



Pharmacogenetics and the treatment of asthma

Heterogeneity defines both the natural history of asthma as well as patient's response to treatment. Pharmacogenomics contribute to understand the genetic basis of drug response and thus to define new therapeutic targets or molecular biomarkers to evaluate treatment effectiveness. This review is initially focused on different genes so far involved in the pharmacological response to asthma treatment. Specific considerations regarding allergic asthma, the pharmacogenetics aspects of polypharmacy and the application of pharmacogenomics in new drugs in asthma will also be addressed. Finally, future perspectives related to epigenetic regulatory elements and the potential impact of systems biology in pharmacogenetics of asthma will be considered.

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Heterogeneity characterizes both the natural history of complex diseases as well as patient's response to treatment. The objective of personalized medicine (PM) is to understand the mechanisms underlying this variability in order to find the most adequate treatment for each individual patient. Asthma is a complex disease, caused by the interaction of multiple genetic and environmental factors [1,2]. There is increasing evidence of asthma heterogeneity based on molecular phenotyping, cluster analysis studies and biomarker studies. There are two major reasons that justify the pharmacogenetics research in asthma: there are interindividual differences in response to commonly used asthma medications and there is a subgroup of patients that does not respond to these drugs and, there is also a small subgroup who have shown an increased risk of rare, severe adverse events during long-acting β -agonists (LABA) treatment [3].

Phenotypes reflect the multifaceted interaction between genetic and environmental factors, resulting in different expressions of

the disease [4]. In recent years, great efforts have been made to characterize phenotypes in asthma [5], using different omics and molecular phenotype techniques [6]. The phenotypic characterization of asthma has revealed different subgroups of patients who share common clinical-biological features, with the final goal of selecting the best treatment for each patient [7]. However, an appropriate phenotypic classification of patients does not seem sufficient to find the best treatment, therefore other factors such as the genetic background should be taken into account.

Pharmacogenomics contributes to understanding the genetic basis of therapy responsiveness and thus, to defining therapeutic targets or molecular markers; these could be used in the evaluation of the effectiveness of new drugs. Its main objective is to find genetic variations that could affect drug responsiveness, increasing efficacy and safety of treatments [8,9]. Currently, there are different methods for studying

María Isidoro-García^{*1,2,3},
Almudena Sánchez-Martín^{2,4},
Asunción García-Sánchez^{2,5},
Catalina Sanz^{2,6}, Belén García-Berrocal^{1,2} & Ignacio Dávila^{2,5,7}

¹Department of Clinical Biochemistry, Pharmacogenetics Unit, University Hospital of Salamanca, Salamanca, Spain

²Institute for Biomedical Research of Salamanca (IBSAL), Allergy Department, Salamanca, Spain

³Department of Medicine, Faculty of Medicine, University of Salamanca, Salamanca, Spain

⁴Department of Pharmacy, Faculty of Medicine, University Hospital of Salamanca, Salamanca, Spain

⁵Department of Biomedical & Diagnostic Sciences, Faculty of Medicine, University of Salamanca, Spain

⁶Department of Microbiology & Genetics, Faculty of Biology, University of Salamanca, Salamanca, Spain

⁷Department of Allergy, Faculty of Medicine, University Hospital of Salamanca, Salamanca, Spain

*Author for correspondence:

Tel.: +34 923 291 100; ext: 55209

misidoro@usal.es

pharmacogenetic variants. Candidate-gene association studies have been profusely used in many pharmacogenetic studies of asthma [10]. Now, approaches have evolved from these individual candidate genes studies to the evaluation of drug metabolism pathways or to genome-wide association studies such as expression quantitative trait loci or RNA expression analysis using microarrays or RNAseq [11], have also contributed to understanding complex metabolic and biological pathways.

A comprehensive understanding of these pathways is essential for the application of pharmacogenetics to asthma therapeutics. In addition, by analyzing genes involved in drug response pathways new candidates related to drug metabolism could be identified.

The rapid development of omic technologies is providing huge quantities of information at different biological levels. Systems biology is defined as a biology-based interdisciplinary field focused on complex interactions within biological systems, applying an integrative perspective to biological and biomedical research [12]. This approach attempts to provide a holistic view of the mechanisms involved in the therapeutic response.

In this review, we will summarize different genetic loci identified in pharmacogenetic studies of asthma treatment. We will also take into account specific considerations regarding allergic asthma, pharmacogenetics aspects of polypharmacy in asthma, the application of pharmacogenomics in new drugs and future perspectives related to epigenetic regulatory elements and the potential impact of systems biology in the pharmacogenetics of asthma.

Genes involved in asthma treatment

Classically, pharmacogenomic studies have focused on the main asthma drugs: inhaled β 2-receptor agonists, inhaled corticosteroids and leukotriene modifiers. Involved drugs are shown in Table 1. In recent years, the development of new technologies and the constitution of collaborative consortia are aimed to identifying new genetic biomarkers involved in asthma drug responsiveness (Table 1).

Inhaled corticosteroids

Inhaled corticosteroids (ICS) are the mainstay of asthma treatment. Different genes involved in corticosteroid response have been described. *CRHR1* is a key regulator of corticosteroid synthesis and catecholamine production. A pharmacogenetic study [13] reported a significant correlation between SNPs located in this gene and improvement of lung function after inhaled corticosteroid therapy. The low-affinity receptor for IgE, FcεRII, is a key molecule for B-cell activation

and growth. A novel variant in the *FCER2* gene has been associated with a differential expression of the FcεRII, higher IgE levels and increased risk of exacerbations in asthmatic children receiving ICS [14]. Other studies have also confirmed the role of *FCER2* in personalized asthma treatment [15,16]. SNPs located in the promoter region of the *GLCCI1* gene, have been identified by Genome Wide Association Studies. These polymorphisms were also associated with lung function after treatment with inhaled glucocorticoids in a pediatric cohort [17]. Nevertheless, this association was not replicated in a larger clinical cohort of adult asthmatic patients [18]. SNPs located in the glucocorticoids receptor gene *NR3C1* have also demonstrated potential effects on corticosteroid response: lymphocytes from individuals with this genetic variation showed greater sensitivity to dexamethasone [19].

Chaperone proteins, including heat shock organizing protein and immunophilins bind to glucocorticoid receptors forming an hetero-complex that cooperatively activates the glucocorticoid receptor. Genetic variations in the gene encoding for STIP1 have been associated with regulation of corticosteroid response in asthmatic subjects, in particular, with changes in FEV1 [20]. In addition, polymorphisms located in the *TBX21* gene have also been associated with improvement of bronchial hyper-responsiveness in children treated with inhaled corticosteroids [21]. These results were replicated in a different population [22].

Significant associations between other genes such as *CA10*, *CTNNA3* and *SGK493* with asthma and glucocorticoid response have been reported [23]. In addition, different SNPs were significantly associated with corticosteroid dose-response in pharmacodynamic studies [24]. RNAseq analysis has also allowed characterizing transcriptomic changes in response to dexamethasone. *CRISPLD2* is an asthma pharmacogenetics candidate with SNPs associated to inhaled corticosteroid resistance in asthma patients [11]. Significant pharmacogenetic loci in *ACOT4*, *ALG8*, *BRWD1*, *NAPRT1* and *SPATA20* and *T-gene*, have been identified in different populations [25,26] by combining expression quantitative trait loci analysis with genome-wide association studies (GWAS).

β -adrenergic receptor agonists

Inhaled β -agonists are the most commonly prescribed drugs for the treatment of asthma. They exert their action by activation of β 2-adrenoreceptors expressed in bronchial smooth muscle cells. Their actions include muscle relaxation, airway dilatation and improvement of airflow [27]. Adenylyl cyclase ADY9 is a protein involved in the β 2-adrenergic receptor pathway. Genetic variants in its coding gene have been

Table 1. Genetic variants related to drug response in asthma.

Gene	Rsid	Drug
<i>ABCC1</i>	rs119774	Leukotriene modifiers
<i>ADCY9</i>	rs2230739	LABA, SABA
<i>ADRB2</i>	rs1042713, rs1800888	LABA
<i>ALOX5</i>	Promoter region, rs892690, rs2029253, rs2115819	Leukotriene modifiers
<i>ARG1</i>	rs2781659rs2781667	SABA
<i>ARG2</i>	rs7140310rs10483801	SABA
<i>CA10</i>	rs967676	Corticosteroids
<i>CRHR1</i>	rs242941, rs1876828, rs242939	Corticosteroids
<i>CTNNA3</i>	rs1786929	Corticosteroids
<i>CYSLTR2</i>	rs912278	Leukotriene modifiers
<i>FBXL7</i>	rs10044254	Corticosteroids
<i>GLCCI1</i>	rs37972	Corticosteroids
<i>GLT1D1</i>	rs517020	Leukotriene modifiers
<i>GSNOR</i>	Promoter region	Albuterol
<i>LTA4H</i>	rs2660845	Leukotriene modifiers
<i>LTC4S</i>	rs730012	Leukotriene modifiers
<i>MLLT3</i>	rs6475448	Leukotriene modifiers
<i>MRPP3</i>	rs12436663	Leukotriene modifiers
<i>NOS3</i>	rs1799983	SABA
<i>NR3C1</i>	rs56149945	Corticosteroids
<i>SGK493</i>	rs1440095	Corticosteroids
<i>SLC22A15</i>	rs1281748, rs1281743	SABA
<i>SLC24A4</i>	rs77441273	SABA
<i>SLCO2B1</i>	rs12422149	Leukotriene modifiers
<i>SPATS2L</i>	rs295137	SABA
<i>STIP1</i>	rs6591838, rs1011219	Corticosteroids
<i>T gene</i>	rs3127412, rs6456042	Corticosteroids
<i>TBX21</i>	rs2240017	Corticosteroids

LABA: Long-acting beta-agonist; SABA: Short-acting beta-agonist.

associated with the degree of acute bronchodilation in response to SABA in ICS treated patients [28] and with lung-function response to LABA and ICS in a Korean population [29]. In addition, other rare variants adjacent to *ADCY9* were associated with albuterol response in a Latin American cohort [30].

One of the best characterized genes in asthma pharmacogenetics is *ADRB2*, the β_2 adrenergic receptor. Multiple SNPs have been identified and associated to treatment response [31,32]. The SNP, Arg16Gly (rs1042713), is the most studied polymorphism and has been associated with a receptor downregulation [33]. Contrasting effects of the Arg16Gly locus during acute versus long-term SABA therapy, which have been

related to receptor kinetics or inflammatory effects, have been reported [33]. Pharmacogenetic studies of the Arg16Gly locus and response to SABA are the rationale for further studies of the *ADRB2* locus in LABA-treated trial cohorts [31,34–38]. Adverse responses associated to Arg16Gly variant during LABA therapy have been described, although this fact has not been confirmed in ulterior studies [37,38].

In addition, associations have been described in pediatric populations [39,40]. However, they do not seem to have any clinical relevance to justify individual genotyping [9]. Other less common variants of the *ADRB2* gene have also been related to asthma treatment [41,42].

ARG1 and ARG2 metabolize L-arginine to generate nitric oxide, which is an endogenous bronchodilator. *ARG1* polymorphisms were associated with the bronchodilator response (BDR) in asthmatics [43,44]. SNPs located in *ARG2* were also associated with airway obstruction and response to steroids [45]. S-nitrosoglutathione reductase is an enzyme that metabolizes S-nitrosothiol, an endogenous bronchodilator that is decreased in asthmatic children and adults [46,47]. Different SNPs have been identified in this gene [47]. An association between the *NOS3* gene polymorphism, that codifies for a protein involved in airway inflammation via nitric oxide pathway, with the response to ICS and LABA combined therapy has been reported [48].

Other gene variants related to β_2 responsiveness have been identified by GWAS studies. Different genetic variants located in the *SLC22A15* gene and associated to BDR have also been reported in Mexican populations [30]. *SPATS2L* has been suggested as a relevant regulator of the β_2 -adrenergic receptor [49,50]. In the childhood asthma management program, cohort of acute BDR to inhaled albuterol, a polymorphism located proximal to several candidate genes, including protein kinase C and interleukin receptors (IL15RA, IL2RA), was detected [51]. *SPATA13-AS1* was also significantly associated with bronchodilation induced by SABA in African-American populations [52].

Leukotriene modifiers

Leukotriene modifiers show anti-inflammatory activity in asthma, improving control and symptoms with minimal side effects. A significant interindividual response measured by lung function has been described with these drugs [53]. There are two groups of drugs: 5-lipoxygenase inhibitors (zileuton) and cysteine leukotrienes receptor antagonists (montelukast, zafirlukast, pranlukast). Different genetic variants have been identified in the pharmacogenetic response to leukotriene modifiers [15].

Multiple drug resistance proteins are transmembrane transports involved in drug response. The *ABCC1* gene encodes for MRP1, which is involved in the transport of LTC₄. SNPs located in the *LTC4* gene have been related to response to montelukast [54]. Other important genes related to the leukotriene modifier response are genes coding for LTA₄ hydrolase [54], *LTC4S* [55] and *ALOX5* [56], although controversial results have been reported [54,56,57]. Polymorphisms in the receptors of cysteinil-leukotriens *CYSLT1* and *CYSLT2* have also been identified [57,58]. Other genes such as *SLCO2B1* could also potentially influence the pharmacokinetics of montelukast [59,60] as well as *GLT1D1* [61] and *MLLT3* [62].

To summarize, genetic studies on corticosteroids, β -adrenergics and antileukotrienes based on pharmacogenetic loci have been discouraging, showing low accuracy in predicting individual responsiveness to a specific therapy. The loci studied seem to account only for a small proportion of the interindividual variability response. Therefore, genetic variants from different genes that additively interact to influence responsiveness to treatment should be simultaneously considered in pharmacogenetics studies. Larger, ethnically diverse clinical trial cohorts using more comprehensive genotyping from a larger catalog of variation from next-generation sequencing may lead to improve PM in asthmatic patients.

Genomics of allergen immunotherapy

As stated, PM takes into account the individual characteristics of each patient in order to improve both efficacy and safety. In some way, the discipline of allergy has anticipated the application of PM, adapting allergen immunotherapy (AIT) to patients in a tailored way. Therefore, allergy practice has been pioneer in the treatment individualization [63], which provides background for other disciplines in this model of PM.

Immunogenomics has appeared as a new omic discipline able to improve the knowledge in the AIT area. This includes the study of the immunogenic aspects associated with the response to vaccines and that would allow the customization of AIT based on genotypic information [64]. Some examples are related to IT of infectious diseases, such as hepatitis or measles [65], in which vaccinomics and predictive vaccinology is evolving in order to identify novel immune profiles and immunogenetic signatures that contribute to explaining the variance in immune response [66].

To initiate, monitor and successfully complete the administration of AIT in allergic asthma, predictive biomarkers are needed. This highlights the necessity to identify suitable candidates able to predict AIT response. To achieve this goal, some studies have been designed to analyze gene expression levels of certain cytokines involved in AIT [67]. While these studies describe possible modifications in the levels of gene expression, there is scarce information addressing changes in the sequences of their coding genes. Variations in the sequence of *HLA* genes related to the response to IT in Hymenoptera venom allergy have been reported. Polymorphisms of *HLA* gene sequences may be related to the success of AIT in these patients [68]. More studies focused on the pharmacogenetic impact on IT are needed to improve its efficacy and safety [69].

Pharmacogenetics & polypharmacy in asthma

Polypharmacy is almost a constant in the treatment of asthma. Thus, combination of ICS, β -adrenergic receptor agonists and leukotrienes modifiers are frequently associated, particularly in moderate-to-severe asthma. In addition, asthmatic patients can be prescribed additional medication for concomitant morbidities. This highlights the importance of taking into account pharmacological interactions as a whole. So, pharmacokinetic aspects of the pharmacogenetic approach can be relevant in these patients. CYP enzymes are a superfamily of mono-oxygenases very important in mammalian metabolism, oxidizing both xenobiotics and endogenous compounds [70]. CYP450 enzymes not only metabolize multiple drugs prescribed in asthmatic patients, but also can be regulated by these drugs. This should be considered in order to prescribe the best combination of medications. Pharmacogenetic analysis of genes coding for these enzymes can contribute to selection of the best approach, avoiding potential adverse effects and increasing safety of the patient. In [Table 2](#) the P450 metabolic patterns of main drugs used in the treatment of asthma are shown. Special consideration should be taken into account in the case of broadly used drugs, such as corticosteroids, that can interfere with a great number of other drugs used for the treatment of comorbidities [71].

PM models allowing the clinician the application of pharmacogenetics to drug response are required. We have recently described a new five-step pharmacogenetic model to be applied in polypharmacy [72]. The initial phase consists in a detailed recording of clinic, epidemiologic and therapeutic information, obtained after clinical consultation. The theoretical analysis of drug interaction and metabolic pathways constitutes the second stage. The third phase is focused on the genotyping of the detailed selected genomic variants potentially involved in patient's prescribed drugs. These variants are genotyped in the laboratory using high-throughput technologies. The fourth stage consists in selecting the most suitable therapy after an integrative analysis of all the information. Finally, the re-evaluation of clinical response according to therapeutic adjusts is mandatory in order to achieve effectiveness [72].

Some studies have analyzed combinations of genes that can be involved in asthma treatment. *CYP3A4* and *SLCO2B1* may affect drug pharmacokinetics to influence responsiveness to ICS and montelukast [33,59,60]. Novel gene–gene interactions of a network of SNPs within different genes predicted SABA bronchodilation more accurately than each individual locus in asthma [33].

Nevertheless, efforts have to be made to decipher the complex network of gene–gene interactions. In this sense, systems biology will provide tools to deeper insight complex gene–gene networks.

Pharmacogenomics & new drugs: future perspective

Whenever it is possible, pharmacogenomics should be used in the development of new drugs. In this sense, the constant decreasing cost of high-throughput technologies will contribute to the application of pharmacogenomics in clinical trials [73]. In addition, rare variants should be considered in pharmacogenetics studies since they may influence therapeutic responsiveness, contributing to more precise predictions for personalized approaches [30,33]. Admixture-based genetic studies could also contribute to identify variations in frequencies between different ancestries. Even common variation can vary in frequency between ancestral or ethnic groups [74].

New therapies such as biological drugs are presently being introduced in asthma. Newer biologic drugs are now targeting the Th2 inflammatory pathway, focusing on IL4, IL4RA, IL5 and IL13, with exciting results [75]. Although, Th17 and Th1 pathways have been explored, results have been discouraging. The application of pharmacogenetics to biologic therapies is the next step in PM in this asthma. Clear phenotyping of patients, use of biomarkers and pharmacogenetics approaches should be incorporated to new clinical trials.

The alpha subunit of the IL4 receptor has also been reported as an interesting new target in asthma. *IL4RA* has been shown to be overexpressed in patients with asthma. We published the first transcriptome study developed in asthma, confirmed the increase in the expression levels of *IL4RA* in these patients [76].

A molecular inhibitor of the IL-4 α receptor subunit has been identified [77] and it is reported that polymorphisms in the gene that codes for IL-4 receptor predict response to the anti-IL-4 α receptor antagonist (pitrankinra) [77], however this molecular inhibitor is no longer being developed. On the contrary, a recent monoclonal antibody that blocks the IL-4 α receptor subunit (encoded by *IL4RA*) is being developed. It produces a dual inhibition of a shared IL-4 and IL-13 proinflammatory pathway and has been shown to be promising in asthma treatment [77–79]. The *IL4RA* gene variants could be a potential pharmacogenetic biomarker in asthma [33].

As a complex disease, interactions between genetic and environmental factors are combined in asthma and can be studied from an epigenetic perspective. Epigenetic factors play an important role in

Table 2. Theoretical drug–drug interaction analysis for P450 enzymes according to the superCYP platform.

Drugs	1A1	1A2	1B1	2A6	2B6	2C8	2C9	2c18	2c19	2D6	2E1	3A4	3A5	3A7
Beclomethasone													Ind	
Budesonide												S		
Ciclesonide												S		
Fluticasone F														
Fluticasone P												S		
Mometasone						Inh								
Deflazacort														
Dexamethasone [†]	Ind	Ind			Ind	Ind	Ind	Ind	Ind	Ind		Ind, Inh, S	Ind, S	Ind, S
Methylprednisol.												Inh, S		
Prednisone	Ind	Ind							Ind			S, Ind, Inh		
Trimacinolone												Ind	Ind	Ind
Formoterol				S		S			S	S				
Salbutamol												Inh, S		
Salmeterol						Inh						S	S	
Terbutaline														
Montelukast						Inh								
Pranlukast														
Zafirlukast		Inh				Inh, S	Ind, S		Inh		Inh			
Aminophylline		S									S	S		
Apratropium														
Teofilina	S, Inh	Inh, S	S			S	S			S	S	S		
Tiotropium										S		S		

Enzyme names are shown in the first row. Metabolic pathways from CYP1A1 to CYP3A7 are represented.

[†]Dexamethasone is also inducer of 3A43, 4A11, and inhibitor of 11A, 11B1, 17A, 27A.

Ind: Inductor; Inh: Inhibitor; Fluticasone F: Fluticasone furoate; Fluticasone P: Fluticasone propionate.

asthma regulation [80,81]. DNA methylation, histone modifications and transcriptional regulation by micro RNA (miRNA), small interfering RNA (siRNA) or long noncoding RNA (lncRNA) could be not only potential biomarkers of the disease but targets of therapeutic interventions [82].

Epigenetic modifications of P450 coding genes such as *CYP3A4* or *CYP2D6* can influence response to drugs metabolized by these enzymes, such as corticoids. Methylation modifications of the promoter region of *ADRB2* have also been associated with asthma severity in small pediatric cohorts [33].

miRNA can also regulate responsiveness to drugs. In this sense, miRNA-21 has been reported as a promising biomarker in response to therapy of asthma in children [83]. In addition, in the above-mentioned first transcriptome analysis developed in B cells in asthma, expression of different ncRNA was detected in asthmatic patients [76]. This could open a new insight regarding modulation of gene expression by RNA different from miRNA. Epigenetic factors should not

only be considered as modulators of response but also as drug targets. Epidrugs are defined as drugs designed to modulate epigenetic factors, although such epidrugs are more developed in other complex diseases, such as cancer.

The high variability observed in asthma phenotypes is determined by the interaction of multiple genes and other environmental factors. Systems biology is focused on understanding the relationship between biological pathways and related factors [12]. There is evidence of a relationship between treatment outcomes and asthma phenotypes that clearly involves diverse pathways and genetic factors [84]. As previously mentioned, candidate-gene approach and genome-wide association studies have provided a wide list of genes associated to the three major classes of asthma medication. The objective of systems biology in pharmacogenomics should be to elaborate the best model of a biological network at the omic level, in order to predict the response to therapy in an accurate manner.

A systems biology approach is characterized by an integrative concept. Different omics levels such as genomics, transcriptomics, proteomics or metabolomics among others, are first, integrated with clinical biological data. By using bioinformatics approaches, data mining, network reconstruction methods and complex machine learning algorithms, the predictive models are generated [84]. Validation of these approaches is then required to reach the final model [85]. Different international consortia such as U-Biopred and Medall, aim to apply Systems Medicine to asthma and allergy [83]. These strategies will contribute to improve not only disease assessment but also therapeutic interventions.

Great efforts are being made to apply systems biology to the genetic background of asthma phenotypes [86] partly because discerning between genetic background associated to drug response, and the associated to the natural history of the disease, is a difficult task. Studies oriented to identify pharmacogenetics markers of drug response by using systems biology are needed to be applied to PM in asthma. Network modeling combined with functional validation, and integrative omics technologies will contribute to the clinical application of asthma pharmacogenomics [85].

Conclusion

Currently direct application of pharmacogenomics to asthma patients is scarce, however, efforts are being made to accelerate clinical translation of basic research. The enormous development of high throughput technologies is providing huge amounts of information

that could be really useful in pharmacogenomic applications. In addition, functional studies in cellular and animal models are required to confirm the relevant role of these potential biomarkers in clinic [87]. The best approach to the application in Personalized Medicine should take into account multiple aspects, such as proper phenotyping of patients, diverse genomes of different ancestries, demographic history, environmental exposures and cultural considerations, pharmacokinetics as well as pharmacodynamics factors, common and rare variants involved in drug response and gene–gene/gene–environmental interaction. These factors are critical not only to achieve the best and safest treatment for an individual patient but also, to design proper clinical trials and drugs in asthma.

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