Review Article

Recent advances in pharmacogenomics research of anti-asthmatic drugs: a narrative review

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Background and Objective: Bronchial asthma, a common respiratory disease in children and young adults, is characterized by hyperresponsiveness and reversible narrowing of the airways which manifest clinically as shortness of breath, cough, and/or wheezing. Although its pathogenic mechanism remains unknown, it's known that asthma patients have substantial interindividual variability in drug responsiveness, among which genetic factors play key roles. For improving the understanding of the biological mechanism of asthma and useful recognition of diagnostic and therapeutic targets, and the main purpose of this article is to optimize drug selection by analyzing genes associated with different drug responsiveness in asthmatic patients through the use of genomic techniques.

Methods: β2-agonists, inhaled corticosteroids (ICS), and leukotriene modulators are the most commonly used to treat asthma, and major genetic variations associated with differential response to these three drugs were identified via candidate gene association analysis, genome-wide association study (GWAS), and RNA sequencing.

Key Content and Findings: Genomics focuses on the effects of genetic variations in a group of genes. Most current studies have focused on the effect of single gene polymorphisms on drug efficacy, but the pharmacogenomics of asthma is inherently complex, with each factor having a small effect on drug responsiveness, and no single locus has yet been able to predict the variability in drug responsiveness.

Conclusions: According to epidemiological researches, a worldwide increase in the prevalence of bronchial asthma over the past four decades was shown. Genomic approaches can be used to screen for genetic variants associated with drug response. Stratifying patients prior to treatment helps to optimize drug selection, maximize the effectiveness of individual treatment, and improve clinical outcomes.

Keywords: Bronchial asthma; genomics; single nucleotide polymorphisms; genetic variants

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Introduction

Bronchial asthma, a common respiratory disease in children and young adults, is characterized by hyperresponsiveness and reversible narrowing of the airways which manifest clinically as shortness of breath, cough, and/or wheezing. Airway inflammation is the pathological features of asthma, which is closely related to immune response cells, inflammation mediators, cytokines and adhesion molecules. The past 3 decades have witnessed a rapid increase in the prevalence of bronchial asthma. It is projected that approximately 400 million people worldwide will experience asthma by 2025 (1). An epidemiological study in the United States revealed that there were more than 20 million people (or 8% of the overall population) with bronchial asthma nationwide in 2016, and the cost of diagnosing and treating the disease was estimated to be 20 billion USD (2). Asthma is mainly treated medically; however, as with most medications used in disease treatment, anti-asthmatic drugs have notably different responsiveness among individual patients, which limits the clinical efficacy of the medications. A lot of elements may affect individual response to medications, including gender, age, diet, smoking, disease status, and drug interactions (3). A large proportion of such interindividual variability in drug responsiveness can be explained by genetic factors, and genetic variation across an array of genes has been revealed as associated with differences in patients' response to anti-asthmatic drugs. Genomics has been used to study the effects of genetic variation of many genes, at the levels of both DNA and RNA. Genomics in the field of drug therapy has focused on how individual genetic differences affect interindividual variability in drug responsiveness. Pharmacogenomics is a new discipline, which offers the possibility of personalized drug selection with genetic information to improve effectiveness or avoid adverse reactions. Here, we have summarized the recent advances in the application of genomics in anti-asthmatic medications. Specifically, several genes associated with common asthma drugs were elaborated. We present the following article in accordance with the Narrative Review reporting checklist (available at https://atm.amegroups.com/article/view/10.21037/atm-22-291/rc).

Methods

Information used to write this paper was collected from the sources listed in *Table 1*.

Genomics: overview and analytic methods

Genomics focuses on the effects of genetic variations in a group of genes. Such changes include single nucleotide polymorphism (SNP), base insertion or deletion, copy number variation (CNV), and variable number of tandem repeats (VNTR). Several of these variants influence the number, timing, and function of encoded proteins, thus affecting certain physiological and pathological processes of the organism and its response to the outside world (4). As shown in *Figure 1*, the commonly used analytical methods in genomics include candidate gene association, genome-wide association studies (GWAS), RNA sequencing, and biological pathway analysis. Candidate gene association analysis is the study of associations between variants in genes of interest and disease phenotypes and is commonly used to analyze alleles in patients with different drug responses. Building on the existing knowledge of the function of a specific gene, it identifies and selects SNPs with potential function, detects their presence in patients and controls having the feature, and finally correlates the gene variants with drug response profiles. The genetic association is large when the minor allele frequencies (MAF) of the SNPs are greater than 10%. The strength of candidate gene association analysis is that it needs a relatively small sample size and is simple and economical to conduct; however, it requires prior knowledge of the function of genes associated with drug response, and selection of genes can be difficult if only limited information is available (5). Meanwhile, GWAS allows the analysis of thousands of SNPs, associating them with specific phenotypes or drug responses. It typically detects SNPs in the set of genomic regions with the greatest inter-individual variation on each individual's DNA microarray, with each SNP being tested independently. The GWAS method is characterized by its powerful statistical ability as it can process large sample sizes and detect and analyze entire genomes (6). In contrast, RNA sequencing helps to discover new genes involved in drug response by analyzing differences in expression profiles, usually in cell lines (7). Biological pathway analysis means that after the identification of candidate genes, other potential genes that influence drug action can be discovered by analyzing genetic networks and pathways (8).

Genomic association of commonly used anti-asthmatic drugs

β2-adrenergic receptor agonists, inhaled glucocorticoids

Table 1 The search strategy summary

Items	Specification
Date of search (specified to date, month and year)	1/1/2021
Databases and other sources searched	PubMed, Index to Chiropractic Index to Chiropractic, MANTIS, ERIC (Educational Resources Information Center), AMED (Allied and Complementary Medicine Database), CINAHL (Cumulative Index to Nursing and Allied Health Literature), EMBASE/Excerpta Medica, Cochrane Database of Systematic Reviews
Search terms used (including MeSH and free text search terms and filters)	Bronchial asthma, genomics, single nucleotide polymorphisms, genetic variants
Timeframe	1987–2020
Inclusion and exclusion criteria (study type, language restrictions etc.)	None used
Selection process (who conducted the selection, whether it was conducted independently, how consensus was obtained, etc.)	Jie Li conducted the selection, consensus was obtained by all researchers discussion
Any additional considerations, if applicable	None used

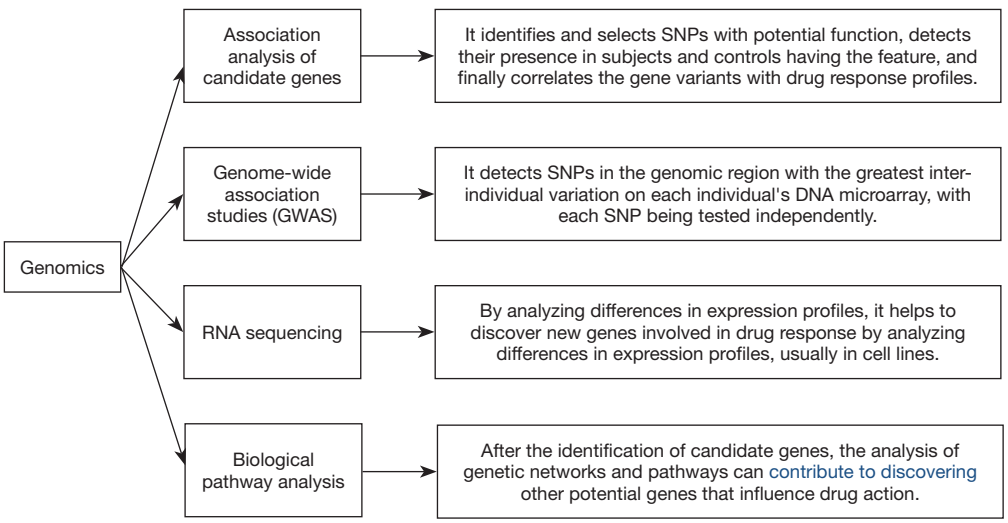

Figure 1 Common analysis techniques in genomics. SNP, single nucleotide polymorphism.

(ICS), leukotriene modulators, and anticholinergics are the most commonly used medications for asthma. These drugs can be divided into 2 groups: (I) anti-inflammatory drugs, which include ICS and long-acting beta agonists (LABA); and (II) drugs for rapid relief of symptoms such as acute bronchial stenosis, chest tightness, and wheezing, including short-acting beta agonists (SABA) (9). To date, most genomic studies on asthma pharmacotherapy have focused on 3 drug classes: beta agonists, ICS, and leukotriene modulators.

β2-agonist-related gene variations

Relying on the duration of action, β2-agonists are fallen into 3 classes: SABA (e.g., fenoterol, isoprenaline, levoproterenol, and salbutamol), LABA (e.g., salmeterol and formoterol), and ultra-long-acting agonists (e.g., vilanterol and indacaterol) (10).

Discovered by Kobilka *et al.* in 1987, the adrenoreceptor beta 2 (*ADRB2*) gene and is localized to chromosome 5q31-q32, an area linked with asthma- associated

phenotypes (11). More than 80 SNPs have been identified for *ADRB2*, the most common being Arg16Gly (rs1042713) and Glu27Gln (rs1042714). The approximated frequency of the Arg16 variant is 39.3% in whites, 49.2% in blacks, and 51.0% in Han Chinese (12). It has been shown that homozygotes of Arg16 have a greater bronchodilating effect of salbutamol compared to homozygotes of Gly16, with a significant increase in forced expiratory volume 1 (FEV1) after drug administration. However, the decline in FEV1 was also faster in individuals with Arg16 genotype after LABA use, and several patients who received the treatment of salmeterol even suffered from severe asthma exacerbations (13). Children who are homozygous for Arg16 have poor outcomes while receiving the treatment with LABA and ICS, and therefore montelukast has been recommended as an alternative to salmeterol as customized second-line asthma controller therapy in asthmatic kids. Other uncommon nonsynonymous coding variants of *ADRB2* have been disclosed. For instance, the SNP rs1800888 encodes a threonine on Thr164Ile; compared with carriers of wild-type Thr164, individuals homozygous for Ile164 are 3- to 4-fold less responsive to LABA (14).

The adenylyl cyclase type 9 (*ADCY9*) gene is part of the signaling pathway of the β2-adrenergic receptor (β2-AR). Slob *et al*. found that the SNP Ile772Met (rs2230739 in *ADCY9*) was related to acute bronchodilation to SABA in asthmatic patients and also with changes in lung function in response to ICS (15). Arginases, which are encoded by *ARG1* and *ARG2*, are metabolized *in vivo* into L-arginine, which in turn generates nitric oxide (NO) in the presence of nitric oxide synthase (NOS), and NO is an endogenous bronchodilator. Ziyab *et al*. found that *ARG1* polymorphisms (rs2781659 and rs2781667) were related to acute SABA-induced bronchodilation in asthmatic patients (16). A Dutch asthma population-based cohort study demonstrated that 2 polymorphisms in *ARG2* (rs17249437 and rs3742879) were related to asthma and more serious airway obstruction (17). The bioactivity of NO is mediated through the formation of S-nitrosothiols (SNOs), whereas S-nitrosoglutathione reductase (*GSNOR*) metabolizes SNO. A recent sequencing study of the *GSNOR* gene in the United States identified 13 SNPs, with an allele frequency of >5%. The authors demonstrated an interaction between *GSNOR* and *ADRB2* in Mexicans, which was believed to be associated with decreased bronchial responsiveness to bronchodilators (18). Through GWAS, Kabesch *et al*. identified 4 asthma-associated SNPs (rs350729, rs1840321, rs1384918, and rs1319797) in the spermatogenesis associated serine rich 2 like (*SPATS2L*) gene on chromosome 2, which may be associated with β2-adrenergic receptor downregulation (19).

ICS-related gene variations

The earliest studies on glucocorticoid responsiveness were focused on the glucocorticoid receptor gene nuclear receptor subfamily 3, group C, member 1 (*NR3C1*), which is located on chromosome 5q31. It has been shown that 2 SNPs of this gene have a potential impact on glucocorticoid responsiveness, one of which, Asn363Ser (rs56149945 in NR3C1), has been recognized in some populations, and lymphocytes of individuals carrying this genetic variant have a higher sensitivity to dexamethasone compared to non-carriers (20).

The corticotropin releasing hormone receptor 1 (*CRHR1*) gene encodes the main receptor for corticotropin-releasing hormone and is a core regulator of corticosteroid synthesis and catecholamine generation. Rijavec *et al*. observed a great association correlation between improved pulmonary function after ICS treatment and *CRHR1* SNPs (rs1876828, rs242939, and rs242941), and individuals homozygous for this polymorphism had significantly higher mean FEV1 than other patients (21). A low-affinity receptor for immunoglobulin E (IgE), a core molecule for B-cell stimulation is encoded by the Fc epsilon receptor 2 (*FCER2*) gene. It was observed that the SNP rs28364072 of *FCER2* is related to a growing risk of re-exacerbation after ICS treatment in asthmatic children, who also had significantly higher serum IgE levels, possibly by a mechanism in which *FCER2* variants adversely affect the normal negative feedback mechanism on IgE synthesis (22). The stress stimulated phosphoprotein 1 (*STIP1*) gene encodes a heat shock protein, which is essential for assembling and activating of the glucocorticoid receptor. It was shown that SNPs (rs6591838, rs2236647, and rs1011219) in *STIP1* are greatly related to improved FEV1 responses in asthmatic patients with reduced lung function after 4 weeks of glucocorticoid treatment (23). Weitzel *et al*. performed RNAseq analysis of the transcriptome of 4 classes of human airway smooth muscle (ASM) cells and identified cysteine rich secretory protein LCCL domain with 2 (*CRISPLD2*), encoding a secreted protein associated with lung growth and endotoxin control (24). The *CRISPLD2* gene was found to have an SNP associated with ICS resistance in asthmatic patients. Reverse transcription polymerase chain reaction (RT-PCR) and western blotting further displayed that dexamethasone

Table 2 Genes associated with asthma drug responsiveness (identified by genomic techniques)

Class	Gene name
β2-receptor agonists	*ADRB2, Arg16, ADCY9, ARG1, ARG2, GSNOR,* and *SPATS2L*
Inhaled glucocorticoids (ICS)	*NR3C1, CRHR1, FCER2, STIP1, CRISPLD2,* and *TBX21*
Leukotriene modifiers	*ALOX5, LTC4S, ABCC1,* and *SLCO2B1*

treatment grew the expression of *CRISPLD2* messenger RNA (mRNA) and protein levels in ASM cells, and functional researches confirmed that *CRISPLD2* could regulate the anti-inflammatory roles of glucocorticoids in ASM (25). Another candidate gene associated with ICS treatment response is T-box transcription factor 21 (*TBX21*). Mice with a targeted deletion of the *TBX21* gene rapidly exhibited airway hyperresponsiveness, increased airway eosinophilia, and accelerated airway remodeling processes. The SNP rs2240017 of *TBX21* was related to improved bronchoprotection (26). Hernandez-Pacheco *et al.* conducted a cohort study and found that patients heterozygous for rs2240017 had significantly lower airway hyperresponsiveness during ICS treatment compared to those homozygous for this SNP (27).

Leukotriene modulator-related gene variations

Leukotriene modulators have potent anti-inflammatory activity and can improve the clinical course of asthma with minimal side effects. Depending on their mechanism of action, they are divided into 2 classes: cysteinyl leukotriene receptor antagonists (e.g., montelukast, zafirlukast, pranlukast, and tomelukast) and 5-lipoxygenase inhibiting agents (e.g., zileuton).

To date, the vast majority of pharmacogenetic studies on leukotriene modulators have focused on the variants of 5-LOX gene (*ALOX5*) and LTC4 synthase (*LTC4S*). Located on chromosome 10q11.12, the *ALOX5* gene has 14 exons. Its activity is related to many repetitive sequences in the promoter area Sp1/Erg1. Mutant *ALOX5* repeat polymorphism has been related to declined exacerbation rates in montelukast-treated asthma patients. Another study in Spain showed a reduced number of acute asthma exacerbations and increased FEV1 in patients with wild-type alleles or heterozygotes; in addition, these patients had increased urinary leukotriene E4 concentrations, reflecting increased leukotriene biosynthesis (28). Candidate gene analysis suggested that other *ALOX5* SNPs (rs2115819, rs4987105, and rs4986832) might also affect the response to montelukast (29). The leukotriene C4 synthase gene (*LTC4S*) is one of to the S-glutathione synthase family, catalyzing the transformation of LTA4 to LTC4. The most significant SNP identified so far is rs730012, which is associated with increased generation of LTC4 in eosinophils (30). Pham *et al.* found a 73% reduction in the risk of acute asthma exacerbations in montelukast-treated patients homozygous for rs730012 (31). The ATP binding cassette C1 (ABCC1) gene, which encodes multi-drug resistance protein 1 (MRP1) and exerts a significant effect on the transmembrane transport of LTC4, has also been studied. A polymorphism of this gene (rs119774 in LTC4) was associated with the montelukast treatment response, and individuals heterozygous for rs119774 had 24% elevated FEV1 compared to those homozygous for this polymorphism (32). Meanwhile, LTA4 hydrolase acts to convert LTA4 to LTB4, and the gene encoding it is located on chromosome 12q22. A polymorphism of this gene (rs2660845 in LTA4) is related to with the risk of acute asthma exacerbations during montelukast treatment. Individuals heterozygous for rs2660845 have a 4-fold higher risk of acute asthma exacerbations than the homozygous individuals (33). The mechanism may be that this SNP lowers LTA4 hydrolase activity, leading to a decrease in LTB4 synthesis, which stimulates the LTC4-synthesis pathway to promote the synthesis of cysteinyl leukotriene. The solute carrier organic anion transporter family member 2B1 (*SLCO2B1*) gene encodes protein 2B1, which exerts a significant effect on the active transport of organic anions by the intestinal wall. rs12422149 is associated with the transport and serum level of montelukast, and individuals with rs12422149 had 39% lower serum level of montelukast than controls (34). A summary of the asthma drug treatment response-related genes is shown in *Table 2*.

Future prospects

Many pharmacogenomic studies conducted so far have had limitations including small sample scale, inaccurate phenotype definition, unreasonable population

stratification, and shortage of reproducibility, which need to be addressed in future studies. High-throughput techniques have made large-size genotyping and expression studies possible in recent years. In addition, gene-environment interactions, mutual effects between variants in various genes and genetic pathways, epigenetic regulation, and transcriptional regulation of small interfering RNAs (siRNAs) and long-stranded non-coding RNAs (lncRNAs) are also topics for future pharmacogenomics studies. For instance, DNA methylation is an epigenetic alternation in which the addition of methyl to the cytosine residues of cytosine- and guanine-rich (CpG islands) DNA fragments within gene promoters stops the binding of transcription elements, which leads to downregulation of gene expression and may affect disease susceptibility (35). Interferon (IFN) gene promoter hypermethylation and interleukin-4 (IL-4) promoter hypomethylation have been revealed as related to elevated airway IgE levels in asthmatic patients, and DNA methylation of the 5-LO promoter regulates the expressions of key genes in the leukotriene pathway (36).

Most current studies have focused on the effect of single gene polymorphisms on drug efficacy, but the pharmacogenomics of asthma is inherently complex, with each factor having a small effect on drug responsiveness, and no single locus has yet been able to predict the variability in drug responsiveness. Therefore, developing statistical models to predict treatment responsiveness based on multiple genetic loci is warranted. Integrative genomics approaches that combine genome-wide SNP data with gene expression profiles will also be useful tools for recognizing new genes or mechanisms that leading to inter-individual modifiability in drug reaction. In recent years, great strides have been made in human genome analysis technologies and international information sharing networks. Large whole-genome sequencing projects, such as the NHLBI Exome Sequencing Project, 1000 Genomes, and gene sequencing projects in African ancestral populations, have achieved excellent results and created databases of rare genetic variants that could serve pharmacogenetic studies in different racial and ethnic groups in the future.

Summary

Although the etiology of asthma is still not fully elucidated, genetic factors have been demonstrated to play key important roles. Response to anti-asthmatic drug therapy varies widely among patients, and some patients may even experience life-threatening adverse drug reactions. Genomic approaches can screen for genetic variants associated with drug response. Stratifying patients prior to treatment helps to optimize drug selection, maximize the effectiveness of individual treatment, and minimize the risk of adverse reactions. Genomics can also offer new visions to the mechanisms of drug action and facilitate the growth of novel therapeutic options in the future.

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Footnote

Reporting Checklist: The authors have completed the Narrative Review reporting checklist. Available at https://atm.amegroups.com/article/view/10.21037/atm-22-291/rc

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at https://atm.amegroups.com/article/view/10.21037/atm-22-291/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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