



Pharmacogenomics and Pediatric Asthmatic Medications

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Abstract: Asthma is a respiratory condition often stemming from childhood, characterized by difficulty breathing and/or chest tightness. Current treatment options for both adults and children include beta-2 agonists, inhaled corticosteroids (ICS), and leukotriene modifiers (LTM). Despite recommendations by the Global Initiative for Asthma, a substantial number of patients are unresponsive to treatment and unable to control symptoms. Pharmacogenomics have increasingly become the front line of precision medicine, especially with the recent use of candidate gene and genomewide association studies (GWAS). Screening patients preemptively could likely decrease adverse events and therapeutic failure. However, research in asthma, specifically in pediatrics, has been low. Although numerous adult trials have evaluated the impact of pharmacogenomics and treatment response, the lack of evidence in children has hindered progress towards clinical application. This review aims to discuss the impact of genetic variability and response to asthmatic medications in the pediatric population.

Keywords: pediatric asthma; pharmacogenomics; beta-2 receptors; inhaled corticosteroids; leukotriene modifiers



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1. Introduction

Asthma is a multifactorial respiratory condition characterized by the narrowing of one's airways and affects over 300 million people, including 7% of children in the US [1]. Approximately 90% of all asthma cases stem from childhood [2], with the biggest burden on the quality of life in children ages 10–14 [3]. Symptoms such as difficulty breathing, shortness of breath, wheezing, tightness of the chest, etc. are early markers to suspect and diagnose asthma. Left untreated or uncontrolled, many childhood asthma cases can continue into adulthood, decreasing quality of life and potentially increasing the risk of developing chronic obstructive pulmonary disease (COPD). Managing asthma alone accounts for approximately \$80 billion spent annually on healthcare in the US [4]. In 2013, children between the ages of 5–17 in the US missed nearly 13 million days of school, an increase from the 10.4 million days in 2008 [5]. With a projected 100 million additional asthma cases by 2025 [6], the importance of finding appropriate treatment and gaining control of symptoms is even more crucial. Common treatment options for asthma are bronchodilators, inhaled corticosteroids (ICS), and leukotriene modifiers (LTM). Goals of therapy include providing symptomatic relief by optimizing airway function, reducing future exacerbations, and minimizing adverse effects from medications. According to the 2021 Global Initiative for Asthma (GINA) guidelines, initial pediatric treatment recommendations include using short acting beta agonists (SABA) and/or low doses of ICS as the first-line of therapy. In situations where symptoms are not adequately controlled, these guidelines provide recommendations when considering additional medications [7].

Despite this, up to 70% of patients are still unable to find proper relief [8]. Improper diagnoses and lack of adherence have been partially blamed; however, genetics have been implicated as well. Providing appropriate therapeutic recommendations could further limit the cases of adverse events from these medications. Up to 3% of pediatric hospital admissions are attributed to asthmatic adverse reactions, ranging from headaches to

adrenal suppression [9]. With widespread intra-variability among medication responses, pharmacogenomics has an emerging place in asthmatic treatment. Groundbreaking discoveries in allele variations and polymorphisms, such as single nucleotide polymorphisms (SNPs), provide opportunities for personalized treatment. Pharmacogenomics highlights the importance of optimizing a patient's response to drug therapy while minimizing adverse reactions. Specifically, breakthrough research completed in 2014 within Cystic Fibrosis patients has allowed therapeutic recommendations to be made for those with the G551D-CFTR variant [10].

Although asthma affects both children and adults, most studies have looked more closely at children, since environmental (i.e., workplace) and social (i.e., smoking) factors are minimized in this patient population. However, there have been no clinically relevant findings that have warranted specific therapeutic recommendations for any asthmatic patient population. Herein is a review of the current pharmacogenomic pediatric findings for beta-2 agonists, ICS, and LTM in asthmatic treatment.

2. Beta-2 Agonists

Beta-2 agonists are a class of bronchodilators commonly used to treat asthma and COPD. Two classes make up these beta-2 agonists: SABAs and long-acting beta agonists (LABAs). As rescue inhalers, SABAs, such as albuterol and levalbuterol, are commonly prescribed to provide immediate relief from asthma symptoms. Onset is typically less than five min and lasts 3–6 h [11]. Conversely, LABAs, such as salmeterol and formoterol may be added alongside ICS in situations where controller inhalers are necessary. Onset is approximately 5–15 min and lasts an average of 12 h [11]. These agonists bind to the β_2 adrenergic receptor found abundantly in the smooth muscles located in the lungs. Activation of these G-protein coupled receptors (GPCR) increases cAMP concentrations which in turn leads to bronchodilation (Figure 1). The β_2 adrenergic receptor is encoded by the ARB2 gene and has garnered significant clinical interest.



Figure 1. Beta-2 Agonists Mechanism of Action. Adapted from [11].

The most studied variation of the beta-2 adrenergic receptor is the ADRB2 gene (Table 1). This gene is found on chromosome 5q31-q32, an area highly associated with asthma. The amino acid at position 16 of the beta-2 receptor is thought to modulate down-regulation and airway responsiveness [12,13]. Studies on children [14,15] and adults [16] have shown that arginine (Arg) at this position displays better bronchodilation response when treated with a SABA [13]. Choudhry et al. studied 684 Puerto Ricans and Mexican children with an average age of 12 and 13, respectively. The presence of Arg at position 16 produced the greatest bronchodilation (10.46 \pm 2.44% Arg/Arg, 6.13 \pm 0.74% Arg/Gly change in FEV1), compared to Gly16Gly when administered albuterol in Puerto Ricans (p = 0.002) [14]. In contrast to these children, there was no genetic association found among Mexican children [14]. Martinez et al. reported that Arg16Arg and Arg16Gly were 5.3 and 2.3 times more likely, respectively, to produce greater bronchodilation compared to Gly16Gly when given albuterol. Included in this study were 496 children with an average of 10.8 years, with at least one non-Hispanic parent [17]. Positive bronchodilation was defined as >15.3% predicted FEV1.

Another pediatric study found favorable results with Arg16Arg alone as opposed to other genotypes when administered fenoterol. In 100 children with an average age of 9.6, Arg16Arg showed better bronchodilation response (108.68 \pm 15.62% post BD FEV1) compared to either Arg16Gly and Gly16Gly (101.86 \pm 14.03% post BD FEV1) [18], when administered this β 2 agonist. A positive response was defined as \geq 12% increase in FEV1. Studies done by Salah [19] and Finkelstein [15] also found that those with Gly16Gly genotypes produced a reduced response, while Arg16Arg displayed a favorable response to albuterol.

An adult study found that the patients with Arg16Arg displayed a better response, measured by peak expiratory flow rate (PEFR), when albuterol was replaced by ipratropium bromide in comparison to the patients with Gly16Gly [20]. Likewise, a pediatric study conducted by Carroll et al. found similar results [21]. Children with the Gly16Gly variation showed a better response, demonstrated by a shorter duration of continuous albuterol treatment (3 ± 0.9 days) and length of ICU stay (43 ± 25 h), compared to those with the Arg variants (4.8 ± 1.9 days and 74 ± 34 h, respectively) [21]. In a prospective case series study, Giubergia [22] observed changes in desensitization over four weeks among 117 Argentinian children treated with albuterol. Although the results were not statistically significant, those with the Arg16Arg genotype displayed a decline in responsiveness to long term treatment.

Focusing on alleles, Jovicic et al. reported that children with the minor G allele demonstrated a better response when given albuterol (GG: $14.4 \pm 6.1\%$ and GA: $10.4 \pm 5.8\%$ change in FEV1 p = 0.044) [23]. Additionally, they found that children with severe asthma were likely to be homozygote for the G allele (p = 0.01) compared to those with the major A allele, and thus would benefit most when treated with albuterol [23].

The amino acid position 27 on the β_2 receptor is also believed to have a role in bronchodilation, however with conflicting reports regarding the SABA response (Table 2) [24,25]. Alghobashy reported greater FEV1/ forced vital capacity (FVC) and FEV1 in children receiving albuterol or terbutaline with the Gln27Glu variants compared to those with Gln27Gln (p = 0.008, p < 0.001, respectively) [26]. However, Giubergia [22] found that Argentinian children with the Gln27Gln and Glu27Glu variants displayed a decline in responsiveness over time compared to those with Gln27Glu (p = 0.001). This decline in pre- and post-albuterol treatment was hypothesized to be from receptor desensitization. In contrast, a smaller study analyzed 31 African American children admitted to the hospital with status asthmaticus. All patients were given the initial treatment of IV steroids and inhaled albuterol with the addition of IV terbutaline, phosphodiesterase inhibitor, and/or aminophylline dependent on response. Approximately 38% of the children with the Gln27Gln variant needed additional terbutaline treatment compared to the ~50% of children with the Gln27Glu variant (p = 533). Only one of the 21 patients with the Gln27Gln variant receiving IV terbutaline needed additional aminophylline treatment, whereas five of the 10 with Gln27Glu did (p = 0.002) [27].

Table 1. SABA and ADRB2 rs1042713 Arg16Gly (+46 A > G).

Study	Population	Medication	Measurement	Results
Choudhry [14]	Puerto Ricans and Mexican	Albuterol	% change in predicted post- and pre- bronchodilator FEV1	Arg16Arg and Arg16Gly showed favorable response compared to Gly16Gly in Puerto Ricans
Finkelstein [15]	Multiethnic	Albuterol	Positive BDR $\geq 15\%$ FEV ₁ response	Arg16Arg were more likely to respond than Arg16Gly or Gly16Gly
Martinez [17]	Hispanic parents or at least one non-Hispanic parent	Albuterol	% change in predicted post- and pre- bronchodilator FEV1	Arg16Arg and Arg16Gly were more likely to respond than Gly16Gly
Scaparrotta [18]	European	Fenoterol	Post BD FEV1(%)	Arg16Arg showed favorable response compared to Gly16Gly or Arg16Gly
Salah [19]	Egyptian	Albuterol	% change in predicted post- and pre- bronchodilator FEV1	Arg16Arg showed favorable response compared to Gly16Gly and Arg16Gly
Carroll [21]	Hispanic, African American, White	Albuterol	Positive Clinical outcomes: ICU stay and duration of therapy	Gly16Gly produces more rapid and positive clinical outcomes than Arg genotypes
Giubergia [22]	Argentina	Albuterol	Change in FEV1 from Day 1 to Day 30	Arg16Arg showed reduced response
Jovicic [23]	Serbian	Albuterol	dFEV1	+46 G alleles (GG, GA) showed favorable response

BDR = Bronchodilator response; FEV₁ forced expiratory volume in 1 s; dFEV1 = percentage difference in FEV1.

Table 2. SABA and ADRB2 rs1042714 Gln27Glu (+79 C > G).

Study	Population	Medication	Measurement	Results
Alghobashy [26]	Egyptian	Albuterol or terbutaline	FVC, FEV1, FEV1/FVC ratio	Gln17Glu showed favorable outcomes compared to Glu27Glu
Giubergia [22]	Argentinean	Albuterol	Change in FEV1 from Day 1 to Day 30	Glu27Glu showed favorable outcomes compared to Gln27Gln
Elbahlawan [27]	African American	Terbutaline \pm aminophylline	Addition of aminophylline	Gln27Gln has a better response to beta-2 agonists than Glu27Glu

FVC = forced vital capacity; FEV1 = forced expiratory volume in 1sec.

Due to conflicting reports on polymorphisms that cause bronchodilation, no clear association at position 27 and a response to SABA therapy has been ascertained [14,15,17,18,21,23]. Some studies [25] have reported no association between SABA (i.e., albuterol) response and ADRB2 polymorphisms. It has been hypothesized that there is a more complex role at position 16 and 27. Jovicic suggested haplotype differences impact therapeutic outcomes more than SNPs, as seen in declining dFEV1 among patients with +46 A/+79 C (p = 0.026) [23].

2.2. SABA and Other Gene Variations

Contradictory findings regarding the ADRB2 gene have promoted interest into other areas (Table 3). The arginase 1 (ARG1) gene is found on chromosome 6q23 and encodes for arginase. Nitric oxide synthase (NOS) uses L-arginine, metabolized by arginase to regulate endogenous nitric oxide (NO), a known bronchodilator. Litonjua found that rs2781659, rs2781663, rs2781665, and rs2749935 SNPs were the most prevalent in bron-

chodilator response among the Childhood Asthma Management Program (CAMP) [28], Leukotriene Modifier or Corticosteroid or Corticosteroid Salmeterol (LOCCS) [29], Effectiveness of Low Dose Theophylline as Add-on Treatment in Asthma (LODO) [30], and the Asthma Trial studies [31]. CAMP was used to initially screen for SNPs and focused on children and their parents while the other three focused only on adults. The SNP, rs2781659, was ultimately found to be most significant for bronchodilation (Bonferronicorrected *p* value = 0.047) [31]. In replication studies, the AA genotype produced the most significant bronchodilation from albuterol in adults compared to either the AG or GG genotypes. Bronchodilation was defined as the percent difference from baseline in FEV1: Asthma trial = 41.39, LOCCS = 7.35, LODO = 11.53. However, Scaparrotta could not find an association with ARG1s, rs2781659 and bronchodilation among asthmatic children given fenoterol (p = 0.02) [18].

The thyroid hormone receptor β (THRB) gene is found on chromosome 3p24.2 and encodes for a portion of the thyroid hormone receptor. Thyroid hormones are necessary for lung development in addition to other organs. THRB variants have been associated with altered airway flow and impact smooth muscle in the lungs, though data on adults are scarce. Initial findings by Duan et al. demonstrated that the SNP, rs892940, was associated with bronchodilation in the CAMP study (population-based p value 0.09) and was further replicated in two out of three adult trials (Sepracor asthma trial; LODO; and LOCCS): namely the Sepracor asthma trial and LODO (combined *p* value 0.0012). Specifically, children with the minor A allele showed better bronchodilation (summary OR 1.34, 95% CI 1.12–1.59) to inhaled albuterol than those with the major allele G [32]. Scaparrotta aimed to confirm that rs892940 (G > A) impacted bronchodilation in children treated with inhaled fenoterol, but could not find any clear association [18]. Duan also identified SNPs in the vitamin D receptor (VDR) and Wilms' tumor 1 (WT1) in both the CAMP and the LODO study. However, bronchodilation response was insignificant or moderate at best when taking both studies together [32]. In a separate GWAS using participants from the CAMP study, Duan found variants in the COL22A1 and CLOCK region in primary and secondary replication cohorts that were associated with bronchodilator response when using as-needed albuterol [33].

SPATA13-AS1 is an anti-sense RNA that has an unknown mechanism and is thought to modulate the expression of ASEF2. This protein is known to have similar function as the guanine nucleotide exchange factor, activating Rho-family GTPase and inactivating RhoA. GTPase activation involves smooth muscle contraction while RhoA inactivation promotes smooth muscle dilation. Padhukasahasram identified SPATA13-AS1 in African American and European populations diagnosed with asthma. The initial discovery group comprised of African Americans between the ages of 12-56 living in south Michigan with no history of pulmonary disease or heart failure. Further replication groups included both healthy and asthmatic African Americans and European Americans with and without genome-wide data [34]. Initially, SPATA13-AS1 and sulfotransferase family 4A member 1 (SULT4A1) were both thought to affect SABA response. However, only SPATA13-AS1 was found to be statistically significant for bronchodilation when considering all the groups combined ($p = 7.38 \times 10^{-7}$). SPATA13-AS1 variations (rs9507294, rs912142, rs2248119, rs9551086, and rs9553225) and their effect size were also explored. In African Americans with genome-wide data, the SABA response to albuterol produced the greatest bronchodilation at 10.53 ± 12.93 change in FEV1 from baseline [34].

A GWAS done on CAMP, LOCCS, LODO, and three others found that variations in serine-rich 2-like (SPATS2L) protein coding gene were involved in bronchodilation [35]. Although little is known about exact function of this gene, Himes determined through replication studies that SNP, rs296137 produced the lowest combined *p* value of 9.7×10^{-7} . Specifically, those with the TT variant had a measured bronchodilation of 16% while CC and TC measured at 10.3% and 11.2%, respectively. This gave rise to the notion that the improvements in bronchodilation seen with the TT variants were due to decreased SPATS2L transcription, causing an increased beta-2 receptor concentration [35].

Israel et al. conducted a GWAS with 724 participants of the SNP Health Association Resource Asthma Resource Project (SHARP) and identified five SNPs that were positively associated with bronchodilation. However, only four of these (rs350729, rs1840321, rs1384918, and rs1319797) were statistically significant for bronchodilator response after receiving albuterol [36]. These SNPs were located on chromosome 2p16.2 which is near the ankyrin repeat (ASB3) gene. Involvement in muscle cell proliferation led the authors to hypothesize that the ASB3 gene expression modulates pulmonary function. It was reported that those homozygous for the minor allele would be expected to produce diminished responses compared to those homozygous for the major allele [36].

The corticotrophin-releasing hormone receptor 2 (CRHR2) has been reported to cause bronchodilation through smooth muscle relaxation [37]. With the goal of finding bronchodilation changes in CRHR2 variants, Poon reviewed 607 individuals in the CAMP study. Initial findings revealed a statistical significance in rs255100, rs7793837, and rs2267715. Homozygotes for the minor alleles had a reduced bronchodilation response to albuterol ($p \le 0.05$) [37]. This was not the case in the adult studies where different variants were found to produce bronchodilation. Minor alleles for SNPs rs2284220, rs7793837, and rs2267716 showed the lowest albuterol response compared to their respective major alleles [37].

Multiple cohorts were involved in a GWAS and meta-analysis study of 949 African American children done by Spear to determine variations in albuterol responsiveness (Study of African Americans, Asthma, Genes and Environments, SAGE I and II; Genes-Environments and Admixture in Latino Americans, GALA I and II; African Americans from the Study of Asthma Phenotypes and Pharmacogenomic Interactions by Race-Ethnicity, SAPPHIRE; and African Americans from the Severe Asthma Research Program, SARP). Bronchodilation was measured by changes in FEV1 before and after receiving albuterol. Identified in the study was the SNP, rs73650726, on chromosome 9q21 with the major A allele producing decreased bronchodilation in both SAGE I and II compared to the minor G allele ($\beta = -3.8$, $p = 7.69 \times 10^{-9}$) [38]. In the meta-analysis of SAGE I, II, and GALA II, SNPs rs7903366, rs7070958, and rs7081864 were found in the Protein Kinase CGMP-Dependent Type 1 (PRKG1) gene. This gene encodes for cGMP-dependent protein kinase which mediates bronchodilation through the nitric oxide (NO) pathway. However, these SNPs were not found in subsequent replication studies (GALA I, SAPPHIRE, and SHARP). Supporting initial findings by Padhukasahasram, Spear et al.'s additional analysis reported statistical significance of SNP, rs9551086 (p = 0.02), in the SPATA13 gene, whereas statistical significance was not reached for genes ADRB2, ADCY9, CRHR2, ARG1, THRB, CRHR2, and other SNPs of SPATA13 [38].

Tal	ole	3.	SABA	and	genetic	variations
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Study	Population	Gene/Location	Medication	Measurement	Results
Litonjua [31]	White	ARG1	Albuterol	% difference in FEV1 between pre- and post-bronchodilator	rs2781659 AA genotype showed favorable response compared to AG or GG genotypes
Scaparrotta [18]	Caucasian	ARG1 THRB	Fenoterol	Increase in FEV1 > 12% from baseline	rs2781659 variants in children inconclusive rs892940 variants in children inconclusive
Duan [32]	White	THRB	Albuterol	% difference in FEV1 pre- and post-bronchodilator	rs892940 A allele showed favorable response over G allele
Duan [33]	White	VDR and WT1	Albuterol	% difference in FEV1 pre- and post-bronchodilator	No statistical significance found

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Study	Population	Gene/Location	Medication	Measurement	Results
Padhukasahasram [34]	African Americans and Europeans	SPATA13-AS1	Albuterol	% change in FEV1 pre- and post-bronchodilator	rs9507294, rs912142, rs2248119, rs9551086, and rs9553225 produced favorable response
Himes [35]	White	SPATS2L	Albuterol	% difference in FEV1 pre- and post-bronchodilator	rs295137 TT produced favorable response compared to CC or TC
Israel [36]	White	Near ASB3	Albuterol	% change in FEV1 pre- and post-bronchodilator	rs350729, rs1840321, rs1384918, and rs1319797 homozygous major allele produce favorable response
Poon [37]	Caucasian	CRHR2	Albuterol	% change in FEV1 pre- and post-bronchodilator	rs255100A, rs7793837T, and rs2267715G produced favorable response in children but not in adults
Spear [38]	Multiethnic	Chromosome 9q21 PRKG1	Albuterol	% change in FEV1 pre- and post-bronchodilator	rs73650726G produced favorable response Findings unsupported in replication

Table 3. Cont.

2.3. LABA with or without ICS and ADRB2 Variations

In cases where controller medications are needed, the 2021 GINA guidelines recommend using ICS/formoterol as opposed to SABA monotherapy [3]. As of 2010, LABA monotherapy has been contraindicated in asthma due to an increased number of adverse events and deaths [7]. Bleecker conducted a study in 2008 using salmeterol with or without fluticasone propionate to analyze the pharmacogenetic effects in individuals ages 12 and older [39]. In this randomized, double-blind, parallel study, it was reported that changes in peak expiratory flow (PEF) were similar, noninferior, and no increase in exacerbations were detected between both treatment groups of all ADRB2 genotypes at position 16 (Table 4). Further analysis among African American patients also revealed no differences in asthma control measures. Similar findings were observed by Bleecker and colleagues, where participants were assigned a budesonide and formoterol combination or fluticasone with salmeterol [40]. Improvements in baseline morning PEF and FEV1 were seen consistently across all genotypes regardless of treatment group (p < 0.001) [40]. Additional studies by Bleecker, Giubergia, and Wang found no pharmacogenetic implications in LABA response [41–43], unlike studies done by Palmer [44] and Zuurhout [45]. These latter two studies found that those with the Arg16Arg genotype had an increased risk of exacerbations in children taking a LABA and ICS (OR 3.40, p = 0.022 and OR 12.13, p = 0.004).

In contrast to the findings of Bleecker [39,40], Wechsler [46] examined two different adult studies: the Salmeterol or Corticosteroids (SOCS) as well as Salmeterol and ICS (SLIC). Those in the SCOS study were randomized to receive either placebo, triamcinolone, or salmeterol whereas those in SLIC were randomized to receive a combination of salmeterol and steady triamcinolone, tapered triamcinolone, or placebo. Wechsler concluded that those with Arg16 did not respond as well when given salmeterol. Although the increase in morning PEF was greater among Arg16Arg individuals in the SLIC study, levels were not sustained through the end of the trial, as seen with the Gly16Gly individuals (difference in morning PEF -36.8, p = 0.05). Those with Gly16 showed greater changes in morning PEF compared to Arg16Arg (p = 0.005) [46]. These results were comparable to the findings of a study done by Lipworth [47]. Children with persistent asthma with Arg16Arg had increased exacerbations and more school absences among those receiving salmeterol versus montelukast (difference in score -0.40, p = 0.005) [47]. Similarly, Basu [48] compared

the albuterol and salmeterol response in participants ages 3 to 22. They found that the Arg16 variants were at higher risk of exacerbations (OR 1.30, p = 0.003) regardless of medication choice. Specifically, the Arg16Arg and Arg16Gly individuals had a higher risk of exacerbations compared to the Gly16Gly individuals (OR 1.74, p = 0.02) [48].

One pediatric study identified associations between Arg16 variants and exacerbations from ICS and LABA therapy. Turner evaluated 4226 children from five trials (BREATHE, PACMAN, GALA II, PASS, and PAGES) and found those with Arg16 had increased risk of exacerbations given ICS and LABA, but not in combination with leukotriene receptor antagonists (LTRAs) (OR 1.52, p = 0.0021) [49]. In addition, the OR was the highest in those administered ICS + LABA compared to SABA and ICS monotherapy, ICS + LTRA, and ICS + LABA + LTRA (OR 1.01, p = 0.95; OR 1.11, p = 0.18; OR 1.11, p = 0.52; OR 0.94, p = 0.65, respectively) [49].

A prospective case-control study done with Egyptian children found significance at ADRB2 codon 16 and 27 (p < 0.05). Pulmonary function tests were assessed using FEV1 and FEV1/FVC. At position 16, those with Gly16Gly showed a decreased response compared to those with Arg16Arg or Arg16Gly. The same decrease in response in those with Glu27Glu compared to those with Gln27Gln or Gln27Glu [26]. However, other pediatric studies could not find pharmacogenetic associations at position 27 [39,42,44].

Table 4. ICS with or without LABA and ADRB2 rs1042713 Arg16Gly (+46 A > G).

Study	Population	Medication	Measurement	Results
Bleecker [39]	Multiethnic	Fluticasone \pm salmeterol	Change in PEF	At position 16, Arg/Arg, Gly/Gly, and Arg/Gly produce similar response
Bleecker [40]	Multiethnic	Budesonide + formoterol or Fluticasone + salmeterol	FEV1, PEF	At position 16, Arg/Arg, Gly/Gly, and Arg/Gly produce similar response
Bleecker [41]	Multiethnic	Fluticasone + salmeterol	FEV1	Improvement in BDR regardless of genotype
Guibergia [42]	Argentinean	Fluticasone + salmeterol	FEV1	No association at position 16 or 27
Wang [43]	Multiethnic	Fluticasone + salmeterol	Varies based on study	No association at position 16
Palmer [44]	Scotland	ICS + LABA or ICS + LABA + montelukast	Exacerbations (school absences, short course of oral steroids, hospital admissions)	Arg16Arg genotypes are at greater risk.At position 27, no association found
Zuurhout [45]	Netherlands	ICS or ICS + LABA	Exacerbations (asthma-related hospital visits and oral steroids)	Arg16Arg genotypes are at greater risk in those taking ICS + LABA
Lipworth [47]	Scotland	Fluticasone + oral montelukast or salmeterol + fluticasone	School absences, FEV1, asthma symptoms	Arg16 variant produced less favorable response with salmeterol
Basu [48]	Scotland	Albuterol or salmeterol	Exacerbations (school absences, oral steroid use, hospital visits)	Arg16Arg genotypes were at greatest risk
Turner [49]	Multiethnic	ICS, LABA, LTM combinations	Exacerbation (varies based on study)	Arg16 variants receiving ICS + LABA were at greater risk
Alghobashy [26]	Egypt	ICS + LABA	FEV1 and FEV1/FVC	Gly16Gly and Glu27Glu produced unfavorable response

3. Inhaled Corticosteroids (ICS)

Depending on age and severity, the GINA guidelines recommend using ICS monotherapy, or in combination as the preferred controller in addition to a rescue inhaler. ICS are commonly prescribed to treat asthma and, to an extent, COPD. Highly effective in reducing inflammation, ICS can significantly improve asthma symptoms and reduce morbidity in both children and adults. The mechanism of action involves decreasing inflammatory mediators such as mast cells, cytokines, and enzymes such as COX-2. Inhalation routes allow for minimal systemic absorption; thus, efficacy and safety are robust. However, side effects are not negligible, especially when used in children for an extended period. Osteoporosis, glaucoma, and metabolic disturbances are possible adverse events of systemic exposure (Figure 2).



Figure 2. ICS Mechanism of Action. Adapted from [50].

Tantisira conducted a GWAS in 2011 and identified the glucocorticoid-induced transcript 1 (GLCCI1) gene and the SNPs, rs37972 and rs37973 (Table 5) [51]. Non-Hispanic white children selected from the CAMP study were given budesonide, and the response was measured by the change in FEV1 from baseline. Although little is known about GLCCI1, those homozygote for the mutant T allele at SNP, rs37972, yielded a poorer response compared to those who were heterozygote (CT) or homozygote (CC) (OR, 2.36; 95% CI, 1.27–4.41) [51]. Additionally, linkage disequilibrium was found with the SNP, rs37973 ($r^2 = 0.99$). Individuals that were homozygote for the wild-type A allele had a better response to budesonide compared to those homozygotes for the mutant G allele ($3.2 \pm 1.6\%$ vs. $9.4 \pm 1.1\%$ increase in FEV1) [51]. Similar findings were seen in a trial conducted by Thompson et al. [52]. Included in that study were 402 European children on long-term ICS treatment (>6 months). Higher steroid doses and increased hospitalization were seen in SNP, rs37973, homozygous for the mutant allele compared to those heterozygous or homozygous wild-type [52]. Unlike Tantisira [51], Vijverberg saw no association with individuals having SNP, rs37972 and ICS response in Northern European children [53]. Additionally, Vijverberg utilized hospital visits and oral steroid use as markers for exacerbation and concluded that the mutant T allele was not associated with an increased risk when treated with budesonide [53]. In contrast, Huang et al. found associations in the GLCCI1 gene in 263 Chinese children. SNPs, rs37969 GG, rs37972 CC, and rs37973 AA produced favorable changes measured by maximal mid-expiratory flow ($p \le 0.05$) [54]. Stress-induced phosphoprotein 1 (STIP1) was also explored in this study and was shown to suppress inflammatory mediators. Although a significant association between SNP rs2236647 CC and the risk of developing asthma was found, there was no association with any SNP and ICS response [54].

It was hypothesized that histone deacetylase I and 2 (HDAC1, HDAC2) play a positive role in airway responsiveness and inflammation. Kim studied 35 adults and 70 children with the HDAC1 SNP, rs1741981 [55]. Bronchodilation was measured as a % change in FEV1 from baseline [55]. Adults with the CC genotype produced diminished responses

compared to the CT or TT genotypes when administered systemic corticosteroids (p = 0.018). The same was true for the children given inhaled corticosteroids. Those with the CC genotype had a FEV1 of 14.1% compared to either the CT or TT (19.4%, p = 0.035).

The corticotropin-release hormone (CRH) is a known mediator to stress and its corresponding receptor, corticotropin-releasing hormone receptor 1 (CRHR1), is hypothesized to have a role in ICS response [56]. In comparison to the unfavorable responses seen in the GLCCI1 variants, Tantisira observed an increase in response in those with the CRHR1 variants among three cohorts of both children and adults treated with an ICS. Response was measured by dFEV1 over a span of eight weeks in the CAMP replication study. Those with the rs242941 mutant TT genotypes displayed a change of 17.80 + 6.77 in FEV1 compared to a change of 7.57 + 1.50 in those with the wild-type CC. This was not seen in the initial adult study treated with flunisolide. SNP, rs1876828 variant, was also associated with triamcinolone responses in the adult replication study but was statistically insignificant in children [54].

Variants in the T-box transcription factor (TBX21), which encodes for transcription factor T-bet, also displayed improvements in ICS response. Children with glutamine at amino acid position 33 in place of histidine (rs2240017) displayed better PC20 [57]. PC20 is the provocative concentration resulting in a 20% drop of FEV1 post methacholine challenge. After four years, PC20 for the 33Q individuals given budesonide was measured to be 27.7 mg/mL, placing them in the non-asthmatic range [57]. Tantisira also conducted a study with a focus on the Fc fragment of IgE low affinity II receptor (FCER2) gene [58]. FCER2 encodes for CD23, causing IgE mediated responses which have been associated with severe asthmatic exacerbations. In this study, 311 Caucasian children were assigned to inhaled budesonide and observed over four years. The SNPs identified to be associated with increased IgE levels and exacerbations were: rs4996974, rs7249320, and rs28364072. Children with the SNP, rs28364072, homozygous for the mutant C allele were at a higher risk of severe exacerbations in both African American and Caucasian populations (HR 3.08 and 3.95, respectively) [58]. Koster replicated these findings in two pediatric cohorts treated with ICS. Children's homozygotes for the variant C allele had a higher risk of severe exacerbations (OR 2.38, 95% CI 1.47–3.85, p = 0.0004), increase in hospital visits (OR 1.91, 95% CI 1.08–3.40, p = 0.03), and were more likely to use higher ICS doses (OR 2.46, 95% CI 1.38–4.39, p = 0.002 [59]. These findings support the need for earlier detection of FCER2 polymorphisms to identify those resistant to steroid treatment and provide timely anti-IgE treatment.

Located on chromosome 5q31-q32, nuclear receptor subfamily 3, group C, member 1 (NR3C1) is a protein-coding gene for glucocorticoid receptors. Keskin studied 82 children with a mean age of 9.6, given inhaled fluticasone propionate specifically evaluating the role of NR3C1 [60]. Of the 82 children, 26 had the rs41423247, GG genotype and displayed a better response compared to those with the CG or CC variations, measured by FEV1 (24.2% vs. 7.9%, p = 0.006) [60]. Stockman also conducted a study involving 734 Caucasian children receiving inhaled fluticasone propionate. Variations among cytochrome p450 (CYP) 3A4, 3A5, and 3A7, which are involved in fluticasone metabolism, were assessed for symptom control using the asthma control score. CYP3A5 and CYP3A7 were not found to have an association, however, CYP3A4 *22 children displayed better asthma control due to the reduced activity of the metabolic enzyme, leading to increased therapeutic outcomes [61]. These findings were not seen in a follow-up study of 64 children treated with beclomethasone [62]. They observed that children with CYP3A5 *3/*3, commonly found among Caucasian populations, displayed better asthma control, compared to either *1/*1 or *1/*3 variations [62]. Pharmacogenomics testing on these CYP enzymes has the potential to provide guidance on future regimens. Children with the CYP3A4 *1/*1 or *1/*3 variation may be advised to use a non-beclomethasone medication, such as budesonide, as their initial ICS. Similarly, those with the CYP3A4 *22 variation may be advised to start therapy with fluticasone.

Study	Population	Gene	Medication	Measurement	Results
Tantisira [51]	White	GLCCI1	Budesonide	Change in FEV1 from baseline	rs37972 TT and rs37973 G allele variants showed unfavorable responses
Thompson [52]	European	GLCCI1	ICS	Exacerbation (hospital visits and oral steroid use)	rs37973 G allele showed unfavorable response
Vijverberg [53]	Europe	GLCCI1	Budesonide	Exacerbation (emergency room visits, hospital visits, oral steroid use)	No association found at rs37972
Huang [54]	Chinese	GLCCI1	ICS	MMEF	rs37969, rs37972, and rs37973 produced favorable response.
Kim [55]	Korean	HDAC1	ICS	% change in FEV1 pre- and post-bronchodilator	rs1741981 CT and TT produced favorable response
Tantisira [56]	Caucasians	CRHR1	Budesonide	% change in FEV1 from baseline	rs242941T produced favorable response
Tantisira [57]	Multiethnic	TBX21	Budesonide	% change in FEV1 and PC20	rs2240017Q produced favorable response
Tantisira [58]	Multiethnic	FCER2	Budesonide	Exacerbations (ER visits or hospitalization)	rs28364072 CC produced unfavorable response
Koster [59]	European	FCER2	ICS, ICS + salmeterol, ICS + salmeterol + montelukast	Exacerbations (hospital visits and/or oral steroid use)	rs28364072 CC produced unfavorable response
Keskin [60]	Turkey	NR3C1	Fluticasone	FEV1 improvement at 4 h	rs41423247 GG produced favorable response
Stockman [61]	Whites	CYP3A4, CYP3A5, and CYP3A7	Fluticasone	Asthma control scores	CYP3A4 *22 produced favorable response
Stockman [62]	White	CYP3A4, CYP3A5, and CYP3A7	Beclomethasone	Asthma control scores	CYP3A5 *3/*3 produced favorable response

Table 5. ICS and genetic variations.

MMEF = maximal mid-expiratory flow.

4. Leukotriene Modifiers (LTM)

Leukotrienes are involved in inflammatory processes and bronchoconstriction, both of which are implicated in asthmatic symptoms. Leukotriene modifiers are considered second line after ICS and LABA for chronic asthma according to the GINA guidelines [3]. Administered orally, these LTMs include zileuton, montelukast, and zafirlukast which are subsequently classified into leukotriene synthesis inhibitors or leukotriene receptor antagonists. Zileuton inhibits the 5-lipoxygenase (5-LO) enzyme, halting the conversion of arachidonic acid into LTA4. Montelukast, zafirlukast, and pranlukast are cysteinylleukotriene receptor (CysLTR) inhibitors, antagonizing the effects of LTC4, LTD4, and LTE4 [63,64].

Similar to bronchodilators and ICS, limitations of leukotriene modifiers are highlighted by genetic variations, emphasizing inter-patient variability leading to exacerbated symptoms [65,66]. In addition, nearly half of the side effects in children taking a LTM are attributed to psychiatric disturbances such as hallucinations and agitation [64]. Genes such as arachidonate 5-lipoxygenase (ALOX5) and cysteinyl-LTs (CysLTs) previously identified and replicated in adult studies have not yet been fully confirmed in children. Identifying variants associated with positive leukotriene modifier response can further benefit children who cannot gain symptom control with ICS or beta agonists.

4.1. Genes That Affect Montelukast Response

Montelukast, favored in the pediatric community for its once-a-day dosing, is an oral medication for chronic asthma and exercise-induced bronchoconstriction (EIB). It binds to the CysT1 receptor (CysLTR1), antagonizing the effects of LTD4, and decreasing bronchoconstriction [66].

Both pharmacodynamic and pharmacokinetic studies have shown to potentially impact montelukast responsiveness in children (Table 6).

Thromboxane A2 (TBXA2), an arachidonic acid derivative, binds to the thromboxane A2 receptor (TBXA2R) and causes pulmonary smooth muscle constriction and platelet aggregation. To determine an association between the TBXA2R gene and LTM response, Kim et al. conducted a study on 695 Korean children with exercise-induced bronchospasms given montelukast. They found that those with the TBXA2R +795 CC or CT variations were 2.5 times more likely to be unresponsive to treatment (p = 0.063) [67]. Responders were defined as >10% in FEV1 after montelukast treatment. In addition, those with both the TBXA2R +795 CT or CC and +924 TT variation were less likely to respond to montelukast treatment (OR 3.67, p = 0.041) [67].

In comparison, Klotsman found a statistically significant association of responsiveness in the ALOX5 variants among children 15 years of age and older. ALOX5 encodes for 5-lipoxygenase (5-LO) and is found on chromosome 10q11.21 [68]. 5-LO is involved in the conversion of arachidonic acid into LTA4 and is the rate limiting step in leukotriene synthesis (Figure 3). Two out of five variants were significantly associated with a positive response to montelukast. Those with the SNP rs4987105 TT genotype produced a mean PEF of 94.8 while those with CC genotypes were 33.7 (p = 0.01). Those with the SNP rs4986832 AA genotype produced a mean PEF of 102.4 while those with the GG genotype were 34.9 (p = 0.01) [69]. Conversely, Telleria et al. studied the promoter region of the ALOX5 gene. Five copies of the transcription factor binding sequence GGGCGG (rs59439148) were recognized as the major allele, with variants hypothesized to produce reduced activity [70]. They found greater improvements with homozygotes wild type (5/5) and heterozygotes (5/4), compared to homozygote variants (4/4) after 6 months of montelukast treatment. Those with the 4/4 repeats displayed higher rates of exacerbations, worsening FEV1, and greater need for rescue inhaler compared to those with the 5/5 or 5/4 repeats ($p \le 0.05$) [70].

Similar to CystLTR1, cysteinyl- leukotriene (CystLT) receptor 2 (CysLTR2) have recently been found on smooth muscle cells. Although the variant function of this gene has yet to be identified, it has been associated with asthmatic treatment response. SNPs, rs912277 TC and rs912278 CC, were found to produce greater PEF (p = 0.021 and p = 0.02, respectively) in a study done by Klotsman [69]. Participants were at least 15 years of age and observed over 12 weeks. TT genotypes in both SNPs produced a mean PEF of 38.8 and 29.1, respectively. In the same study, they assessed leukotriene C4 synthase (LTC4S). LTC4S converts leukotriene A4 to leukotriene C4, increasing CysLT levels contributing to asthmatic inflammation (Figure 3). However, no association was found in montelukast treatment in either FEV1 or PEF in SNP, rs730012 [69]. Furthermore, Kang could not establish statistical significance in those with the LTC4S polymorphisms between responders and non-responders (p = 0.702) in 100 Korean asthmatic children [71]. Lee claimed that montelukast responsiveness is associated with total IgE and PC20 levels, opposed to FEV1 [72]. This study also observed CysLTR1 variations with exercise-induced bronchoconstriction (EIB). However, no correlation to montelukast responsiveness, measured by >10% increase in FEV1 post exercise challenge, was found [72]. Whelan investigated 13 children, ages 10–16 and found a positive correlation in montelukast responsiveness and LTC4S. Statistical significance in those with the LTC4S AC genotype produced a greater decrease in fraction of exhaled nitric oxide (FENO) (slope -3.13%/day), which was correlated with a decrease



in airway inflammation. Those with the AA genotype did not produce any noticeable change in FENO, suggesting montelukast use in these patients may not be beneficial [73].

Figure 3. Leukotriene Modifiers Mechanism of Action. Adapted from [68].

A study by Kang on 10 Korean asthmatic children investigated prostaglandin D2 receptor (PTGDR), a derivative of arachidonic acid implicated in eosinophilia migration [71]. Over the span of eight weeks children receiving montelukast with the rs803010 TT genotype had a greater FEV1 fall post-exercise challenge compared to those with the TC or CC genotype (63.8% vs. 36.2% p = 0.038). No difference in response was found when analyzing both PTGDR and LTC4S variants [71].

Lipworth observed 62 children with ADRB2 Arg16Arg variants and found montelukast reduced school absences and symptoms compared to those treated with salmeterol. All children also received inhaled fluticasone throughout the one-year study. It was concluded that the use of montelukast and an ICS may be more beneficial than the recommended ICS and LABA combination [47] (Table 7).

Organic anion transporter polypeptide 2B1 (OATP2B1) are drug transporters found in the liver, intestine, and kidney and are responsible for reuptake of various substrates. This transporter is encoded by the gene solute carrier organic anion transporter family member 2B1 (SLCO2B1). OATP2B1 SNPs rs12422149 and rs2306168 have been associated with montelukast absorption [74]. Mougey utilized the Asthma Symptoms Utility Index (ASUI) to measure drug responsiveness and found that those with the rs12422149 GG genotype demonstrated greater improvement at three months and six months compared to the those with the AG genotype [74]. Similarly, a study by Li with 50 Chinese children with an average age of 4.4 years old found lower montelukast clearance in the SLCO2B1 rs12422149 GG genotype compared to the GA and AA (0.77 ± 0.21 vs. 0.94 ± 0.26 , p = 0.020) [75]. Those with the GG genotype displayed better responsiveness to montelukast due to lower drug clearance leading to increased plasma concentrations. Li also examined CYP2C8 variations, however no association was found with montelukast clearance in Chinese children [75]. These results may favor genetic testing to identify SLCO2B1, rs12422149 GG variants, which presumably should see the greatest effect from montelukast treatment among LTM

Study Population Gene Measurement Results Combination of +795 CT/CC and FEV1 Kim [67] Korean TBXA2 +924 TT showed unfavorable response rs4987105 TT and rs4986832 AA ALOX5 PEF variants showed favorable outcomes PEF Klotsman [69] Multiethnic CystLTR2 rs912277 TT and rs912278 TC variants FEV1 and PEF LTC4S produced favorable response No association found at rs730012 % change in FEV1, exacerbations, rs59439148 5/5 and 5/4 copies Telleria [70] Spain ALOX5 and rescue inhaler need showed favorable outcomes No significance at rs730012 LTC4S \geq 10% increase in FEV1 post Kang [71] Korean rs803010 TT produced favorable PTGDR exercise challenge response LTC4S >10% increase in FEV1 post No significance at SNP rs730012 Lee [72] Korean CystLTR1 exercise challenge No significance found African rs730012 AC produced favorable Whelan [73] American and LTC4S **FENO** response Caucasian rs12422149 GG produced favorable Asthma symptom utility index Mougey [74] Multiethnic SLCO2B1 response (ASUI) No association at rs2306168 Decreased clearance in rs12422149 GG Chinese SLCO2B1CYP2C8 Li [75] Drug clearance No association found

medications [76]. Those without the SLCO2B1, rs12422149 GG variants may see better efficacy on a different LTM [77].

Table 6. Montelukast and genetic variations.

Table 7. Montelukast Combination and ADRB2.

Study	Population	Gene	Medication	Measurement	Results
Lipworth [47]	Scotland	ADRB2	Fluticasone + montelukast or salmeterol + fluticasone	School absences, FEV1, asthma symptoms	Arg16Arg produced favorable responses to fluticasone and montelukast

4.2. Genes Affecting Other Leukotriene Modifier Responses

Zileuton is a 5-LO inhibitor that leads to decreased leukotriene synthesis, inflammation, and bronchoconstriction (Figure 3). Those on zileuton should monitor their ALT regularly [78]. Data on zileuton responsiveness is scarce as most studies utilized montelukast as the drug of choice. Tcheurekdjlan looked at Puerto Rican and Mexican youths with an average age of 12.3 taking a leukotriene modifier and albuterol. Bronchodilator responsiveness, measured by FEV1, was found to be greater in those taking LTM compared to those did not (p = 0.001) [79]. In addition, leukotriene A4 hydrolase (LTA4H) was investigated. LTA4H converts LTA4 to LTB4, which contributes to neutrophilic asthma characterized by severe airway obstruction. The LTA4H SNP rs2540491 minor A allele produced a change of 7–10% in FEV1 compared to the major G allele which produced a change of -0.31% in FEV1 (Table 8). These results were seen in the Puerto Rican population, but not in the Mexican population. The LTA4H SNP rs2540487 GA heterozygotes also produced a change of more than 10% in FEV1 (p < 0.001) compared to homozygotes major or minor (2.5 % change in FEV1, p = 0.180 and 0.679, respectively) [79]. Arachidonate 5lipoxygenase activating protein (ALOX5AP) modulates downstream leukotriene synthesis along with ALOX5, converting arachidonic acid into leukotriene A4 (Figure 3). No association was found between ALOX5AP, rs10507391 and rs955196 variants with leukotriene

modifier bronchodilation. Interactions between LTA4H, ALOX5AP, and their variants were also analyzed for bronchodilation. The presence of ALOX5AP, rs10507391 major A allele and LTA4H minor allele variants contributed to bronchodilation, whereas the presence of ALOX5AP, rs9551963 minor C allele and LT4AH minor allele variants contributed to bronchodilation. These findings were significant in Puerto Rican populations but not Mexican populations [79].

Table 8. Leukotriene Modifier and Genetic Variants.

Study	Population	Gene	Medication	Measurement	Results
Tcheurekdjlan [79]	Mexican and Puerto Ricans	LTA4H Alox5ap	Albuterol + leukotriene modifiers (montelukast, zafirlukast, and zileuton)	% change in FEV1 pre and post bronchodilator	LTA4H rs2540491 A variants and rs2540487 GA variants produced favorable response No association of ALOX5AP variants alone rs10507391 A allele and rs9551963 C allele magnifies LTA4H response

5. Conclusions

A tailored approach to asthmatic treatment may be warranted based on genetic variability. Beta-2 agonists have been the most widely studied in both adult and pediatric populations. However, results surrounding ADRB2 gene variations at both position 16 and 27 are conflicting, promoting interest into the impact of diverse patient populations. Among the ICS studies, budesonide and fluticasone have shown to be associated with conflicting treatment response. Similarly, montelukast and zileuton have shown to be associated with inconsistent treatment response among the leukotriene modifiers. GINA guidelines also recommend adding on biologics such as omalizumab (Xolair) or dupilumab (Dupixent) [80]. These biologics are indicated in children aged six and older with severe symptoms, despite optimizing therapy with high dose ICS-LABA-oral corticosteroids.

Pharmacogenetic testing in asthmatic adults has shown cost effectiveness and increased quality of life when adding a LTM to patients identified as exhibiting reduced ICS response [80]. Current guidelines recommend increasing ICS-LABA dosing to reduce exacerbations, or alternatively using a LTM as a controller therapy. Identifying children who may be genetically predisposed to ICS unresponsiveness may incline providers to initiate alternative LTM therapy earlier in the patient's course of treatment. There are no studies to date on the effectiveness of pharmacogenomic testing for asthmatic biologics. However, future trials on the stepwise therapy model may be questioned as some children may be better suited for biologics rather than LTMs. Potential testing on certain genetic markers, such as drug transporter or CYP450 enzymes, can additionally guide clinicians when choosing initial medications among drug classes. Future studies should be conducted to evaluate the effectiveness of pharmacogenomic testing in children. Although preemptive pharmacogenomic testing for asthma is not currently recommended, due to the lack of evidence and accuracy, the hope for universal testing at an early age has the potential to eliminate prolonged medication trial and error. Unfortunately, limitations in many of these studies include the small sample size and lack of diversity. With recent discussions on race and ethnicity, there is a need for further stratification based on genetic ancestry beyond the non-Hispanic white population. Some studies utilized measurable outcomes such as PEF and FEV1, whereas others used exacerbation rates and asthma scores, which further complicates drug responsiveness. Additionally, many studies have included both adults and children. These results cannot be extrapolated specifically to children. Larger pediatric asthmatic studies [81,82] could improve confidence for the translation of genotype to phenotype, with the common goal of developing the best course of treatment for each individual child.

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