turn, these gene–gene interactions could result in a magnification, loss, or neutralization of an apparent genetic effect. Gene–gene and gene–environment interactions represent a challenge for pharmacogenetic research, particularly in the management of persistent asthma where combination therapy is the standard of care [1, 77, 78].

Gene–gene interactions likely differ between admixed populations of varying ancestries resulting in variable genotype associations between different ethnic groups. The rationale for

admixture-based approaches in asthma pharmacogenetics is based on the observation that African American asthmatics have an increased likelihood for treatment failures and differential responses to LABA and ICS therapy compared to non-Hispanic Whites making the hypothesis that they could be caused by genetic variants from a specific ancestry [12, 79]. For example, in the Genetics in Latino Americans (GALA) cohort, Gly¹⁶Arg genotypes had an additive effect on albuterol bronchodilation in Puerto Ricans but not Mexican Americans [41]. A gene–gene interaction between Gly¹⁶Arg in *ADRB2* and variation in the S-nitrosoglutathione reductase gene (*GSNOR*) which encodes a key regulator of the endogenous bronchodilator, S-nitrosoglutathione, was associated with albuterol bronchodilation in Puerto Ricans from GALA, but not Mexican Americans [80]. Admixture-based genome-wide studies such as Mapping by Admixture Linkage Disequilibrium (MALD) are powerful approaches that could be used in admixed populations or ethnic groups that experience differential responses to specific therapies to identify genetic loci that harbor gene variants associated with these responses. SNPs in *ADRB2* (Gly¹⁶Arg), *SPATS2L* (rs295137), and *GLCCI1* (rs37972) have frequencies that vary in African and European ancestral populations and, hypothetically, might contribute to the differential responses to LABA and ICS therapy between African Americans and non-Hispanic Whites [12, 79, 81, 82].

Biologic therapies targeting novel pathways are currently being developed for the treatment of refractory asthma; therefore, it will become imperative to design pharmacogenetic studies that will identify those who will experience beneficial effects. For example, pitrakinra is a molecular inhibitor of the IL-4 α receptor subunit (encoded by *IL4RA*) which regulates the interleukin-4 inflammatory pathway and T-helper2 lymphocyte-mediated allergic inflammation. Specific variants in *IL4RA* have been associated with antigen-induced airway responsiveness in a trial cohort of atopic asthmatics randomized to pitrakinra; and, more recently, with a reduction of asthma exacerbations during treatment with pitrakinra in a phase IIb clinical trial [83, 84].

Conclusions

Most pharmacogenetic studies in asthma have been limited to candidate gene analyses in small populations which have identified SNP's that may “tag” for other causative variants. Investigators have also used replication in additional cohorts or in vitro cell-based models to validate the functional consequence of gene variation on therapeutic responses. Future pharmacogenetic approaches will continue to focus on larger clinical trial populations using unbiased genome-wide approaches to identify novel genetic loci of treatment response and genotype-stratified trials powered for risk genotypes. Current massively parallel DNA sequencing technologies will also allow for whole-genome and whole-exome sequencing that can identify rare variants, polynucleotide insertion–deletions, or duplications that may be in linkage disequilibrium with associated SNP's and potentially elicit strong effects on drug response phenotypes.

As the costs of genotyping and DNA sequencing continue to decline and our understanding of the genetic mechanisms of treatment response improves, panels of biomarkers will then be developed to determine which combination therapies are the most effective with the least risk for an individual asthma patient. Before we can usher in an era of personalized medicine for the treatment of asthma, it will be important to improve our ability to analyze large volumes of genetic data to detect and replicate associations with therapeutic responses in large clinical trial cohorts using a combination of study designs, analytical methods, and in vitro functional studies.

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Fig. 1. Pharmacogenetics research studies the role of genetic variability in determining interindividual responses to pharmacological therapies by analyzing the interaction of genotype and exposure to a medication, a gene–environment interaction

Fig. 2.

The ACRN Beta Agonist Response by Genotype (BARGE) Trial and changes in morning PEFR in 37 Arg¹⁶ homozygotes and 41 Gly¹⁶ homozygotes during treatment with regular albuterol or placebo for 16 weeks. Arg¹⁶ homozygotes experienced no change in PEFR while Gly¹⁶ homozygotes experienced an improvement in peak flow rates (PEFR) during regular albuterol therapy. Arg¹⁶ homozygotes experienced an improvement in PEFR during placebo treatment. (Reprinted from The Lancet, Israel et al. [45]; with permission from Elsevier.)

Table 1
Pharmacogenetic candidate genes for response to inhaled β_2 -adrenergic receptor agonists

Drug classes	Gene	Associated variants	Study designs	Cohorts (n) and population size	Response phenotype [reference]
Inhaled β_2 -adrenergic receptor agonists:	<i>CRHR2</i>	rs7793837	Retrospective	n=2: 1,186–2,145	Acute FEV1 bronchodilation [58, 63••]
	<i>ADCY9</i>	rs2230739 (Met ⁷⁷² Ile)	Retrospective	n=2: 436–2,145	Acute FEV1 bronchodilation [20, 63••]
Short-acting beta agonists (albuterol)	<i>ADRB2</i>	rs1042713 (Gly ¹⁶ Arg)	Retrospective and prospective, Genotype-stratified	n=5: 16–707 n=3: 78–190	Acute FEV1 bronchodilation [38–42] Long-term PEFR response [43–45]
	<i>ARG1</i>	rs2781659, rs2781667	Retrospective	n=3: 200–2,145	Acute FEV1 bronchodilation [59, 60, 63••]
	<i>ARG2</i>	rs17249437, rs3742879	Retrospective	n=1: 200	Acute FEV1 bronchodilation [60]
	<i>NOS3</i>	rs 1799983 (Asp ²⁹⁸ Glu)	Retrospective	n=1: 81	Acute FEV1 bronchodilation [62]
	<i>SPATS2L</i>	rs295137	GWAS	n=1: 2,145	Acute FEV1 bronchodilation [63••]
Long-acting beta agonists (salmeterol and formoterol)	<i>ADCY9</i>	rs2230739 (Met ⁷⁷² Ile)	Retrospective	n=1: 86	Long-term FEV1 response [72]
	<i>ADRB2</i>	rs1042713 (Gly ¹⁶ Arg)	Retrospective	n=1: 48	Long-term PEFR response [46]
			Retrospective and prospective, Genotype-stratified	n=5: 87–2,655 n=2: 87–152	No effect on PEFR response [43, 47–49, 51] Bronchoprotection [49, 50]
			Prospective, genotype-stratified	n=1: 62	Preference for montelukast or LABA as add-on to ICS [52]

Candidate genes are summarized by drug class, associated polymorphisms (rs number and coding change, if relevant), study design, number of cohorts studied, population size, and response phenotype for which a pharmacogenetic effect has been detected

PEFR Peak flow rate, LABA long-acting beta agonist, ICS inhaled corticosteroid

Table 2

Pharmacogenetic candidate genes for response to inhaled corticosteroids (ICS)

Drug class	Gene	Associated variants	Study designs	Cohorts (n) and population size	Response phenotype [reference]
Inhaled glucocorticoids: (fluticasone, budesonide, flunisolide, triamcinolone)	<i>CRHR1</i>	rs242941, rs1876828	Retrospective	n=1: 1,117	FEV1 response [68]
	<i>STIP1</i>	rs2236647, rs6591838, rs1011219	Retrospective	n=1: 382	FEV1 response [69]
	<i>TBX21</i>	rs2240017 (His ³³ Glu)	Retrospective	n=2: 53–701	Bronchoprotection [70, 71]
	<i>GLCCI1</i>	rs37972=rs37973	GWAS	n=1: 1,053	FEV1 response [74••]
	<i>T</i> Gene	rs3127412, rs6456042, rs3099266, rs2305089	GWAS	n=1: 815	FEV1 response [75••]
	<i>CYP3A4</i>	CYP3A4*22	Retrospective	n=1: 413	Asthma control [76]
	<i>ADCY9</i>	rs2230739 (Met ⁷⁷ Ile)	Retrospective	n=1: 86	Long-term FEV1 response [72]

Candidate genes are summarized by drug class, associated polymorphisms (rs number and coding change, if relevant), study design, number of cohorts studied, population size, and response phenotype for which a pharmacogenetic effect has been detected