Pharmacogenomics and Personalized Medicine

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REVIEW

Pharmacogenetics of Pediatric Asthma: Current Perspectives

This article was published in the following Dove Press journal:
Pharmacogenomics and Personalized Medicine

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Abstract: Asthma is a chronic respiratory disease that affects 339 million people worldwide and has a considerable impact on the pediatric population. Asthma symptoms can be controlled by pharmacological treatment. However, some patients do not respond to therapy and continue suffering from symptoms, which impair the quality of life of patients and limit their daily activity. Genetic variation has been shown to have a role in treatment response. The aim of this review is to update the main findings described in pharmacogenetic studies of pediatric asthma published from January 1, 2018 to December 31, 2019. During this period, the response to short-acting beta-agonists and inhaled corticosteroids in childhood asthma has been evaluated by eleven candidate-gene studies, one meta-analysis of a candidate gene, and six pharmacogenomic studies. The findings have allowed validating the association of genes previously related to asthma treatment response (*ADRB2, GSDMB, FCER2, VEGFA, SPAT2SL, ASB3*, and *COL2A1*), and identifying novel associations (*PRKG1, DNAH5, IL1RL1, CRISPLD2, MMP9, APOBEC3B-APOBEC3C, EDDM3B*, and *BBS9*). However, some results are not consistent across studies, highlighting the need to conduct larger studies in diverse populations with more homogeneous definitions of treatment response. Once stronger evidence was established, genetic variants will have the potential to be applied in clinical practice as biomarkers of treatment response enhancing asthma management and improving the quality of life of asthma patients.

Keywords: treatment response, short-acting beta-agonists, inhaled corticosteroids, candidate-gene studies, genome-wide association studies, whole-genome sequencing

Introduction

Asthma is a heterogeneous respiratory disease characterized by chronic airway inflammation, reversible airflow obstruction, and airway hyperresponsiveness.[1] Asthma symptoms include wheeze, dyspnea, chest tightness, and cough. These symptoms may resolve spontaneously, but most patients need a pharmacological treatment to control them.[2] However, pharmacotherapy is not always effective, and some patients may develop worsening episodes of the baseline disease situation, known as exacerbations. These acute episodes are responsible for limitations in patient's daily activity and may cause disability, the need for intubation, and can even be life-threatening.[1,2]

It has been estimated that 339 million people worldwide have asthma, and 420 thousand deaths per year are linked to this disease.[1] Moreover, although asthma affects people of all ages, it has a towering impact on the pediatric population, being the most prevalent chronic disease in children.[3] The global prevalence of pediatric asthma is about 11.5%, but there is a large variability of prevalence

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DovePress
http://doi.org/10.2147/PGPM.S201276

between regions, reaching values of 18.8% and 24.3% in Latin America and Oceania, respectively.[4] Despite the scarce mortality of childhood asthma (global death rate: 0.0–0.7/100,000), children or young adults represent a considerable fraction of people who die from asthma. As an example, in the United Kingdom between 2012 and 2013, from a total of 194 deaths related to asthma, 28 of them occurred to people under 20 years old (14.4%).[5]

In order to enhance asthma management in terms of better diagnosis and more precise treatment, different disease subtypes sharing some common clinical characteristics, triggers, or type of inflammatory processes have been identified.[6] Although to date no consistent findings have been discovered,[7] the relationship between asthma phenotypes and treatment response may be used to select the most appropriate therapy for each patient.[2,6] Nonetheless, despite following asthma guidelines,[2] non-response to the pharmacological treatment is not uncommon in pediatric nor adult asthma.[8] Thus, there is a need to establish new biomarkers that could allow improving disease management.

Genetic variants are known to have a role in asthma treatment response with different medications given that these traits have been shown to be heritable.[9] During the last decades, different approaches have been developed to identify genetic markers associated with complex diseases, most of them based on identifying variants affecting only one base pair, which are called single-nucleotide polymorphisms (SNPs).[10] Candidate-gene studies have been performed to identify genetic variants in specific genes previously associated with the disease and the pharmacological treatment.[11] Genome-wide association studies (GWAS) have emerged as a pharmacogenomic approach to identify novel genetic markers without a prior hypothesis of the mechanisms involved in treatment response. GWAS data can be obtained both with genotyping microarrays and by means of high-throughput DNA sequencing. The microarrays used for genome-wide genotyping focus on certain SNPs that are representative of the variation across the genome, taking advantage of the linkage disequilibrium (LD) between variants. Thus, genotyping data allows subsequent inference of genetic variants throughout the whole genome.[10] Furthermore, the more recent development of high-throughput DNA sequencing has allowed performing whole-genome sequencing (WGS), attaining a higher resolution of the genomic variation than genotyping arrays.[12]

The evidence of the role of genetic variants on asthma treatment response has been summarized in some recent reviews.[13–18] Thereby, this review aims to update the current findings described in pharmacogenetic studies of pediatric asthma published from 2018 through 2019.

Methods

A literature research was performed in PubMed using different keywords combinations (Table S1). The inclusion criteria of the studies were: 1) studies published in PubMed from January 1, 2018, to December 31, 2019, 2) studies focused on pharmacogenetics of asthma, and 3) papers written in English. The exclusion criteria were: 1) studies focused only on adulthood asthma, 2) animal or in-vitro model studies, 3) studies not assessing asthma treatment response, and 4) reviews, editorials, opinion articles or case studies. A stepwise evaluation of the studies according to the eligibility criteria was conducted based on the title, the abstract, and finally the full text. At least two different authors independently evaluated each paper.

Short-Acting Beta-Agonists (SABA)

SABA are one of the main reliever medications in children and adolescents with asthma due to its rapid effect relieving asthma symptoms.[2] The mechanism of action of these drugs consists in the activation of the β_2 adrenergic receptor, which results in the relaxation of the bronchial smooth muscle and the consequent bronchodilation.[19] Unlike long-acting beta-agonists (LABA), SABA have both rapid-onset bronchodilation and a shorter half-life.[19] Genetic variants contribute to differences in SABA response in children with asthma.[20,21] To study the genes involved in SABA response, one of the parameters most frequently analyzed as an outcome has been the bronchodilator response (BDR), based on changes in lung function after the administration of SABA.[22] Also, lung function parameters such as forced expiratory volume in the first second (FEV_1), forced vital capacity (FVC), and the ratio between them (FEV_1/FVC), have been used to evaluate treatment response.

Candidate-Gene Studies of SABA Response

ADRB2 gene has been the most studied candidate gene of SABA response.[16,18,23] It encodes the β_2 adrenergic receptor, which is implicated in the bronchodilation process and is the biological target of β_2 adrenergic agonists.[19] In fact, in the reviewed period four candidate-gene studies have assessed the effect of the SNPs rs1042713 (arginine to glycine [Arg16Gly]) and rs1042714 (glutamic acid to

glutamine [Glu27Gln]) on changes in lung function after SABA administration in European[24,25] and Egyptian[26,27] populations (Table 1). However, the results were not entirely consistent across studies. Scaparrotta et al[24] identified that G allele carriers for the SNP rs1042713 had a lower post-bronchodilator FEV_1 (β for the G allele: −0.244, *p*-value=0.02) while Jovicic et al[25] reported the opposite effect (*p*-value=0.044). Additionally, when both SNPs were analyzed as a haplotype, inconsistent results were also found since the AC haplotype was associated with a worse response to SABA in European children[25] (*p*-value=0.026) while in Egyptian children the same haplotype was associated with a better response (*p*-value=0.027).[27] All these inconsistencies might be due to the heterogeneity in statistical approaches. Scaparrotta et al applied linear regression models adjusted for confounders, while the other studies used parametric/non-parametric tests that do not allow adjusting for covariates. On the other hand, none of these studies found an association of the SNP rs1042714 with SABA response.[24–27]

Sordillo et al[28] conducted a longitudinal study in non-Hispanic white children (n=604) that were followed up 4–18 years. Four SNPs suggestively associated with SABA response by previous GWAS[21,29,30] (rs11252394, rs6988229, rs295137, and rs2626393) were studied for association with asthma treatment response and age interaction analyzing BDR after albuterol administration as outcome. The SNP rs295137 near *SPATS2L* was associated with an increase in BDR (β for the T allele: 1.3, *p*-value<0.05) consistently with the results previously reported.[29] This effect was progressively mitigated for each year of aging (β: −0.06, *p*-value<0.0125). In contrast, the SNP rs2626393 near *ASB3* was found to be associated with a decrease in BDR (β for the C allele: −0.92, *p*-value<0.05), similarly to the findings of a previous GWAS for which this SNP is a proxy,[30] and also its effect was reduced by aging (β: 0.05, *p*-value<0.0125). This SNP is in high LD with rs350729, a polymorphism near *ASB3* previously associated with BDR, which has been identified as an expression quantitative trait locus (eQTL) of 52 genes that interact with *ADRB2* and *ASB3*.[30] In addition, these variants were also studied only with the data collected from 15 years of age and a similar effect of the rs2626393 remained significant at these older ages (*p*-value<0.05).[28] The association of both genes and SABA response is plausible since *SPATS2L* appears to regulate the expression of the β_2 adrenergic receptor[29] and *ASB3* regulates the muscle cells differentiation process and its expression is modified by β_2 agonists.[31]

Pharmacogenomic Studies of SABA Response

During the reviewed period, three pharmacogenomic studies of SABA response have been performed, one based on genotyping array data and two based on WGS (Table 1). A GWAS performed by Spear et al[32] identified a population-specific genome-wide significant variant (rs73650726 on 9q21) in African Americans (n=949), which was associated with a decrease of BDR after albuterol administration (β for the A allele: −3.8, *p*-value=7.69×10^{-9}). This SNP does not map to any gene, but it is in high LD ($r^2 \geq 0.8$) with other SNPs located within enhancer histone marks in lung tissue.[33] Furthermore, a meta-GWAS across African Americans and Latinos (n=2,779) allowed the identification of three SNPs in the *PRKG1* gene related to SABA response: rs7903366 (β for the T allele: 1.23, *p*-value=3.94×10^{-8}), rs7070958 (β for the A allele: −1.24, *p*-value=4.09×10^{-8}), and rs7081864 (β for the A allele: 1.23, *p*-value=4.94×10^{-8}). Nevertheless, these SNPs were assessed for replication in three independent African American and Latino cohorts and none of them demonstrated consistent effects. The *PRKG1* gene encodes an isoform of the protein kinase cGMP-dependent, which is a key mediator of the nitric oxide (NO) pathway. NO is involved in several pathophysiological processes in the airways related to asthma status,[34] and it is also involved in the bronchodilator effect on the bronchial smooth muscle of β_2 agonist drugs such as albuterol.[35]

In 2018, Mak et al[36] conducted a GWAS of SABA response based on WGS data in childhood asthma analyzing the extreme of the distribution in BDR after albuterol administration as outcome. A trans-ethnic meta-analysis in African American and Latino children (n=1,441) identified 27 SNPs suggestively associated (*p*-value<7.06×10^{-6}) with BDR of which three SNPs were significantly associated after Bonferroni correction (*p*-value<3.53×10^{-7}) and two reached the commonly used genome-wide significance threshold for GWAS (*p*-value<5×10^{-8}). These two SNPs were located on chromosome band 5p15.2 near *DNAH5*, and both of them were associated with a better response to albuterol (rs17834628, odds ratio [OR] for the A allele: 1.67, 95% confidence interval [CI]: 1.29–2.16, *p*-value=1.18×10^{-8} and rs35661809, OR for the G allele: 1.59, 95% CI: 1.20–2.10, *p*-value=3.33×10^{-8}). Despite the associations of these SNPs reached genome-wide

Table 1 Summary of the Genetic Associations with Short-Acting Beta Agonist Response Described in Pharmacogenetic Studies

rsID	Chr	Position[a]	Gene/Nearest Gene	Effect Allele	Outcome[b]	Effect[c]	p-value	Sample Size	Population	Reference
Candidate-Gene Association Studies										
rs1042713	5	148,206,440	*ADRB2*	G	Post-FEV_1	β=−0.244	0.02	100	EUR	Scaparrotta et al[24]
rs1042713	5	148,206,440	*ADRB2*	G	dFEV_1	+	0.044[d]	54	EUR	Jovicic et al[25]
rs1042713/ rs1042714	5	148,206,440/ 148,206,473	*ADRB2*	AC haplotype	dFEV_1	–	0.026	54	EUR	
rs1042713/ rs1042714	5	148,206,440/ 148,206,473	*ADRB2*	AC haplotype	Post-FEV_1	+	0.027	75	Egyptians	Toraih et al[27]
rs295137	2	201,150,040	*SPATS2L*	T	BDR	β_{SNP}=1.3 $\beta_{SNPxAge}$=−0.06	p_{SNP}<0.05[e] $p_{SNPxAge}$<0.0125[e]	604	Non-HIS white	Sordillo et al[28]
rs2626393	2	52,965,931	*ASB3*	C	BDR	β_{SNP}=−0.92 $\beta_{SNPxAge}$=0.05	p_{SNP}<0.05[e] $p_{SNPxAge}$<0.0125[e]	604	Non-HIS white	
rs2626393	2	52,965,931	*ASB3*	C	BDR among older than 15	β_{SNP}=−1.3 $\beta_{SNPxAge}$=0.06	p_{SNP}=0.043[e] $p_{SNPxAge}$<0.05[e]	604	Non-HIS white	
Pharmacogenomic Studies										
rs73650726	9	85,152,666	9q21	A	BDR	(D): β=−3.8 (R): β=1.71/−6.22/ −0.65/−6.12	(D): 7.69×10^{-9} (R): 0.87/0.11/ 0.49/0.04	(D): 949 (R): 247/149/1325/290	(D): AA (R): MEX/PR/ AA/AA	Spear et al[32]
rs7903366	10	53,689,774	*PRKG1*	T	BDR	(D): β=1.23 (R): β=1.02/−0.51/ 0.91/−0.27	(D): 3.94×10^{-8} (R): 0.3/0.61/ 0.10/0.83	(D): 2779(R): 247/149/ 1325/290	(D): AA, HIS (R): MEX/PR/ AA/AA	
rs7070958	10	53,691,116	*PRKG1*	A	BDR	(D): β=−1.24 (R): β=1.04/−0.53/ 0.87/−0.4	(D): 4.09×10^{-8} (R): 0.29/0.6/ 0.11/0.76	(D): 2779 (R): 247/149/1325/290	(D): AA, HIS (R): MEX/PR/ AA/AA	
rs7081864	10	53,690,331	*PRKG1*	A	BDR	(D): β=1.23 (R): β=1.03/−0.53/ 0.84/−0.36	(D): 4.94×10^{-8} (R): 0.3/0.6/0.13/ 0.78	(D): 2779 (R): 247/149/1325/290	(D): AA, HIS (R): MEX/PR/ AA/AA	

rs17834628	5	12,978,566	*LINC01194, LINC02220, DNAH5*	A	BDR	(D): OR=1.67 (R): OR=1.09	(D): 1.18×10^{-8} (R): 0.3	(D): 1441(R): 2167	(D): AA, HIS (R): AA, MEX, PR	Mak et al[36,f]
rs35661809	5	12,968,341	*LINC01194, LINC02220, DNAH5*	G	BDR	(D): OR=1.59 (R): OR=0.94	(D): 3.33×10^{-8} (R): 0.59	(D): 1441 (R): 2167	(D): AA, HIS (R): AA, MEX, PR	
NA	1	114,177,000:114,178,000	*MAGI3, PHTF1, RSBN1*	NA	BDR	NA	4.40×10^{-9}	483	MEX	
NA	11	27,507,000:27,508,000	*LOC105376671, LGR4, LIN7C*	NA	BDR	NA	6.59×10^{-9}	483	MEX	
NA	19	10,424,000:10,425,000	*ZGLP1, ICAM5, FDX1L, RAVER1*	NA	BDR	NA	3.12×10^{-11}	475	AA	
NA	4	73,478,000:73,479,000	*ADAMTS3, COX18*	NA	BDR	NA	6.25×10^{-8}	1441	AA, HIS	
NA	8	97,926,000:97,927,000	*SDC2, CPQ, LOC101927066, TSPYL5*	NA	BDR	NA	1.32×10^{-7}	1441	AA, HIS	
rs12051168	16	84,879,324	*CRISPLD2*	C	Post-FEV_1	NA	1.6×10^{-2}	302	Costa Ricans	Kachroo et al[40,f]
rs12051168	16	84,879,324	*CRISPLD2*	C	Post-FEV_1/FVC	NA	3.5×10^{-3}	302	Costa Ricans	

Notes: [a]Positions based on GRCh37/hg19 build. [b]Definition of treatment response. [c]+ means a better response while − a worse response. [d]Referred to a recessive model. [e]Multiple comparisons adjusted by Bonferroni correction. [f]Based on whole-genome sequencing data.

Abbreviations: rsID, reference SNP cluster ID; Chr, chromosome; Post-FEV_1, post-bronchodilator forced expiratory volume in one second; EUR, Europeans; $dFEV_1$, change in forced expiratory volume in one second before and after bronchodilator administration; BDR, bronchodilator response; (D), discovery phase; (R), replication phase; MEX, Mexicans; PR, Puerto Ricans; AA, African Americans; HIS, Hispanics/Latinos; OR, odds ratio; NA, not available; Post-FEV_1/FVC, ratio post-bronchodilator forced expiratory volume in one second and forced vital capacity.

significance, none of them replicated in five independent African American and Latino studies, analyzed separately or meta-analyzed. These findings are biologically plausible since genetic variants on *DNAH5* have been previously associated with lung function in chronic obstructive pulmonary disease (COPD)[37] and immunoglobulin E (IgE) levels.[38] Moreover, combined effects of common and rare variants on BDR were identified in three population-specific loci (two in Mexicans and one in African Americans) and in two loci shared among African American and Latino populations which reached genome-wide significance (Table 1).[36] Interestingly, one of the loci identified may have a functional role in response to SABA since it is located near *ADAMTS3*/*COX18*, a locus previously associated with the response to β-adrenergic drugs in animal models to treat cardiovascular diseases.[39]

The first WGS family-based analysis of lung function in Latino children with asthma (n=302) was recently conducted by Kachroo et al,[40] analyzing not only baseline but also post-bronchodilator lung function measurements. In this study, the SNP rs12051168 from the *CRISPLD2* gene was suggestively associated with the baseline FEV_1/FVC ratio (p-value=9.1×10^{-6}) and it was nominally associated with post-bronchodilator measurements of FEV_1 (p-value=1.6×10^{-2}) and FEV_1/FVC (p-value=3.5×10^{-3}). Interestingly, *CRISPLD2* encodes a secreted lipopolysaccharide-binding protein that protects against bacterial infections[41] and has a role in lung development.[42] Also, this gene has been previously nominally associated with ICS response and BDR,[43] and its gene expression levels have been found to be changed by indacaterol.[44]

Inhaled Corticosteroids (ICS)

Based on its efficacy, effectiveness, safety, and cost, ICS are the preferred treatment to control asthma symptoms as well as to prevent the development of asthma exacerbations.[2] According to the clinical features of the patient and the degree of asthma severity, ICS may be used at different doses or may be combined with other pharmacological therapies such as LABA or leukotriene receptors antagonists (LTRA).[2] Corticosteroids contribute to control asthma symptoms due to its anti–inflammatory and immunosuppressive effects as a result of the interaction with the glucocorticoid receptor (GR).[45] Nonetheless, many factors such as an incorrect inhaler technique,[46] a poor adherence,[47] comorbidities,[48] lung microbiome dysbiosis,[49–52] and genetic variants,[13,17] may contribute to a loss in asthma control and to the development of asthma exacerbations despite ICS-contained therapies. The identification of these factors is essential to differentiate children with difficult-to-treat asthma from those that are resistant to pharmacological therapies.[53] Treatment response to ICS is usually evaluated by the development of asthma exacerbations while on ICS treatment, by clinical measurements (eg fractional exhaled nitric oxide [FENO], FEV_1, and FEV_1/FVC), and by the assessment of the asthma control test (ACT) score.

Candidate-Gene Studies of ICS Response

Several candidate-gene studies have been performed to evaluate the influence of genetic variants on treatment response to ICS (Table 2).[26,54-59] Similarly to the response to SABA, the *ADRB2* gene is one of the most extensively analyzed in pharmacogenetic studies of ICS.[16,18,23] In 2018, Sood et al[54] studied two SNPs (rs1042713 and rs1042714) from the *ADRB2* gene in a European American and African American cohort (n=373) of children with asthma under ICS treatment. In this study, treatment response was defined as the prescription of systemic corticosteroids due to asthma exacerbations in the last 12 months. Asthma individuals with CC genotype at the SNP rs1042714 had an increased risk of asthma exacerbation despite ICS treatment in comparison with heterozygous individuals (CG; p-value=0.04) and homozygous individuals (GG; p-value=0.013).[54] In the same year, Alghobashy et al[26] also evaluated these two SNPs in Egyptian children with asthma (n=52) treated with ICS in combination with LABA and assessed lung function measurement (FEV_1 and FEV_1/FVC) as the primary outcome of treatment response. Worse treatment response to a combination of ICS plus LABA was reported for homozygous GG at rs1042713 (p-value<0.05) and homozygous GG at rs1042714 (p-value<0.05) individuals. Given that all the patients were treated with ICS plus LABA, this study design does not allow assessing whether the effect of the SNP conditions the response to ICS or LABA. However, no effect of rs1042713 in FEV_1 or FEV_1/FVC was found in a meta-analysis in five mixed pediatric populations under ICS and LABA treatment performed by Wang et al.[60]

In 2019, Farzan et al[55] assessed the association of a polymorphism in the *GSDMB* gene (rs7216389) at the locus 17q21 with ICS response by means of a meta-analysis (n=4,454) of different ethnic populations, including Europeans (n=2,888), Hispanics/Latinos (n=916), African Americans (n=468), and East Asians (n=182).

Table 2 Summary of the Genetic Associations with Inhaled Corticosteroids Response Described in Pharmacogenetic Studies

rsID	Chr	Position[a]	Gene/ Nearest Gene	Effect Allele	Outcome[b]	Effect[c]	p-value	Sample Size	Population	Reference
Candidate-Gene Association Studies										
rs1042714	5	148,206,473	*ADRB2*	C	Systemic corticosteroids	–	0.04 heterozygous 0.013 homozygous	373	EA, AA	Sood et al[54]
rs1042713	5	148,206,440	*ADRB2*	G	FEV_1	–	0.04 homozygous<0.001 heterozygous	52	Egyptians	Alghobashy et al[26]
rs1042713	5	148,206,440	*ADRB2*	G	FEV_1/FVC	–	0.02 homozygous 0.01 heterozygous	52	Egyptians	
rs1042714	5	148,206,473	*ADRB2*	G	FEV_1	–	<0.001 homozygous <0.001 heterozygous	52	Egyptians	
rs1042714	5	148,206,473	*ADRB2*	G	FEV_1/FVC	–	0.05 homozygous 0.02 heterozygous	52	Egyptians	
rs7216389	17	38,069,949	*GSDMB*	T	Hospitalizations/ER visits	OR=1.32	$<1\times10^{-4}$	4454	EUR, HIS, AA, EA	Farzan et al[55]
rs7216389	17	38,069,949	*GSDMB*	T	Hospitalizations/ER visits	OR=1.33	0.004	2888	Non-HIS whites	
rs7216389	17	38,069,949	*GSDMB*	T	Hospitalizations/ER visits	OR=1.31	0.01	916	HIS	
rs7216389	17	38,069,949	*GSDMB*	T	OCS	OR=1.19	0.01	4050	EUR, HIS, AA, EA	
rs7216389	17	38,069,949	*GSDMB*	T	OCS	OR=1.26	0.002	2492	EUR	
rs7216389	17	38,069,949	*GSDMB*	T	Hospitalizations/ER visits among children >5 years	OR=1.32	$<1\times10^{-4}$	4254	EUR, HIS, AA, EA	
rs7216389	17	38,069,949	*GSDMB*	T	OCS among children >5 years	OR=1.2	0.01	3771	EUR, HIS, AA, EA	
rs13431828	2	102,954,653	*IL1LR1*	C	Hospitalizations/ER visits	OR=1.32	0.02[d]	2412	EUR, AA, HIS	Dijk et al[56]
rs13431828	2	102,954,653	*IL1LR1*	C	Hospitalizations/ER visits/OCS	OR=1.31	0.02[d]	2412	EUR, AA, HIS	
rs28364072	19	7,755,285	*FCER2*	G	FENO	β=–0.12	0.018	593	EUR	Karimi et al[57]
rs28364072	19	7,755,285	*FCER2*	G	FENO in well-controlled asthma	β=–0.17	0.011	341	EUR	
rs13925	20	44,644,965	*MMP9*	A	FEV_1 change after 6 months of ICS	+	0.046	127	EUR	Dragicevic et al[58]
rs20544	20	44,645,010	*MMP9*	T	ACT score change after 12 months of ICS	+	0.03	127	EUR	

(*Continued*)

Table 2 (Continued).

rsID	Chr	Position[a]	Gene/ Nearest Gene	Effect Allele	Outcome[b]	Effect[c]	p-value	Sample Size	Population	Reference
rs3025039	6	43,752,536	*VEGFA*	T	Change in FEV_1 after 12 weeks of ICS	–	0.04[e]	128	Asians	Wan et al[59]
rs3809324	12	48,399,028	*COL2A1*	T	Change in FEV_1 after 12 weeks of ICS	–	0.048[e]	128	Asians	
rs3025039	6	43,752,536	*VEGFA*	T	Change in FEV_1/FVC after 12 weeks of ICS	–	0.004[e]/0.016[f]	128	Asians	
Pharmacogenomic Studies										
rs5995653	22	39,404,249	*APOBEC3B-APOBEC3C*	A	Hospitalizations/ER visits/OCS	(D): OR=0.66 (R): OR=0.76	(D): 4.8×10^{-6} (R): 7.52×10^{-3}	(D): 1347 (R): 1697	(D): AA, HIS (R): EUR	Hernandez-Pacheco et al[73]
rs5995653	22	39,404,249	*APOBEC3B-APOBEC3C*	A	FEV_1 after 6 weeks of treatment with ICS	(R): OR=2.16	(R): 4.91×10^{-3}	(R): 166	(R): AA, HIS	
rs62081416	18	6,605,442	*L3MBTL4-ARHGAP28*	A	Hospitalizations/ER visits/OCS	(R): OR=2.44	(R): 1.57×10^{-5}	(R): 1347	(R): AA, HIS	
rs3827907	14	21,238,798	*EDDM3B*	C	(D): Change in ACT score after 6 weeks ICS (R): Exacerbations in the last year	NA	(D): 7.79×10^{-8} (R): 0.041/0.029	(D): 244 (R): 1461/563	(D): AA (R): AA/HIS	Levin et al[74]
rs2392165	7	33,159,914	*BBS9*	G	Change in coughing and wheezing by self-report	β=–0.53	0.02	175	Non-HIS whites	Wang et al[79]

Notes: [a]Positions based on GRCh37/hg19 build. [b]Definition of treatment response. [c]+ means a better response while – a worse response. [d]Multiple comparisons adjusted by FDR-Benjamini Hochberg. [e]Dominant model. [f]Kruskal–Wallis *p*-value.

Abbreviations: rsID, reference SNP cluster ID; Chr, chromosome; EA, European Americans; AA, African Americans; FEV_1, forced expiratory volume in one second; FEV_1/FVC, ratio forced expiratory volume in one second and forced vital capacity; ER, emergency room; OR, odds ratio; EUR, Europeans; HIS, Hispanics/Latinos; EA, East Asians; OCS, oral corticosteroids; FENO, fractional exhaled nitric oxide; ICS, inhaled corticosteroids; ACT, asthma control test; (D), discovery phase; (R), replication phase; NA, not available.

This locus has not only shown a consistent relationship with childhood-onset asthma[61,62] but has also been associated with ICS response in asthma.[63] They measured treatment response according to the development of asthma exacerbations, defined as 1) oral corticosteroid (OCS) prescription and 2) hospitalizations/emergency room visits (ER) due to asthma. The SNP rs7216389 was associated with a worse response to ICS for both outcomes (OR for the T allele: 1.19, 95% CI: 1.04–1.36, *p*-value=0.01 for OCS prescription, and OR: 1.32, 95% CI: 1.17–1.49, *p*-value=$<1 \times 10^{-4}$ for hospitalizations/ER visits). Moreover, stratified analyses by age and ethnicity showed similar results, except for pre-school children (2–4 years of age) (*p*-value>0.05), and OCS prescription in Hispanics/Latinos (*p*-value>0.05).

A recent study by Dijk et al[56] also evaluated the role of a gene identified by previous GWAS of asthma,[14,64] *IL1RL1*, on the response to ICS measured as asthma exacerbations (OCS use and Hospitalizations/ER visits). For that purpose, a study focused on Europeans (n=720) was analyzed as discovery, and replication was assessed in Hispanics/Latinos (n=876), African Americans (n=525), and Europeans (n=301). This gene encodes the interleukin 1 receptor-like 1 (IL1RL1), which acts as a decoy receptor for interleukin 33 (IL33), and it is known that the IL33/IL1RL1 signaling pathway is related to the type 2 inflammation.[65] For the six SNPs analyzed, a meta-analysis across the 2,412 samples allowed finding consistent effects for the C allele of the SNP rs13431828 for ER visits/hospitalizations (OR=1.32, 95% CI: 1.08–1.62, adjusted *p*-value=0.02) and risk of exacerbations (OR=1.31, 95% CI: 1.07–1.59, adjusted *p*-value=0.02).

Karimi et al[57] evaluated a SNP located in the *FCER2* gene (rs28364072) and its relationship with FENO in European children with asthma under ICS treatment (n=593). This gene encodes CD23, the low-affinity Fc receptor for IgE which is involved in the regulation of IgE,[66] and besides that, the G allele of the SNP rs28364072 has been previously associated with low-response to ICS in childhood asthma.[67–69] However, Karimi et al identified the opposite effect, since carriers of the G allele had a lower concentration of FENO, suggesting a better ICS response (β for log-transformed FENO levels: −0.12, 95% CI: −0.23, −0.02, *p*-value=0.018). Nevertheless, when stratified analyses based on asthma control status were performed, this effect was not observed in patients with partially controlled and uncontrolled asthma.[57]

Some studies have evaluated the effect of genetic variants not only on ICS response but also on LTRA. Dragicevic et al[58] conducted a randomized longitudinal study in European children with asthma (n=127) who were treated with ICS or LTRA and evaluated the effect of two *MMP9* gene SNPs on treatment response. This gene encodes matrix metallopeptidase-9 (MMP-9), which is involved in airway remodeling and inflammation. MMP-9 expression levels are reduced in central airways and alveolar parenchyma of asthma patients compared to healthy controls.[70] Carriers of the A allele of the SNP rs13925 showed an improvement in FEV_1after 6 months of treatment (*p*-value=0.046), but the long-term effect after 12 months was not significant (*p*>0.05). Besides, carriers of the T allele of rs20544 demonstrated a higher increase in ACT score after 12 months (*p*-value=0.03).[58] However, stratified analysis by pharmacological treatment did not show any genetic association either with ICS or LTRA (*p*-value>0.05). Thereby, the randomization of the evaluated medications limited the assessment of treatment response in this study. In addition, Wan et al[59] evaluated the effect of 27 SNPs in three genes (*VEGFA, TBX21*, and *COL2A1*) previously reported to be associated with asthma in a study of Asian children with asthma (n=128). These patients were treated with ICS during the last 12 weeks and LTRA as required to prevent asthma exacerbations. Carriers of the T allele of the SNP rs3025039, located within *VEGFA*, had lower increments of FEV_1 (*p*-value=0.04) and FEV_1/FVC (*p*-value=0.004) than non-carriers after ICS treatment. *VEGFA* encodes the vascular endothelial growth factor A, which is implicated in both physiological and pathological angiogenesis and it has also been observed to be overexpressed in asthma patients.[71] Likewise, for the SNP rs3809324 in *COL2A1*, carriers of the T allele showed similar outcomes, with a lower improvement of FEV_1 after ICS treatment (*p*-value=0.048).[59] *COL2A1* encodes the α-1 chain of type II collagen which is a structural component of the extracellular matrix, and it has been previously associated with lung function in adulthood asthma patients under fluticasone treatment.[72]

Pharmacogenomic Studies of ICS Response

In 2019, two GWAS have assessed ICS response in pediatric asthma (Table 2).[73,74] Hernandez-Pacheco et al[73] conducted the largest meta-GWAS of ICS response to date in Hispanic/Latino and African American asthma patients (n=1,347). The definition of treatment response was the

presence of asthma exacerbations during the last 12 months, considering as exacerbations ER visits, hospitalizations, or the administration of OCS because of asthma. Fifteen independent SNPs were suggestively associated with ICS response (p-value$\leq 5 \times 10^{-6}$) and one of them replicated in Europeans (n=1,697) at a nominal significance level (rs5995653, p-value=0.008). This SNP located in the *APOBEC3B-APOBEC3C* intergenic region demonstrated a protective effect for asthma exacerbations in a meta-analysis across Hispanics/Latinos, African Americans, and Europeans (OR for the A allele: 0.70, 95% CI: 0.61–0.81, p-value=3.31×10^{-7}). The same SNP was also associated with improvement of FEV_1 after ICS treatment (OR for the A allele: 2.16, 95% CI: 1.26–3.70, p-value=4.91×10^{-3}). *APOBEC3B* and *APOBEC3C* encode two subunits of the apolipoprotein B mRNA-editing catalytic polypeptide 3 (APOBEC3), which is involved in RNA editing and participate in the innate immunity against viral infections.[75,76]

Levin et al[74] performed a GWAS in African American adults with asthma (n=244) who were under ICS treatment for 6 weeks controlling for adherence and examined the association of genetic variants with ICS response. In this case, the definition of the treatment response was measured by changes in ACT score after 6 weeks with ICS therapy and the predictors were the combined effect of the SNP and SNP x ICS treatment interaction and relevant covariates. Establishing a threshold on p-value$<5.0 \times 10^{-7}$, three SNPs (rs3827907, rs73906251 and 2629529) were found to be associated with asthma control status mediated by ICS treatment. Nevertheless, only *EDDM3B* rs3827907 remained genome-wide significant after Bonferroni correction for multiple testing (p-value=7.79×10^{-8}). These three SNPs were attempted to be replicated in independent samples of African American (n=803) and European American (n=98) adults, and in two studies focused on Hispanic/Latino (n=1,461) and African American (n=563) pediatric populations. In these validation cohorts, the definition of ICS treatment response was the presence of asthma exacerbations during the last year. The rs3827907 from *EDDM3B* nominally replicated in the pediatric studies focused on African Americans (p-value=0.041) and Hispanics/Latinos (p-value=0.029). Furthermore, the SNP rs3827907 was found to be an eQTL associated with a decreased gene expression of *RNASE2* (p-value=6.10×10^{-4}) and *RNASE1* (p-value=7.92×10^{-4}) both in asthma and healthy individuals. Interestingly, *RNASE2* encodes the eosinophil-derived neurotoxin (EDN), a protein found in eosinophil cytoplasmic granules and that has been suggested to be a biomarker of eosinophilic inflammation.[77,78]

Interestingly, Wang et al conducted a pharmacogenomic study of placebo response in non-Hispanic white children with asthma and attempted to evaluate the top hits on patients under pharmacological treatment (budesonide or nedocromil).[79] A significant interaction was found between the SNP rs2392165 near *BBS9* with ICS use on wheezing/coughing (p-value$_{interaction}$= 1.48×10^{-7}), being associated with better ICS response (β for the G allele: −0.53, p-value=0.02). *BBS9* is implicated in lung development and ciliary function.[79]

Discussion

Between 2018 and 2019, the pharmacogenetic studies conducted in pediatric asthma have been mainly focused on therapeutic response to ICS and SABA albeit some of them have studied simultaneously the response to ICS and LABA/LTRA. Altogether, eleven candidate-gene studies,[24–28,55–59] a meta-analysis of a candidate gene,[60] and six pharmacogenomic studies (one of them in adults but including replication in children) have been performed.[32,36,40,73,74,79]

During this period, candidate-gene studies reported the association of genes previously described in pharmacogenetic studies of pediatric asthma with treatment response (*ADRB2, GSDMB, FCER2*, and *VEGFA*).[13,16-18] Additionally, other candidate genes have been related for the first time to this phenotype in children (*SPATS2L, ASB3, IL1RL1, MMP9*, and *COL2A1*). Although several findings support previous evidence of some of these genes in asthma treatment response, inconsistent results across the literature or even across the studies included in this review have been found. For instance, although *ADRB2* is one of the most studied candidate genes so far, its role in asthma treatment response is still not clear.[23] In fact, conflicting results were reported for variants of this gene within the period reviewed, which could be due to the small sample sizes (48±27 individuals), differences in statistical approaches, and the lack of multiple comparison adjustments. Moreover, most of the studies of *ADRB2* have focused on the same polymorphisms within this gene.[24–27,54] Recently, GWAS have strongly associated different SNPs within some of these candidate genes (*ADRB2, IL1RL1*, and *FCER2*) with related phenotypes such as lung function, suggesting that future studies could focus on other genetic variants that might have a role in treatment response.[80–83]

The application of pharmacogenomic approaches without a prior hypothesis has provided new insights, enabling researchers to discover novel associations of genetic variants across the whole genome with the treatment response in pediatric asthma (*PRKG1, DNAH5, CRISPLD2, APOBEC3B-APOBEC3C, EDDM3B*, and *BBS9*). Moreover, the relationship of these genes with asthma treatment response may be plausible since other studies have also reported them with asthma-related phenotypes, such as lung function (*PRKG1*,[82] *DNAH5*,[83] and *BBS9*[84]), allergic sensitization (*DNAH5*[38]), asthma susceptibility (*PRKG1*[85]), and childhood-onset asthma (*CRISPLD2*[86]). Nonetheless, the replication of pharmacogenetic findings is still scarce. Hernandez-Pacheco et al did not find any consistent association of 22 SNPs associated with treatment response by previous GWAS.[73] Similarly, Spear et al and Mak et al failed to replicate the association of SNPs associated with BDR by previous candidate-gene association studies or GWAS.[32,36] Differences in the statistical power of candidate-gene studies and GWAS and the analysis of different racial/ethnic groups could explain the inconsistent results among studies.

It should also be noted that albeit childhood-onset and adult-onset asthma have been identified as different phenotypes and usually do not share the same genetic components, some similarities have been identified.[62] Interestingly, a GWAS reported the association of a SNP within *EDDM3B* with ICS response in adults as discovery, and this finding was replicated in childhood asthma.[74] Since this gene is related to eosinophilic inflammation,[74,77,78] this feature may be common in both phenotypes and may condition treatment response to ICS in both age groups. Moreover, some of the candidate genes associated during this period with treatment response in childhood asthma had been previously reported with ICS response in asthma adult patients (*COL2A1*[72]) and with bronchodilator response both in children and adults (*ASB3*[30] and *SPAT2SL*[29]). On the other hand, two SNPs from *GLCCI1*, a gene extensively studied in pediatric pharmacogenetic studies of asthma,[87] were associated with ICS response in adult asthma as well.[88,89] Nevertheless, the effect of the SNPs within *ASB3* and *SPAT2SL* on SABA response was found to be mitigated by aging.[28] Therefore, it is important to continue investigating whether the genetic component of asthma treatment response is shared between adults and children.

Pharmacogenetic studies are aimed to establish genetic markers that may be applied to the clinical practice to improve asthma management. The implementation of genetic variants described in pharmacogenetic studies, such as the SNP rs295137 near *SPATS2L*, into clinical predictive models of ER management failure in children with moderate-to-severe asthma has demonstrated to improve their sensibility and specificity, compared to models incorporating only clinical information.[90] Nevertheless, given the discrepancies found in the literature, the small effect size of polymorphisms associated with asthma treatment response, and the lack of replication across populations, the clinical relevance of genetic variants remains unreliable.

To improve future pharmacogenetic studies, standardized methods and further analyses are required. Notably, the studies conducted in 2018 and 2019 focused on different populations, had heterogeneous eligibility criteria (Table S2) and analyzed different outcomes that may reflect different underlying mechanisms of treatment response. Studies focused on SABA response used lung function measurements (mainly BDR) as a treatment response measure. Nonetheless, most studies that assessed ICS response analyzed asthma exacerbations as the main outcome (46% of the studies), but they also examined other measurements of treatment response such as lung function measurements (27%), FENO (9%), ACT score (9%), or self-reported asthma symptoms (9%). Since asthma is a multifactorial disease, different phenotypes with different underlying etiology may not share the same genetic architecture and the effect of genetic variants may even be conditioned by ethnicity. Moreover, some limitations are shared among the assessed studies, especially in those focused on ICS response: the analysis of self-reported exacerbations as the main outcome, the concomitant use of other medications, or the lack of information about the type of ICS and dosage. To overcome the limitations, studies could analyze cohorts that represent more homogeneous populations in terms of asthma phenotype and demographic features, but trying to reach the largest sample sizes as well. Furthermore, collaboration among researchers is needed to validate the reported results and to evaluate them in different populations. The establishment of the Pharmacogenomics in Childhood Asthma (PiCA) consortium has allowed in the last years performing multiethnic pharmacogenetic analyses in pediatric populations.[91] Moreover, the integration of clinical data with the knowledge coming from multiple omics will help to understand in detail how genetic variants are

implicated in different pathways that condition treatment response in asthma patients.

In conclusion, pharmacogenetic studies of pediatric asthma have recently moved from candidate-gene approaches to the study of the whole genome variation and have improved the representation of different racial/ethnic groups. However, stronger evidence is needed to move forward towards the application of genetic markers in clinical practice. Once genetic variants were established as biomarkers of treatment response, precision medicine based on pharmacogenetics would be feasible in clinical practice. This will improve the safety and effectiveness of asthma therapy and will avoid using a specific medication in potentially non-responder patients, diminishing not only the costs associated with the treatment but also potential side-effects.

Author Contributions

All the authors were involved in the conception and design of the review, the acquisition and interpretation of the data, the drafting or revision of the manuscript, and the approval for the final version. All the authors agree to be accountable for all the aspects of the work.

Funding

Supported by grant SAF2017-83417R by the Spanish Ministry of Economy, Industry, and Competitiveness, the State Research Agency, and the European Regional Development Funds from the European Union (MINECO/AEI/FEDER, UE) to MP-Y and FL-D. AE-O received salary support from grant SAF2017-83417R by the Spanish Ministry of Economy, Industry, and Competitiveness. MP-Y was also supported by the Ramón y Cajal Program by the Spanish Ministry of Economy, Industry, and Competitiveness (RYC-2015-17205).

Disclosure

The authors report no conflicts of interest in this work.

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