

Asthma Pharmacogenomics: 2015 Update

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Abstract There is evidence that genetic factors are implicated in the observed differences in therapeutic responses to the common classes of asthma therapy such as β 2-agonists, corticosteroids, and leukotriene modifiers. Pharmacogenomics explores the roles of genetic variation in drug response and continues to be a field of great interest in asthma therapy. Prior studies have focused on candidate genes and recently emphasized genome-wide association analyses. Newer integrative *omics* and system-level approaches have recently revealed novel understanding of drug response pathways. However, the current known genetic loci only account for a fraction of variability in drug response and ongoing research is needed. While the field of asthma pharmacogenomics is not yet fully translatable to clinical practice, ongoing research should hopefully achieve this goal in the near future buttressed by the recent precision medicine efforts in the USA and worldwide.

Keywords Asthma · Genes · Pharmacogenomics · Pharmacogenetics · GWAS · Systems biology

Introduction

Asthma is a chronic inflammatory respiratory condition that affects greater than 300 million people in the world of all races and ethnic groups and both pediatric and adult populations [1]. The disease is characterized by airway obstruction caused by a combination of airway smooth muscle hyperresponsiveness and airway inflammation leading to symptoms of cough, wheezing, and dyspnea [2]. The economic costs associated with asthma have been found to be one of the highest among chronic diseases with drug therapy as a major contributor [3].

The three main drug classes for asthma include short-acting β 2-agonist (SABA) and long-acting β 2-agonist (LABA), inhaled corticosteroids (ICSs), and leukotriene modifiers (LTMs). Therapy is prescribed in a stepwise approach based on clinical parameters and events such as frequency of asthma exacerbations [4]. Although the disease has complex pathobiology with a significant degree of heterogeneity and potential phenotypes [5••], there is evidence that genetic or heritable factors are implicated in observed differences in therapeutic responses to drugs [6, 7] and pathogenesis depends on phenotype [8]. Pharmacogenomics is the “study of the role of inherited and acquired genetic variation in drug response” [9] including both DNA and RNA elements [10]. Broadly speaking, the term pharmacogenomics can be extended to include other elemental human building blocks, such as the proteome, metabolome, or microbiome. Pharmacogenetics is a subset of pharmacogenomics and focuses on heritable DNA sequences of individual genes predicting treatment response. The goal of pharmacogenomics is to facilitate “the identification of biomarkers that can help...optimize drug selection,

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dose, and treatment duration and avert adverse drug reactions...provide new insights into mechanisms of drug action...and contribute to development of new therapeutics” [11]. There has been a shift from individual candidate gene studies for evaluation of drug pathways to genome-wide association studies (GWASs) to identify novel variations affecting drug response. Ultimately, there is a need for systems biology including other *omics* approaches, given the variability of drug response that involves multiple factors [12]. The goal of personalized medicine for asthma has yet to be realized, although there continues to be progress. This review will highlight important studies over the past few years in asthma pharmacogenomics and explore future directions in the field. Table 1 summarizes the asthma pharmacogenomic findings since 2013.

Short- and Long-Acting β 2-agonists

Short-acting β 2-agonists are the most commonly prescribed medication for asthma and most effective for reversal of airway obstruction. Long-acting β 2-agonists are prescribed with ICS for additional asthma control [2]. Both SABA and LABA bind to the β 2-adrenergic receptors (β 2-ARs) located on smooth muscle cells of the lower respiratory tract. The β 2-AR subsequently couples to adenylate cyclase via trimeric G protein leading to production of cyclic adenosine monophosphate (cAMP) and activation of protein kinase A (PKA). PKA phosphorylates regulatory proteins involved in muscle tone, and cAMP produces retention of intracellular calcium with both processes causing relaxation of the airway smooth muscle [13]. Population-based studies have suggested that a substantial portion of SABA response in the lung is determined genetically [14]. There are numerous pharmacogenomic studies regarding β 2-agonist response as recently reviewed by Ortega [15•].

The candidate gene approach has been used in many asthma pharmacogenetic studies.

The *ADRB2* gene encodes the β 2-AR and has been the most studied in drug response, most notably the common coding variant Arg16Gly (rs1042713) [16, 17]. Based on an in vitro study with human smooth muscle cells, cells with the Gly16 variant underwent enhanced β 2-agonist-promoted downregulation compared to the Arg16 variant [18]. This variant has been the focus of most pharmacogenetic studies of *ADRB2*, and the effect of genotype on treatment response to β 2-agonists appears more evident for children than adults with asthma. Taylor et al. had retrospectively examined asthma control during long-term treatment with salbutamol and salmeterol with the major finding that Arg16 homozygotes had increased frequency of major exacerbations with chronic dosing of salbutamol compared to placebo [19]. Another trial showed a small decline in morning peak expiratory flow rate

(PEFR) in patients homozygous for Arg16 with regular albuterol usage with effect magnified during a run-out period [20]. However, the decrease in peak flow was only 30.5 L/min compared to Arg homozygotes which used as needed albuterol. Both of these studies formed the basis for the Beta Agonist Response by Genotype (BARGE) trial by the Asthma Clinical Research Network (ACRN) [21••]. This genotype-stratified, cross-over trial of Arg16 and Gly16 homozygotes found that Arg16 homozygotes had lower morning PEFR during treatment with albuterol than during the placebo period, although the difference in PEFR was only -10 (-19 to -2 , $p=0.02$), making the clinical significance uncertain.

Studies have also focused on the Arg16Gly variant for LABA therapy [22–24] mostly showing no difference in PEFR responses in asthmatics with different Arg16Gly genotypes during LABA therapy. The most notable study was a genotype-stratified trial from ACRN entitled Long-Acting Beta Agonist Response by Genotype (LARGE) trial [25]. Primary finding revealed and agreed with other retrospective studies is that there was no significant effect on AM PEFR with LABA/ICS. However, in a pre-specified secondary outcome variable (methacholine PC20, a measure of airway responsiveness), Gly/Gly subjects demonstrated doubling in PC20 when LABA therapy was added to ICS, indicating enhanced bronchoprotection with no effect noted in Arg/Arg subjects. A subsequent trial performed with LABA alone and in combination with ICS also showed no evidence of pharmacogenetic effect of β -receptor in either Arg or Gly genotypes [24]. This study was important as the LABA and LABA/ICS design would be able to determine if corticosteroids could have confounded study results.

Other recent studies have further explored the *ADRB2* gene. Lipworth et al. showed that pediatric patients with the Arg16 genotype may benefit from montelukast rather than salmeterol as an add-on therapy to ICS as the Arg16 genotype confers increased susceptibility to exacerbations in children with asthma on regular LABA therapy, although the study was limited, given the absence of Gly16 homozygotes for comparison [26]. The Pharmacogenetics of Asthma Medication in Children: Medication with Anti-inflammatory Effects (PACMAN) cohort study also explored the Arg16 genotype and treatment outcome in 597 children treated with ICS and LABA. Arg16 homozygotes also had increased risk of exacerbations with combined LABA and ICS [27]. Lastly, Ortega et al. had explored rare variants in *ADRB2* with usage of an African American, non-Hispanic white, and Puerto Rican cohort. It was found that Ile164 and -376 ins were associated with adverse events during LABA therapy, namely increased asthma-related hospital admissions for all ethnic groups [28].

In summary, despite the importance of the receptor as the start of the beta-agonist response, the functional polymorphism at position 16 seems not to have enough clinical effect to justify genotyping of all subjects.

Table 1 Recent studies in asthma pharmacogenomics

Drug class	Gene	Associated variant	Notes	Reference(s)
β 2-agonist LABA	<i>ADRB2</i>	rs1042713 (Arg16Gly)	Proof-of-concept randomized control trial in children. The Arg16 genotype may benefit from montelukast rather than salmeterol as an add-on therapy to ICS	[26]
LABA	<i>ADRB2</i>	rs1042713 (Arg16Gly)	Case-control study within PACMAN cohort. Also found pediatric Arg16 homozygotes that use LABA in addition to ICS at increased risk for asthma exacerbations	[27]
LABA	<i>ADRB2</i>	Ile164, -376ins	First study to identify pharmacogenetic interaction between rare variants and asthma severity during LABA therapy	[28]
β 2-agonist	<i>THRB</i>	rs892940	Candidate gene approach examining in vitro response of epithelial/smooth muscle cells to isoproterenol and analysis of possible transcription factor genes	[32]
SABA	<i>ASB3/SOCS</i>	rs350729 rs1840321 rs1384918 rs1319797 rs11252394	GWAS of acute BDR from SHARP, found 4 SNPs in the same region of chromosome 2, suggesting novel genomic region associated with BDR	[35]
SABA	Several potential biological candidate genes		Another GWAS examining BDR with multiple definitions of BDR	[36]
SABA	<i>SPATA13-AS1</i>		GWAS of BDR in African Americans with replication in African American cohorts and European American cohorts	[37]
SABA	<i>SLC22A15</i>	rs1281748 rs1281743	GWAS of BDR in Latino children. Study utilized admixture mapping. Found 16 rare variants	[39•]
Glucocorticoid ICS LABA LTM	<i>CRHR1</i> <i>CHRM2</i> <i>HSP8A</i> <i>COL2A1</i>	Multiple (see text for full details)	Analysis of asthma candidate genes in small Caucasian cohort on ICS, ICS/LABA, and LTM. Confirmed prior associations with <i>CRHR1</i> in addition to other novel associations. Most notable was between <i>CRHR1</i> variants and inverse response between ICS and LTM	[49]
Corticosteroid	<i>HDAC1</i>	rs1741981	Investigation in case-controlled pediatric and adult cohort regarding the HDAC role and mechanism of corticosteroids. HDAC1 variant was related to asthma severity	[52]
ICS	<i>ZNF432</i>	rs3752120	Investigation whether or not ICS usage could influence the effect of SNPs associated with BDR in pediatric and adult cohort. Identified gene/variant of uncertain significance	[53]
ICS	<i>CYP3A4</i>	rs35599367 (CYP3A4*22)	Analysis of variants involved in fluticasone metabolism in children. Found improvement in asthma control scores in children treated with fluticasone that had CYP3A4*22	[54]
ICS	<i>GLCCI1</i>	rs37972	GWAS of response to ICS in CAMP cohort with replication in four independent populations. Identified variant in <i>GLCCI1</i> associated with decreased response to ICS based on functional analysis. Two subsequent studies did not replicate finding as discussed in the text	[55•, 56, 57]
ICS	<i>FBXL7</i>	rs10044254	First GWAS analyzing difference in self-reported asthma symptoms and response to ICS in CAMP cohort. Results not replicated in adult cohorts	[59]
ICS	<i>CA10</i> <i>SGK493</i> <i>CTNNA3</i>	rs967676 rs1440095 rs1786929	First GWAS of atopic vs. non-atopic asthma phenotypes in children and response to ICS	[60]
ICS	Metabolic genes related to lung function and asthma risk	rs6924808 rs10481450 rs1353649 rs12438740 rs2230155	Study incorporated pharmacodynamic principles of drug response in pharmacogenetic GWAS revealing 5 loci with significant effects on corticosteroid dose-response curves	[61]
ICS	<i>CRISPLD2</i>		RNA-Seq analysis characterizing change of airway smooth muscle cells in response to GC in vitro revealing gene that modulates cytokine function	[63]

Table 1 (continued)

Drug class	Gene	Associated variant	Notes	Reference(s)
ICS	<i>SPATA20</i>	rs6504666 rs1380657	Example of drug response eQTL identifying new genes/variants with respect to ICS response	[64•]
	<i>ACOT4</i>	rs12891009		
	<i>BRWD1</i>	rs2037925		
	<i>ALG8</i>	rs2836987		
	<i>NAPRT1</i>	rs1144764		
Leukotriene modifiers		rs3793371	First GWAS for leukotriene modifier response	[76]
	<i>MRPP3</i>	rs12436663		
	<i>GLT1D1</i>	rs517020		

Candidate studies of other β 2-adrenergic receptor pathway genes have also been performed. Adenylyl cyclase type 9 (AC9) was examined in vitro and in vivo at a common variant Ile772Met. Data suggested that the AC9-Met772 polymorphism was associated with “glucocorticoid-specific up regulation of the bronchodilatory response in both transfected lung cells and in childhood asthma” from the Childhood Asthma Management Program (CAMP) cohort [29]. More recently, in a smaller Korean pediatric cohort, results have suggested that ADCY9 gene polymorphisms alone and in combination with ADRB2 gene polymorphisms contribute to response to combination therapy in asthma [30].

Other studies have included investigation of the nitric oxide biosynthetic pathway, which consists of enzymes that metabolize arginine and synthesize nitric oxide resulting in bronchodilation. For instance, *ARG1* (rs2781659) was significantly associated with bronchodilator response (BDR) by screening the CAMP cohort and the children’s parents with usage of family-based association testing and was subsequently verified in three other cohorts [31].

Lastly, Duan et al. evaluated differential expression of transcription factors in epithelial and smooth muscle cells with exposure to isoproterenol for clinical effect in relation to BDR. A subsequent analysis of transcription factor genes revealed a non-coding SNP (rs892940) located in the 5’ of the *THRB* gene that was associated with response to β 2-agonists in the CAMP trial with replication in two adult asthma populations [32].

Whole-genome pharmacogenomic studies or GWASs are performed to identify loci that could affect drug response or result in adverse reactions. This approach has enabled discovery of novel and less obvious genes in disease that may not be apparent from candidate gene studies [33]. For instance, Himes et al. published a GWAS of BDR in 1644 European Americans from six drug clinical trials with two replication cohorts identifying SNP rs295137 near the *SPATS2L* gene, although the *p* value fell just short of genome-wide significance [34•]. Subsequent siRNA-mediated *SPATS2L* knock-down resulted in increased β 2-adrenergic receptors. These data suggest that *SPATS2L* may be an important regulator of β 2-adrenergic receptor downregulation.

Recently, Israel et al. performed a GWAS of BDR involving 444,088 SNPs from 724 individuals from the SNP Health Association Resource (SHARe) Asthma Resource Project (SHARP) building on prior candidate gene studies and GWAS [35]. The study found four SNPs (rs350729, rs1840321, rs1384918, and rs1319797) associated with BDR located in the same region of chromosome 2, suggesting a novel genomic region associated with acute BDR. The nearest significant gene associations are gene coding for ankyrin repeat (*ASB3*) and suppressor of cytokine signaling (*SOC3*) box-containing protein 3 with perhaps a possible physiological role related to BDR and smooth muscle proliferation.

Another GWAS examining BDR with multiple definitions of BDR to SABA in the CAMP cohort with replication in cohorts with multiple phenotypes identified an intergenic SNP (rs11252394), which was near several excellent biological candidate genes including protein kinase C theta (*PRKCC*), interleukin receptors (*IL15RA*, *IL2RA*), and other genes [36].

Padhukasahasram et al. had performed a GWAS of SABA medication response identifying *SPATA13-AS1* as being significantly associated with SABA BDR in healthy African Americans and replicated in two African American cohorts and one European American cohort with asthma [37]. The mechanism of *SPATA13-AS1* and SABA BDR is unknown.

A prior Bayesian analysis by Himes et al. extended GWAS to include a Bayesian network approach and found 15 SNPs in the CAMP cohort predictive of BDR [38]. This approach is important, given utilization of Bayesian networks to provide analysis of complex pharmacogenetic data.

Rare variants have also been explored and may account for uncommon or severe responses associated with LABA therapy. Drake et al. performed a GWAS of BDR in 1782 Latino children with additional replication studies in 531 Latinos [39•]. The study also utilized admixture mapping to test for correlation between BDR and local genetic ancestry to complement the GWAS approach. The results were significant for 16 rare variants significantly associated with BDR including two rare variants in *SLC22A15* (rs1281748 and rs1281743), a gene expressed within the cytoplasm and membrane of bronchial epithelial cells.

Further research is needed especially in the adult population to implement any pharmacogenomics related to SABA and LABA into clinical practice at this juncture.

Corticosteroid Pathway

Inhaled corticosteroids are a first-line therapy and are an effective anti-inflammatory treatment for persistent asthma [2]. Glucocorticoids (GCs) act by binding an intracellular glucocorticoid receptor and subsequently translocating into the nucleus to alter transcription of genes through various mechanisms well described in the literature [40, 41]. Studies have also shown that glucocorticoids in vitro cannot only prevent but also reverse desensitization caused by chronic β 2-agonist exposure [42]. It is postulated that GC-induced upregulation of mitogen-activated protein kinase phosphatase 1 and subsequent decreased levels of pro-inflammatory phosphodiesterase 4 may explain this effect with respect to LABAs [43, 44]. Responsiveness to ICS therapy has been found to vary between individuals [45]; however, therapeutic responses to corticosteroids are influenced by genetics [7, 46]. Similar to the study of SABA and LABA pharmacogenetics, the corticosteroid pathway has been explored with candidate gene studies and GWAS. This pathway has also recently incorporated integrative analyses as well.

Candidate gene approaches have also been used to study the corticosteroid pathway. Tantisira et al. evaluated three independent cohorts including adults and children randomized to ICS therapy and identified two variations (rs242941 and rs1876828) in the corticotropin-releasing hormone receptor 1 (*CRHR1*) gene associated with therapeutic response to ICS [47•]. A subsequent study examined the chromosome 17 inversion polymorphism that encompasses *CRHR1* in both CAMP and an adult cohort and found an association between the chromosomal inversion and pharmacogenetic response to ICS [48]. Mougey et al. had performed an ancillary study to a prior large clinical trial [49]. This study consisted of an analysis on asthma candidate genes in a small Caucasian cohort on ICS, ICS/LABA, or montelukast with primary outcome consisting of Asthma Control Questionnaire (ACQ) scores and percent change in forced expiratory volume in 1 s (FEV1). The results had confirmed the association with *CRHR1* and ICS and also revealed other novel associations. Three SNPs in *CHRM2* (rs8191992, s6962027, and rs6967953) showed improvement in lung function with ICS/LABA. A single SNP in *HSP8A* (rs1461496) was associated with response to ICS/LABA therapy with homozygotes for the minor allele showing an increase in adjusted change in FEV1. There was also a single SNP in *HDAC2* (rs3757016) associated with favorable response to montelukast therapy. A novel association between *COL2A1* (rs2276458, rs2276455, rs2276454) and change in FEV1 on ICS was also detected.

CRHR1 variants (rs739645, rs1876831, rs1876829, rs1876828) were associated with improvement in lung function with ICS except rs242941, which was associated with a decrease in lung function. In contrast, the above four *CRHR1* variants were inversely related to response to montelukast with decrease in lung function. This was the first report of inverse association between genetic variants and responses to ICS and LTM and could be helpful in choosing optimal controller medication.

Another study had evaluated eight glucocorticoid complex genes and response to ICS in one adult cohort and found three SNPs (rs2236647, rs6591838, and rs1011219) within a heat shock-organizing protein *STIP1* resulting in improved lung function [50]. A SNP (His33Glu) in *TBX21*, which encodes for a transcription factor T-bet shown to be important in immune response, had been evaluated with respect to therapeutic response to ICS in the CAMP cohort. This variant was associated with resolution of airway responsiveness as measured by PC20 while on ICS. Subsequent functional analyses with cellular models suggested that *TBX21* may affect cytokines. A smaller Korean cohort ($n=53$) replicated the importance of *TBX21* with respect to ICS therapy based on FEV1 rather than PC20 [51].

Candidate epigenetic genes in the corticosteroid pathway have also been explored. Kim et al. had postulated from basic science research that histone deacetylase (HDAC) may play an important role in the mechanism of action of corticosteroids [52]. This study evaluated asthma severity and SNPs in *HDAC1* and *HDAC2* in a case-controlled cohort of pediatric and adult asthmatics and found that one SNP (rs1741981) in *HDAC1* was related to asthma severity with further mechanistic studies needed to clarify its role.

Given that patients may take both SABA/LABA and ICS, one study by Wu et al. had investigated with use of the CAMP cohort with replication in an adult cohort the question whether or not the use of ICS could influence the effect of SNPs associated with BDR [53]. Combined analyses resulted in identification of one SNP (rs3752120) located in the zinc finger protein gene (*ZNF432*) with uncertain biological significance. It was also suggested that treatment with ICS appeared to modify the effect of SNPs on BDR. Other candidate gene studies have also explored the interaction between these pathways such as variations in adenylyl cyclase type 9 (*ADCY9*) [29] and metabolism in the cytochrome complex (CY3A4) [54].

As with the β 2-agonist pathway, GWASs have also been important in understanding the glucocorticoid pathway. Tantisira et al. had performed a GWAS to assess response to inhaled corticosteroids in the CAMP cohort with use of a family-based screening algorithm and with replication in four independent populations including adult patients that identified rs37972, which mapped to the glucocorticoid-induced transcript 1 gene (*GLCCI1*) [55•]. This variant was associated

with decreased FEV1 response to ICS based on further functional analysis. rs37972 was in complete linkage disequilibrium with rs37973, which downregulates *GLCCI1* expression and could cause a decreased response to ICS. Hosking et al. performed a subsequent study in 1924 non-Hispanic white subjects testing for associations between rs37973 and measures of ICS response in subjects treated with ICS; no significant association was noted [56]. Vijverberg et al. also assessed whether variation in rs37972 could be associated with increased risk of asthma exacerbations, uncontrolled disease, or need for higher ICS dosages in three north European populations consisting of children and young adults [57]. This study did not find that this variant leads to higher ICS dosages or higher risk of uncontrolled asthma/exacerbations. However, Hosking's study consisted mostly of adults with adult-onset asthma possibly representing a different asthmatic phenotype compared to Tantisira's initial study. Vijverberg's study had used clinical outcomes, which were different than lung function measures in Tantisira's study.

Another GWAS using the SHARP cohort and consisting of three cohorts and a replication cohort identified variants in the *T* gene (rs3127412, rs6456042) via this population-based GWAS, contrasting to the hits found with use of family-based screening algorithms in the *GLCCI1* study [58].

Park et al. had performed the first GWAS that analyzed differences in self-reported asthma symptoms in response to ICS in the CAMP trial as compared to prior studies mainly focusing on lung function and exacerbations [59]. Although three significant SNPs were found, these findings were not replicated in adult cohorts. Most notably, rs10044254 was found in an intronic region of the *FBXL7* gene with functional studies performed. This study overall suggested that a specific genetic mechanism regulating symptomatic response to ICS in children may not carry over to the adult asthma population.

Another recent GWAS had addressed the issue of relating ICS response to specific asthma phenotypes. Perin and Potočnik had performed a GWAS in different phenotypes of childhood asthma and analyzed correlation between SNPs and clinical parameters [60]. This study was the first to investigate a correlation among recently identified SNPs, clinical data, and asthma phenotypes defined as atopic based on skin prick testing and IgE levels versus non-atopic in combination with treatment response to ICS. Three SNPs including rs967676 (*CA10*), rs1440095 (*SGK493*), and rs1786929 (*CTNNA3*) were found to be important on clinical parameters in asthma and glucocorticoid response. *SGK493* was a risk allele for non-atopic asthma and was a new association with severity of airway hyper-reactivity. In addition, *CA10* was also associated with treatment outcome in atopic asthmatics, although some effects on disease behavior parameters were observed only in the non-atopic group, suggesting a genetic heterogeneity between the groups. Lastly, asthmatics with *CTNNA3* genotypes of CT or TT in SNP rs1786929 had better response

to ICS compared to homozygotes for allele C with CC homozygotes not benefiting from ICS therapy, all making this a potential useful biomarker to predict outcome with ICS.

Wang et al. performed a GWAS that utilized an alternative approach incorporating pharmacodynamic principles of drug response into a pharmacogenetic GWAS [61] as described in prior literature [62•]. This adult study involved the Dose of Inhaled Corticosteroids with Equisystemic Effects (DICE) trial and replication in three other independent cohorts with varying doses of ICS combined with multiple longitudinal data points. There were five loci detected with significant effects on corticosteroid dose-response curves including rs6924808, rs10481450, rs1353649, rs12438740, and rs2230155. The pharmacodynamic model approach is unique to date, and the integration of biochemical processes of drug response into GWAS had proved to be statistically more powerful for gene detection compared to traditional single-dose approaches.

There have been multiple new studies related to ICS response utilizing newer analytical methods including RNA-Seq analysis, expression quantitative trait loci (eQTL), and GWAS incorporating pharmacodynamic principles. Himes et al. had applied RNA-Seq analysis to characterize changes of airway smooth muscle cells in response to GC in an in vitro model with resultant identification of *CRISPLD2* as a glucocorticoid-responsive gene that modulates cytokine function [63]. Further biological testing with quantitate RT-PCR, western blotting, and RNA-mediated knockdown of this gene suggested anti-inflammatory effects of glucocorticoids in ASM.

A recent analysis by Qiu et al. implemented an integrative approach with an eQTL analysis combining GWAS data with expression microarrays from lymphoblastoid cell lines derived from asthmatic subjects in the CAMP trial treated with dexamethasone (drug response eQTL) and subsequently tested the associations of eQTL with longitudinal change in airway responsiveness to methacholine on ICS [64•]. The eQTL analysis technique in addition to other techniques such as methylation, metabolite, or protein levels has been recently reviewed (Fig. 1) [65]. There were multiple novel genome-wide significant pharmacogenetic loci identified in both Caucasian and African Americans including rs6504666 (*SPATA20*), rs12891009 (*ACOT4*), rs2037925 (*BRWD1*), rs2836987 (*BRWD1*), rs1380657 (*SPATA20*), rs1144764 (*ALG8*), and rs3793371 (*NAPRT1*). This study represented the first eQTL study for asthma pharmacogenomics. Another drug-specific eQTL had been performed with testing in Swedish human osteoblast-like cells to dexamethasone and subsequent analysis of clinical response in a small pediatric cohort revealing changes in Tenascin-C (*TNC*) expression [66].

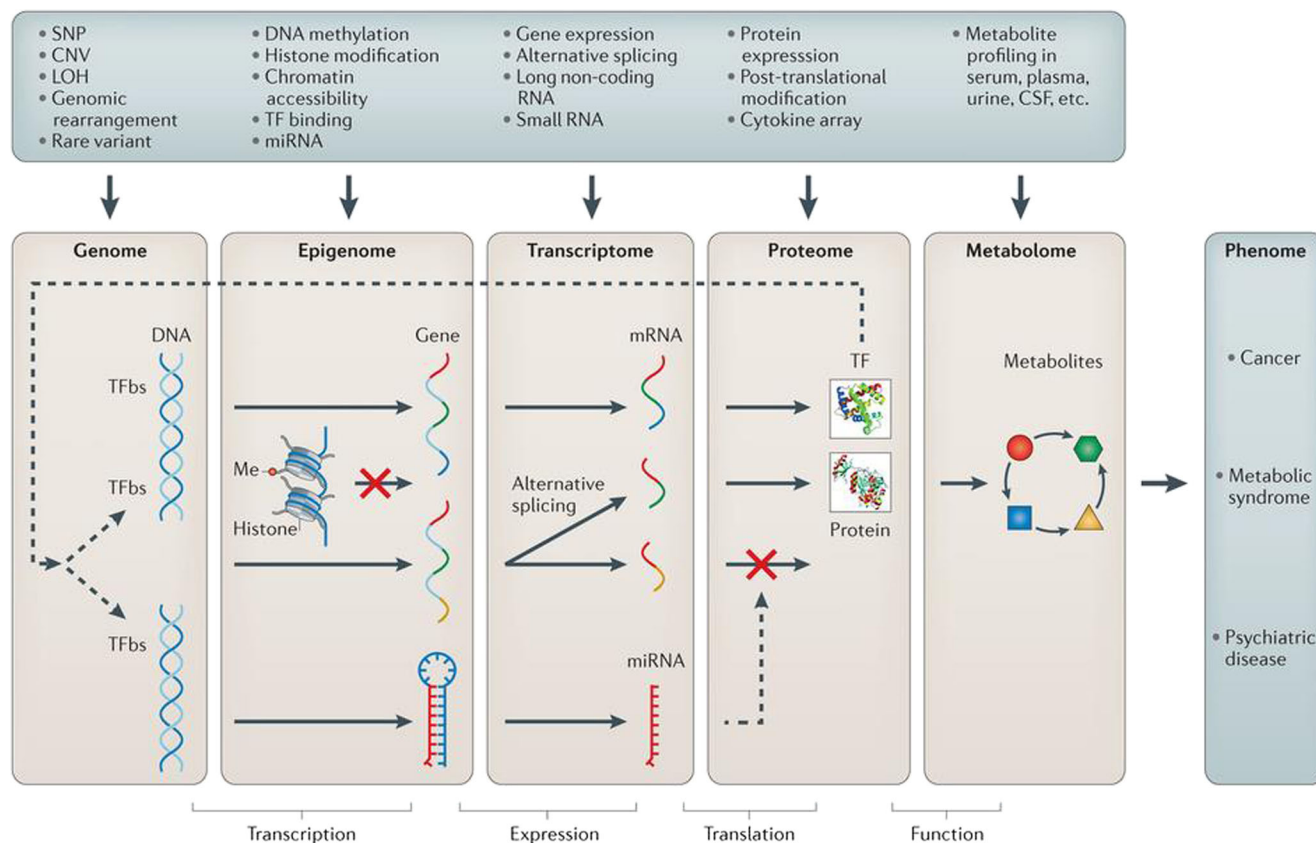


Fig. 1 Complex genetic diversity is located within and between various levels resulting in a clinical phenotype. There is a need for a network/systems biology approach to integrate data and to uncover genotype-phenotype interactions. See original article for full explanation of figure.

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Leukotriene Modifiers

The leukotriene pathway has an established role in asthma, and studies have shown a role for variability of genes in both disease susceptibility and medication effect [67]. Arachidonic acid is converted to leukotriene A₄ (LTA₄) by the enzyme 5-lipoxygenase (5-LO). LTA₄ is then converted to leukotriene C₄ by leukotriene C₄ synthase (LTC₄S) [68]. LTA₄ is transported extracellularly with further modifications to leukotriene E₄ and D₄, which bind to receptors present on leukocytes and lung smooth muscle cells such as cysteinyl leukotriene receptor 1 (cysLTR1) causing smooth muscle contraction among other actions.

Candidate gene studies have focused on variants of the 5-lipoxygenase gene (*ALOX5*), *LTC4S* (encoding for leukotriene C₄ synthase) [69], *LTA4H* (LT A₄ hydrolase), and MRP1 (multidrug resistance protein) and cysteinyl leukotriene receptors [70–72]. Telleria et al. had studied 61 patients with moderate persistent asthma with tandem repeat polymorphisms in the promoter of *ALOX5* and found that the wild-type allele (at least five tandem repeats) had less exacerbations, improved FEV₁, and less albuterol usage on

montelukast [73]. Kang et al. had performed a trial in children with montelukast showing significant effect of the presence of PTGDR –441C allele on responsiveness of LTRA during an exercise challenge [74]. Variants in the *SLCO2B1* gene have also been reported. This gene influences metabolism of drugs, affects montelukast plasma levels, and alters asthma control in patients taking montelukast [75].

Dahlin et al. have an in press article that is the first GWAS of leukotriene modifier response in asthma with previously unreported loci related to therapeutic responsiveness of LTMs [76]. This study utilized DNA and phenotypic information from two placebo-controlled trials ($N=526$) in which zileuton response was examined with 12-week change in FEV₁ following treatment with the top 50 SNP associations replicated in an independent zileuton treatment cohort and two independent cohorts of montelukast response. The resultant combined analysis showed rs12436663 in *MRPP3*-achieved genome-wide significance ($p=6.28 \times 10^{-8}$) with homozygous carriers having significant reduction in mean FEV₁ change following zileuton treatment. In contrast, rs517020 in *GLT1D1* had association with worsening responses to both montelukast and zileuton.

Future Directions

There has been much progress in the field of asthma pharmacogenomics with candidate gene studies, GWAS, and newer integrative techniques. However, the above genetic loci likely only account for a fraction of the variability in treatment response to the major classes of asthma therapy and are likely gossamer strands in a complex web of many different genomic influences such as gene-by-environment interactions, epigenetic regulation, and interactions between variants in different genes and genetic pathways. Limitations in current studies have included small sample sizes, heterogeneous populations such as pediatric and adult, possibly different asthma phenotypes, lack of drug levels, lack of a single or composite measure of drug response, lack of replication, and overall complexity of asthma as a disease. Functional assessment has been performed in some of the above studies in attempt to ascertain significance of genetic findings in contrast to certain clinical studies with findings of uncertain possible mechanism (e.g., *ZNF432*, *THRB*).

It is postulated that asthma is a syndrome containing different phenotypes, although it is unclear if these phenotypes could be classified by environmental triggers, immunologic features, molecular markers, or other schema [77, 78]. The great majority of the above studies explored response to drug phenotypes based on BDR, PC20, spirometry, and clinical

parameters such as self-reported symptoms. One of the above studies did explore atopy versus non-atopic patients [60]. Ultimately, asthma research needs to improve phenotyping or *endotyping* by molecular and other techniques such as omics [5•, 8]. One promising biomarker may be studying volatile organic compounds in exhaled breath as a novel metabolite [79]. Other biomarkers have been used in asthma biologic therapy such as the association with high periostin levels (a surrogate for activity of IL-13) and the humanized monoclonal anti-IL-13 antibody lebrikizumab [80].

Epigenetic regulation also plays a role in respiratory diseases and drug response including asthma [81]. For instance, increased methylation has correlated with differences in gene expression and may be related to asthma phenotypes, although it is difficult to discern as allergen exposure could also affect this pathway [82]. The literature has primarily described differential epigenome-wide DNA methylation patterns in childhood obesity-associated asthma [83], enhancers associated with TH2 memory cell differentiation and asthma [84], and β 2-adrenergic receptor gene methylation associated with decreased asthma severity in inner-city schoolchildren [85]. Other epigenetic mechanisms including histone modifications and inhibitors and RNA pathways such as microRNA (miRNA) and long non-coding RNA (lncRNA) [86–88] are also being explored as biomarkers and potential therapeutic interventions. For instance, miRNA-126 inhibition in experimental

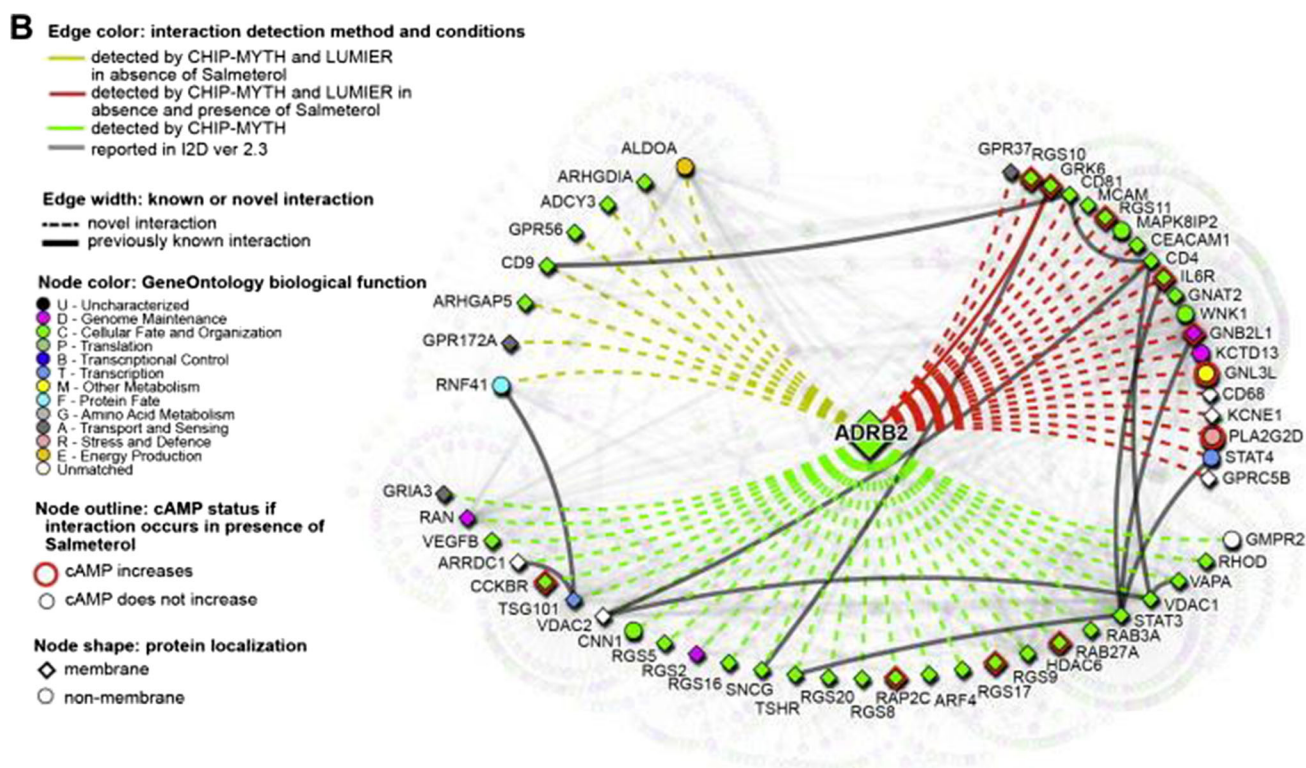


Fig. 2 Stimulation of ADRB2 results in perturbation of a wide variety of signals and proteins emphasizing the need for network/systems approach to asthma pharmacogenomics. See original article for full explanation.

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studies abolished house dust mite-induced airway hyperresponsiveness, inflammation, and mucus secretion [89]. Solberg et al. reported alterations of nine airway epithelial miRNAs in steroid-naïve asthma subjects compared to the same subjects following ICS therapy [90].

Asthma pharmacogenomics requires an integrative approach in order to achieve the ultimate goal of personalized medicine. Systems biology in a disease state has been defined as “an approach to understanding living systems that focuses on modeling diverse types of high-dimensional interactions to develop a more comprehensive understanding of complex phenotypes manifested by the system” [91]. There has been the development of multiple omics including the genome, epigenome, transcriptome, proteome [92, 93], metabolome [94], and microbiome, yielding a complex system applicable to the respiratory system. Figure 1 shows the complex diversity of genomic data contributing to clinical phenotypes. Most of the studies cited in this review are based on single omics or genomic analysis. Two recent studies have utilized a systems biology approach to analyze asthma and understand drug response or drug pathways. Sharma et al. published a unique study using multiple omics data or a network approach that identified the *GAB1* signaling pathway as an important novel modulator in asthma by creating an interactome [95•]. “Seed genes” were used as the starting point for the analysis to establish asthma association, and genomic, gene expression, and drug response data were utilized from the CAMP cohort with functional validation that found a link between *GAB1* and glucocorticoids. Kittanakom et al. have used a novel split-ubiquitin membrane yeast two-hybrid (MYTH) technology called CHIP-MYTH to study the G protein-coupled receptors (GPCRs) involved in the β 2-AR pathway in the presence or absence of salmeterol and resultant signaling cascade [96]. This study was able to reveal a complex network of protein-protein interactions not otherwise known as displayed in Fig. 2 and places into perspective the progress from studying ADRB2 as a candidate gene to a new understanding of this gene in a complex pathway. These studies reflect both the power and need for integrating multiple omics data into the study of asthma pharmacogenomics.

Lastly, these evolving data will need to be translated into clinical practice with the ultimate goal of personalized medicine and care of the asthmatic patient. Aspects of the health-care system must also be augmented including electronic medical records, point-of-care decision support, balancing of cost-effectiveness for potential genetic-based prescribing, and utilization of biobanks in order to enable a platform for pharmacogenomics [97]. A model for “personal omics” has been reviewed in the literature [98], and pharmacogenomic guidelines for clinical application of drug therapy for other conditions have been published [99], thereby providing templates for future personal asthma therapeutics.

Conclusions

Asthma pharmacogenomics continues to be an evolving field. The studies cited in this paper have showed the transition from initial candidate gene approaches (single omics) to GWAS to the analyses of complex networks with the use of systems biology/systems genomics and multiple omics. These newer techniques should continue to provide insights into not only the pathobiology of asthma but also potential new targets and information about drug response. Ultimately, though, the field has not been translated into personalized medicine that is ready for clinical use at this time. President Barack Obama of the USA had announced the Precision Medicine Initiative in his 2015 State of the Union Speech [100], which should continue to accelerate research and translate into providing guidance about the best treatment for a particular patient in not only asthma but also other diseases.

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Compliance with Ethics Guidelines

Conflict of Interest Joshua S. Davis, Scott T. Weiss, and Kelan G. Tantisira declare no conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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