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Authors

Khare, Manaswitha

Piparia, Shraddha

Tantisira, Kelan

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Pharmacogenetics of childhood uncontrolled asthma

Manaswitha Khare[1,2,*], **Shraddha Piparia**[3,*], **Kelan G Tantisira**[3,4]

[1.]Division of Pediatric Hospital Medicine, Department of Pediatrics, University of California San Diego, San Diego, CA

[2.]Division of Pediatric Hospital Medicine, Department of Pediatrics, Rady Children's Hospital of San Diego, San Diego, CA

[3.]Division of Pediatric Respiratory Medicine, Department of Pediatrics, University of California San Diego, San Diego, CA

[4.]Division of Pediatric Respiratory Medicine, Department of Pediatrics, Rady Children's Hospital of San Diego, San Diego, CA

Abstract

Introduction: Asthma is a heterogenous, multifactorial disease with multiple genetic and environmental risk factors playing a role in pathogenesis and therapeutic response. Understanding of pharmacogenetics can help with matching individualized treatments to specific genotypes of asthma to improve therapeutic outcomes especially in uncontrolled or severe asthma.

Areas covered: In this review, we outline novel information about biology, pathways and mechanisms related to interindividual variability in drug response (corticosteroids, bronchodilators, leukotriene modifiers and Biologics) for childhood asthma. We discuss candidate gene, genome-wide association studies and newer omics studies including epigenomics, transcriptomics, proteomics, and metabolomics as well as integrative genomics and systems biology methods related to childhood asthma. The articles were obtained after a series of searches, last updated November 2022, using database PubMed/CINAHL DB.

Expert opinion: Implementation of pharmacogenetic algorithms can improve therapeutic targeting in children with asthma, particularly with severe or uncontrolled asthma who typically have challenges in clinical management and carry considerable financial burden. Future studies focusing on potential biomarkers both clinical and pharmacogenetic can help formulate a prognostic test for asthma treatment response that would represent true bench to bedside clinical implementation.

Correspondence: ktantisira@health.ucsd.edu.
*These authors contributed equally

Declaration of interest

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1. Introduction

Asthma is a complex chronic disease in children ranking among top 20 conditions worldwide for disability-adjusted life years and affects about 6% of children worldwide(1, 2). It is a heterogenous, multifactorial disease with multiple genetic and environmental risk factors. Severe asthma is characterized by persistent asthma symptoms, and increased medication use leading to excessive health care utilization (3). Availability of targeted therapies, better understanding of structural and immune pathophysiology in asthmatic lung, as well as genetic and epigenetic mechanisms of asthma have helped define asthma based on etiologies and clinical biomarkers as a step towards improved precision medicine (4–6).

Asthma symptoms are treated mainly using three classes of medications, inhaled short and long-acting β2-agonists (SABA and LABA), inhaled corticosteroids (ICS) and systemic corticosteroids, and leukotriene antagonists. Standard treatment regimens for persistent asthma include inhaled corticosteroids (ICS) alone or combined with long-acting β2-agonists (LABA) and short-acting β2-agonists (SABA) as needed (7). Recent introduction of biologic drugs or monoclonal antibodies led to a radical change in therapeutic approach of severe asthma (8–12). The monoclonal antibodies targeting IgE, interleukin (IL)4/IL13 and IL5 T2-driven inflammation significantly reduce use of oral corticosteroids and exacerbations in patients with severe asthma (13). Although all asthma medications are effective in majority of patients, there is interindividual variability in therapeutic response. Identifying patients who are more or less likely to respond to a given medication is necessary to improve asthma control, and thereby reduce morbidity and healthcare utilization.

Several pathways have been implicated as pharmacogenetic targets in asthma, including β2 adrenergic receptor pathway (*ADRB2, PDE4*), leukotriene modifier pathway (*ALOX5, ALOX5AP, LTA4H, LTC4S, CYSLTR1, CYSLTR2*), and glucocorticoid pathway (*CRHR1, NR3C1, STIP1, HSP90AA1, HSP90AB1, HSPA8, DNAJB1, FKBP4, FKBP5, PTGES3*) (14–20).

Understanding pharmacogenetics can help match specific genotypes to individualized treatments that minimize side effects while improving therapeutic outcomes. In this paper, we reviewed the most recent advances in the fields of pharmacogenomics and uncontrolled childhood asthma and report salient findings and contributions to our current understanding of disease endotypes from different studies including candidate gene studies, GWAS, multiomics and integrative genomic studies. To achieve this, we conducted a thorough search of two major databases, PubMed and CINAHL DB, using specific search terms such as pharmacogenetics, severe asthma, pediatric asthma, uncontrolled asthma, and multi-omics asthma. This search was carried out in October 2022, and we included papers from the previous decade, yielding a total of 521 articles. We identified 85 articles that met our

review criteria after a manual screening process that included looking for duplicates across databases, full text availability, review papers, and relevant discussions for pediatric cohorts as shown in Figure 1.

Our review discusses the challenges of incorporating the findings of these articles into clinical practice, as well as future research opportunities.

2. Body

Over the past few years, GWAS have revealed multiple novel pharmacogenetic variants related to clinical response to different classes of asthma medications including inhaled corticosteroids, bronchodilators, leukotriene modifiers and biologics, like *ADRB2, THRB* for LABA, *ASB3/SOCS, SPATA13-AS1, SLC22A15* for SABA, *ZNF432, CYP3A4, GLCCI1, FBXL7, CRISPLD2, CA 10, SKG493, CTNNA3, SPATA20, ACOT4, BRDW1, ALG8, NAPRT1* for ICS and *ALOX5, LTC4S* for leukotriene modifiers (21–23).Optimal clinical response to treatment may be variable based on racial/ethnic backgrounds due to genetic differences. Epigenetic factors may also play a key role in the modulation of gene expression patterns and protein interactions of inflammatory cytokines that are crucial for asthma pathogenesis and treatment response. Knowledge about specific genetic variants related to treatment effectiveness may help develop promising pathways for novel therapies in severe or uncontrolled asthma.

2.1 Pharmacogenetics of standard asthma drug classes

Pharmacogenomic approaches have explored effects of genetic variation on treatment response in pediatric asthma. Through candidate gene studies and GWAS, novel pharmacogenetic loci and SNPs associated with therapeutic response to different classes of asthma medications have been identified.

2.1.1 Pharmacogenetics of Corticosteroid Response: Inhaled corticosteroids are the most commonly prescribed asthma medications for the long-term control of persistent asthma, but 25–30% of patients do not respond (24). Several studies looking at SNPs of candidate genes have been reported that might influence clinical response to ICS in children with asthma. The biology of these SNPs focuses on the anti-inflammatory effects of corticosteroids (25).

2.1.1.A. Candidate Gene Studies: Our group examined gene expression data from CD4+ lymphocytes in the Asthma BioRepository for Integrative Genomic Exploration (Asthma BRIDGE) and discovered that SMARCD1 gene expression (SWI/SNF-related matrix-associated actin-dependent regulator of chromatin subfamily D member 1) was associated with worsening asthma control with ICS use, and that this relationship worsened with age (26).

Stockmann et al. studied allelic variations in genes involved in fluticasone propionate (FP) metabolism and pediatric asthma control by genotyping 9 SNPs in the *CYP3A4, CYP3A5*, and *CYP3A7* genes. They compared genotype information with asthma control scores and

found that the presence of *CYP3A4*22* was associated with decreased hepatic *CYP3A4* expression and activity and improved asthma control in FP treated children (20).

Vijverberg et al. performed a meta-analysis of three cohort studies including Pharmacogenetics of Asthma Medication in Children: Medication with Anti-Inflammatory effects in Netherlands, BREATHE and Paediatric Asthma Gene Environment Study and evaluating 17 genes with a role in glucocorticoid signaling or association with asthma. SNPs rs138335 and rs138337 in *ST13* (coding for cochaperone of the glucocorticoid receptor) were associated with increased risk of exacerbations (defined as hospital visits and oral corticosteroid (OCS) use) (27).

In 82 children (mean age 9.6+−3.2 years) with moderate-severe asthma exacerbations, Keskin et al. evaluated the role of genetic variations in the therapeutic response to high-dose ICS. The children were genotyped for eight SNPs that were a priori associated with ICS response in chronic asthma treatment: NR3C1 rs41423247; CRHR1 rs242939, rs242941, and rs1876828; *TBX21* rs2240017; *GLCCI1*; and T gene rs3099266 and rs2305089, and treated these children with high-dose fluticasone propionate followed by inhaled fluticasone propionate for 6 days. They found that homozygosity for the G allele at rs41423247 of the *NR3C1* gene was associated with a higher improvement in FEV1 at 4 h in children with moderate-to-severe asthma exacerbation treated with high-dose ICS (28).

Sahli et al. investigated the effect of glucocorticoid-induced transcript 1 (GLCCI1) and stress-induced phosphoprotein 1 (STIP1) gene polymorphisms on ICS response in Tunisian asthma patients and discovered that the G allele of rs37973 was associated with poor ICS response after 12 weeks of treatment (29). This study also sought to investigate short term (4-week) and long term (24 week) response to ICS, however did not have adequate sample size to arrive at meaningful conclusions.

Genetic variations in *TBX21* and Fc fragment of IgE receptor II *FCER2* contributed to variability in ICS response by alteration of inflammatory mechanisms in asthma. Other genes including *CRHR1*, *STIP1*, *NR3C1*, *DUSP1*, *HDAC*, *GLCCI1*, *ORMDL3*, and *VEGF* led to variations in ICS response by altering anti-inflammatory pathways of ICS (30).

2.1.1.B. GWAS studies: GWAS of asthma exacerbations in children of European descent treated with ICS from eight studies identified ten significant variants; one variant, rs67026078, mapping to *CACNA2D3* and *WNT5A*, was subsequently replicated among Europeans, but not in non-European populations. SNP rs11681246 was negatively associated with asthma exacerbations in Europeans, and rs76390075 was negatively associated with asthma exacerbations in non-European population (31, 32).

Our group analyzed statistically powerful variants from among 534,290 SNPs and identified genetic variations in glucocorticoid-induced transcript 1 gene (*GLCCI1*) that are linked with decreased lung function in subjects treated with ICS (in white population). The SNP rs37973 was associated with higher risk of poor response to ICS with those homozygous for the mutant allele two-and-a-half times more likely to have an impaired ICS response compared to those homozygous for the wild-type allele (33). This variant accounted for 6.6% of the

variability relating to the lowest-quartile response, suggesting variation at this locus may be related to poor response in a significant proportion of patients. However, this study only looked at 100 top-powered SNPs. Comprehensive analyses of other SNPs in larger and more diverse populations are needed to identify other significant functional variants that can influence ICS response.

2.1.2 Pharmacogenetics of Bronchodilators: Bronchodilator medications are the most prescribed asthma medications globally. Short acting bronchodilators are used for the rapid, but temporary, relief of asthma symptoms. In contrast, long-acting beta-agonists, in combination with ICS, are used for the control of asthma.

2.1.2.A. Pharmacogenetics of Short-acting beta-agonists: Israel et al. performed a GWAS of response to short acting β2 agonists and examined 444,088 SNPs in 724 patients from the SNP Health Association Resource (SHARe) Asthma Resource Project (SHARP) and identified four SNPs, rs350729, rs1840321, rs1384918, and rs1319797 that all map to a region on chromosome 2 near the *ASB3* gene, that is associated with smooth muscle proliferation (34). This study however only examined variants with allele frequencies of greater than 5% given the rarity of individual SNPs.

Tse et al. examined 53 SNPs previously associated with asthma development, phenotypes, or bronchodilator or corticosteroids response and studied their association with ED management failure in pediatric patients. SNP rs295137 in *SPATS2L* was significantly associated with increased odds of ED management failure and two SNPs in IL33, rs7037276 and rs1342326 were associated with decreased odds of ED management failure in this study (35). As ED management failure is a broad outcome, it is unclear from this study if these SNPs modify pharmacological response or influence clinical parameters by other mechanisms.

Scaparrotta et al. studied influence of SNPs of *ADRB2* and new candidate genes *THRB* and *ARG1* on acute response to SABA in children with asthma and identified that presence of Arg/Gly or Gly/Gly genotypes in position 16 of *ADRB2* (rs1042713) was significantly associated to a worse BD response (36).

2.1.2.B. Pharmacogenetics of long-acting beta-agonists: Recent systematic reviews on genetic variants associated with long-acting β2-agonists (LABA) response in asthma patients found that *ADBR2* rs1042713 variant is most consistently associated with response to LABA in children (37). The incidence of severe adverse events are reported to be highest in the 4–11 year age group (38) and children who are homozygous for Arg at codon 16 may be at higher risk for adverse effects from LABA (39).

Ruffles et al. performed a pragmatic RCT in England and Scotland in children aged 12–18 years and measured change in Pediatric Asthma-Related Quality of Life Questionnaire (PAQLQ) as primary outcome. Their study demonstrates that genotype directed prescribing in Arg16Gly genotype (AA genotype) of second-line controller (LABA or a leukotriene receptor antagonist) was associated with a larger improvement in PAQLQ versus standard care, p=0.041 (40).

Ancestry based pharmacogenetic studies of children, adolescents, and adults from Best African Response to Drug (BARD) trials performed by Ortega et al. identified pharmacogenetic locus on chromosome 12 fine mapped to a locus adjacent to *RNFT2* and *NOS1* (rs73399224). The authors report significantly improved response to step up therapy from low-dose ICS to the quintuple dose of ICS versus 100 μg fluticasone plus salmeterol. This group also replicated rs5752429 and rs73399224 in independent African American cohorts (41).

Recently Slob et al. conducted meta-GWAS of asthma exacerbations in children and young adults treated with LABA. They identified eight independent SNPs suggestively associated with exacerbations, two of these SNPs were near genes *TBX3* and *EPHA7*, previously implicated in response to SABA. Given small effect sizes of individual SNPs on asthma related outcomes, very large sample sizes are required to detect statistically significant effects. Future larger studies investigating the effects of LABA and SABA use on these genes may be beneficial (42).

2.1.3 Pharmacogenetics of Leukotriene modifiers: Leukotriene modifiers are easy to take (oral pills) asthma controller medications, but with a large proportion of patients that do not clinically respond (43). Variants of the 5-lipoxygenase gene (*ALOX5*), *LTC4S* (encoding for leukotriene C4 synthase), *LTA4H* (LT A4 hydrolase), and *MRP1* (multidrug resistance protein) and cysteinyl leukotriene receptor genes are the most studied candidate genes related to leukotriene modifier class of medications (44). Telleria et al. studied patients with moderate persistent asthma with polymorphisms in *ALOX5* gene and found that wild type allele had less exacerbations and improved FEV1 on Monteluekast (45). Klotsman et al. studied associations between polymorphisms in 10 candidate genes (*ALOX5, ALOX5AP, LTC4S, CYSLTR1, CYSLTR2, PLA2G4A, CYP2C9, CYP3A4, ADRB2, and NR3C1*) and response to montelukast in 174 patients and found that patients with polymorphisms in *CYSLTR2* (rs91227, rs912278) and *ALOX5* (rs4987105, rs4986832) genes had 18–25% improvement in peak expiratory flow (46). Owing to the estimated 16% of false discoveries in this study, larger studies considering broader spectrum of asthma severity and control are needed to replicate these genotype-phenotype correlations. Kang et al. studied polymorphisms of the leukotriene C4 synthase (*LTC4S*) −444A/C and *PTGDR* −441T/C related to Monteleukast treatment and found significant effect of the presence of *PTGDR* −441C allele on responsiveness of LTRA during an exercise challenge (47). This study also found an enhancement of eosinophil counts associated with *PTGDR and LTC4S* polymorphisms in Korean children with asthma.

2.1.4 Pharmacogenetics of Asthma Biologics: Increasing knowledge of molecular mechanisms of asthma have led to mechanism-based treatments such as biologics. However, biologics are only recommended for uncontrolled asthma despite high dosages of conventional asthma treatment for patients with specific asthma phenotypes. Challenges remain in the application of biologics due to lack of clinically available biomarkers that can individualize pediatric asthma management and guide treatment strategies (48) and few pharmacogenetic studies have been done. Condreay et al. investigated genetic associations predicting response to mepolizumab-treatment in 1192 patients with severe

eosinophilic asthma enrolled in two studies, DREAM and MENSA. While they didn't find any significant variants in a GWAS analysis, which was admittedly underpowered, the authors also performed a candidate gene analysis. There they found that the intronic variant rs1021621 (A > G), in gene *POU2F1*, was significantly associated with a 20% reduction in clinically significant exacerbations (CSE) rate in patients treated with mepolizumab (49).

2.2 Multi-ancestry association studies and Pharmacogenomics:

Minorities in the United States experience health dissimilarities in a wide range of diseases, with variations in prevalence, mortality, and treatment outcomes. These differences are partly due to social and environmental factors too, but a portion of this variability is also explained by genetic variation. Pharmacogenomics has sought to understand how genetic variants affect drug response to improve drug development and therapy through which many pharmacogenomic relevant biomarkers have been identified. Not always do these clinical biomarkers replicate in different populations because of factors such as frequency of SNPs, linkage disequilibrium, as well as confounding environmental factors and are often studied for European ancestry (50). In the US, Puerto Ricans have the highest rate of asthma followed by African Americans, white people, and then Mexicans.

Multiple studies have been conducted to investigate different drug responses for different medications, such as bronchodilator response (BDR), ICS, leukotriene modifiers. It is crucial to remember that phenotypic and genetic indicators of long-term therapy response rely on how the result is defined. Mak, et al. (51) studied a large cohort of 1441 minority children with asthma identifying as Puerto Ricans, Mexicans, and African Americans from GALA II/SAGE II cohorts. They selected 250 participants from the tails of BDR distribution for each ethnic group. Population specific analysis and multivariant analysis (combining all three populations) was conducted using Logistic Regression (low vs high responder status). Twenty-seven variants were identified which were then prioritized using Diverse Convergent Evidence that revealed the SNP SLC39A8 in *NFKB1* to be highly associated with regulatory function in bronchial smooth muscle cells. Previous BDR associations of ADCY9 and CRHR2 for common variants were not replicated in this study. In rare variant analysis, the opposite result was seen. However, none of the 27 variants were found to be significantly associated with BDR statusin GALA I, SAGE I, HPR, SAPPHIRE, and CHOP. It is important to note that GALA I and SAGE I are minority cohorts.

N. Sharma et al. performed a case control study (52) on 550 north Indian asthmatic children vs control subjects (275 subjects each) to study association of *FCER2* gene using IgE levels for four subgroups of asthma (intermittent, mild, moderate, and severe). *FCER2* has been studied in both white and African American subjects by our group (53) and three SNPs were significantly associated with elevated IgE levels and severe exacerbations. One of these three SNPs (rs7249320) was replicated significantly along with another variant rs28364072 in north Indian subpopulation. The authors showed strong evidence of association, however, the small sample size and lack of replication poses a huge threat to validity.

With regard to ICS response, Hernandez-Pacheco et al. (31) identified asthma exacerbations in 1347 admixed children belonging to African Americans and Hispanics/Latinos treated with ICS-response for GALA II and SAGE II. The study was then replicated for 1697

patients from six European studies. Of the 15 SNPs associated in the first, only 11 SNPs had MAF>=1% in the European population. A novel association of rs5995653 was revealed although it was not genome wide significant. The Best African Response to Drug (BARD) study, noted that adults and adolescents responded better to LABA-containing medication versus children responded better to high-dose ICS monotherapy. Ortega et al. conducted whole-genome admixture mapping (41) in 249 children and 267 adults from BARD to study responsive ness with different combinations: (i) low dose ICS (FP 50mcg in children and 100 mcg in adults and adolescents) to step-up of double, (ii) low dose ICS (FP 50mcg in children and 100 mcg in adults and adolescents) to step-up of quintuple, or (iii) addition of LABA to an ICS (FP100SAL and FP250SAL). The authors found a locus adjacent to *RNFT2* and *NOS1* (rs73399224) had better response for quintuple ICS versus ICS/LABA combination therapy with an odds ratio of 0.17. In adults, rs5752429 showed better response for quintuple ICS versus 2.5xICS with an odds ratio of 3.35. Both variants were replicated in independent African American cohorts. However, since BARD did not include any non-Africans, it is not certain if the association of variants is broadly generalizable.

A recent meta-GWAS of asthma exacerbations in a multi-ethnic cohort (Europeans, Hispanics/Latinos, Singaporean Chinese, African Americans) analyzed 9.6 million genetic variants and identified *VCAM1*, *EXTL2* and *PANK1* as functional loci for asthma exacerbations applicable to people across different ancestral backgrounds independent of the time period assessed (54).

2.3 Pharmacogenomics of Obesity related Asthma:

Obesity is a growing pediatric disease that increases the risk of incident asthma and worsens disease severity (55). Airway dysanapsis, obesity-related dyspnea, heightened ventilatory needs with obesity, obesity-specific comorbidities, and circulating cardiometabolic factors are all observed in children with comorbid obesity and asthma (56–58). The inflammatory processes underlying diseases could be potential links between these two diseases (59–63). Crucially, obese asthmatics tend to be relatively resistant to conventional asthma therapies.

Other studies demonstrated that obese asthma phenotype can be reversed by weight loss with improved lung function, decreased symptoms, and decreased medication usage that in turn can lead to improved health care utilization (64–67).

A study of genetic pleiotropy between asthma and obesity in a community-based sample of twins revealed that a substantial proportion (8%) of the phenotypic variation in asthma and obesity was a result of genetic pleiotropy, common set of genes increasing susceptibility to both asthma and obesity (68). Specific regions of the human genome have been identified in other studies to be related to both asthma and obesity including *SMAD3, ACOXL, MYL6, ERBB3, COL16A1, UNC13D, POU2F1, TBL1XR1* (60, 63, 68). Chromosome 5q containing genes *ADRB2* (codes for adrenergic β 2 receptor influencing airway tone and resting metabolic rate) and *NR3C1* (codes for glucocorticoid receptor). The *TNF alpha* gene complex located on Chromosome 6 influences the immune and inflammatory response that might play a role in pathogenesis of both asthma and obesity. Chromosome 12q contains genes regulating inflammatory cytokines that are associated with both asthma and obesity. Variants in Vit D receptor gene have been associated with asthma related phenotypes (69,

70). Rastogi et al. studied epigenetic footprint in obese asthmatic children and found that dysregulated DNA methylation is associated with non-atopic inflammation observed in pediatric obesity-associated asthma (71). Given common susceptibility loci, investigations into their pharmacogenetic role in asthma are warranted.

Adipokines are adipocyte-secreted cell signaling proteins or cytokines that regulate various biological actions that might be implicated in inflammatory pathogenesis of both asthma and obesity. Some adipokines like leptin or resistin are produced in excess in obesity while adiponectin is reduced in obesity (72, 73). Systemic inflammation in obesity may up-regulate the asthma pathogenesis, which is likely modified by adipokines and other systemic inflammatory markers (74–78). Airway epithelial cells express receptors for adipokines suggesting that the effect of adipokines on airway might play a role in pathogenesis of asthma in obesity (78). The direct effect of adiponectin on treatment response in asthma has not yet been clinically investigated, however a study investigating the association of two adipokines, adiponectin and leptin, with the degree of emphysema, pulmonary function and glucocorticoid responsiveness in patients with chronic obstructive pulmonary disease (COPD) found that higher plasma adiponectin level predicted more favorable relief of symptoms and hyperinflation during glucocorticoid treatment (79). Future studies directed at genetics and pharmacogenetics of adipokines can potentially clarify obesity related asthma phenotype further. Figure 2 depicts the inflammatory effect of dysfunctional adipose tissue on respiratory epithelium in the lung (80).

2.4 Multi-Omics:

Multi-omics studies in childhood asthma involve the integration of data from multiple levels of the genome, such as genomics, transcriptomics, epigenomics, and proteomics. The goal of these investigations is to better understand the underlying mechanisms of asthma and to discover new biomarkers and treatment targets. These multi-omics investigations have recently become more popular in the study of childhood asthma. They have provided new insights into the complex molecular and cellular mechanisms underlying asthma pathogenesis. Some studies, for example, have linked asthma to changes in the expression of genes involved in immune response and inflammation, as well as changes in the epigenetic regulation of these genes. Other research has revealed possible biomarkers for asthma, such as particular protein levels and microRNAs, as well as new treatment targets, such as epigenetic enzymes.

Multi-omics research has also highlighted the necessity of understanding the development and progression of asthma by taking into account interactions between multiple levels of the genome, such as the connection between genetics and epigenetics. They have also demonstrated the complexity of asthma, which incorporates various genetic and environmental components, as well as the significance of taking asthma heterogeneity into account. Integrative genomic approaches combining gene expression profiles with genome-wide genotype data are recently being used to gain insight into biological networks associated with therapeutic response illustrating the utility of systems biology approaches in asthma (81).

2.5.1 Epigenomics—Several studies were conducted to find association between DNA methylation and asthma treatment response.

Wang et al. assessed the impact of the ICS response on DNA methylation in peripheral blood cells (PBCs) and analyzed the association of CpG sites with treatment response in 152 pediatric from the Childhood Asthma Management Program (82). This study found that an increase in Forced Expiratory Volume in one second (FEV1) after treatment with Inhaled Corticosteroids (ICS) was associated with relative hypermethylation of cg20434811, cg02822723, cg14066280, cg27254601, and cg23913400, as well as relative hypomethylation of cg24937126 and cg24711626. This group also examined epigenome-wide DNA methylation in other asthma cohorts including Childhood Asthma Management Program (CAMP); Children, Allergy, Milieu, Stockholm, Epidemiology (BAMSE); and Genetic Epidemiology of Asthma in Costa Rica Study (GACRS). Outcomes in this study included the absence of emergency department visits and/or hospitalizations and the absence of oral corticosteroid use while on inhaled corticosteroid therapy. They found that relative hypomethylation of cg00066816 was associated with absence of ER visits and/or hospitalizations in all cohorts and lower *IL12B* gene expression in BAMSE cohort (82). Relative hypermethylation of cg04256470 was associated with absence of oral corticosteroid use in all cohorts and higher *CORT* gene expression in CAMP (83). This study relied on the use of the Illumina HumanMethylation27 assay, which may not be comprehensive enough to capture all relevant aspects of methylation patterns.

Li et al. identified two functional circulating microRNAs (miRNAs; hs-miR-155–5p and hs-miR-532–5p) in the serum that were significantly associated with changes in dexamethasone-induced transrepression of NF-κB, indicating that these two miRNAs are predictive of asthma ICS treatment response over time measured by change in FEV1 over four years. The area under the receiver operating characteristic (AUROC) curve reached 0.86, suggesting that these two may be potential serum biomarkers to characterize the response to ICS treatment (84).

Another study conducted by Xiao et al. (85) studied Von Willebrand factor A domain-containing protein 1 (*VNN1*), a protein that plays a role in corticosteroid responsiveness. The study found that VNN1 mRNA expression and CpG4 promoter methylation were increased in nasal epithelial cells of asthmatic children who responded well to corticosteroid treatment, but not in those who were poorly responsive. This indicated that *VNN1* may be a biomarker that may be used to identify children with a biologic basis for poor corticosteroid response, and that addressing the *VNN1* pathway may be a helpful therapeutic strategy in these kids to improve corticosteroid response. However, the study only focused on children hospitalized for asthma exacerbation, and it is not clear if the findings would apply to non-hospitalized children or adults with asthma.

To support the notion that optimal prediction models for personalized medicine are most likely to originate from a combination of omics and clinical characteristics, a study (86) investigates the possibility of using miRNA as a biomarker to predict asthma exacerbations in 153 children from CAMP. The study was done in the ICS arm of CAMP and therefore predictive of the exacerbation response to ICS. The study discovered that 12 miRNAs were

strongly related with future exacerbations, each doubling of these miRNAs' expression was associated with a 25–67% increase in exacerbation risk. The predictive value of a 3-miRNA (miR-146b-5p, miR-206 and miR-720) model was shown to be comparable to that of an established clinical model of exacerbations, and when paired with clinical parameters, the ability to predict future exacerbations was greatly boosted. The study also discovered that miR-206 was very effective at distinguishing exacerbation state. The work has several features, including a large sample size of pediatric asthma patients from the CAMP cohort, physiologically significant miRNAs discovered by modeling, and comparison to a previously validated asthma exacerbation clinical score.

2.5.2 Transcriptomics and Integrative Genomics Pharmacogenetic Studies—

Transcriptomics is the study of the entire set of RNA molecules in a cell, tissue, or organism, known as the transcriptome. In recent years, this field has been extensively applied to the study of childhood asthma, with the goal of understanding the disease's underlying molecular mechanisms and identifying potential therapeutic targets. Childhood asthma is characterized by complicated alterations in the expression of genes involved in the immune response, inflammation, and airway remodeling, according to transcriptomics research. Asthma, in particular, has been linked to the activation of immune cells such as T-helper 2 cells and eosinophils, as well as increased production of genes implicated in inflammation such as cytokines and chemokines.

Multiple studies have focused on the role of gene expression, with or without concomitant genotype data, on the response to ICS treatment. We conducted a pharmacogenomic expression quantitative trait loci (eQTL) analysis with >300 expression microarray data from dexamethasone treated, and untreated cells derived from Childhood Asthma Management Program (CAMP) participants and identified 2484 cis-eQTL affecting 767 genes following dexamethasone treatment. This study emphasizes the method of identifying eQTL after relevant environmental disruption could help with identification of true pharmacogenetic variants (87).

Our group also explored potential molecular mechanisms for glucocorticoid (GC) insensitivity in pediatric asthma showed that lymphoblastoid cells derived from poor corticosteroid responders (PSR) asthmatic children had lower glucocorticoid receptor (GR) protein expression than good corticosteroid responder (GSR) lymphoblastoid cells. This study demonstrated a potential novel mechanism of GC insensitivity resulting from limited GR nuclear bioavailability likely due to decreased baseline GR protein expression and rapid hormone-induced downregulation (88).

Himes et al. studied transcriptomic changes in four primary human airway smooth muscle (ASM) cell lines that were treated with dexamethasone using a high-throughput sequencing method, RNA-Seq. They identified 316 differentially expressed genes, including *DUSP1, KLF15, PER1, TSC22D3* that are well known glucocorticoid-responsive genes, and less investigated *C7, CCDC69, CRISPLD2* genes. This study identified *CRISPLD2* as an asthma pharmacogenetics candidate gene that regulates anti-inflammatory effects of glucocorticoids in the ASM. By quantitative RT-PCR and Western blotting this group identified that

dexamethasone treatment significantly increased *CRISPLD2* mRNA and protein expression in ASM cells (89).

Treatment with lebrikizumab was linked to improved lung function in adults (90). Patients with high pretreatment serum periostin levels improved more quickly with lebrikizumab than patients with low periostin levels. A study (91) focused on examining the relationship between serum periostin and peripheral blood eosinophils and age in asthmatic children. The researchers also wanted to see if these biomarkers could predict clinical benefit from type 2 pathway-directed therapy in children with asthma. The study noted that serum periostin and peripheral blood eosinophils were strongly inversely linked with age, and serum periostin was significantly higher in pediatric asthma patients compared to adult asthma patients. *CCL23*, *SIGLEC8*, *PTGDR2*, *CACNG6*, *IDO1*, and *HSD3B7* were among the most positively correlated genes. Other than type 2 inflammation, the study discovered, other factors may influence serum periostin and blood eosinophil levels in children with asthma. Lebrikizumab is a good illustration of how genomes can be used to anticipate whether a therapy will work.

Hernandez-Pacheco et al. conducted a combined analysis of transcriptomic and genetic data in relation to treatment responses and found that *LTBP1* gene was the most consistently associated gene in a favorable ICS response (92).

Transcriptomics is being utilized to better understand how environmental factors affect asthma. This helps identify particular environmental triggers that may contribute to the development and aggravation of asthma, resulting in better preventative and management methods.

2.5.3 Proteomics—Proteomics is the broad study of proteins, including their structure, function, and interactions. This field has been intensively applied to the research of childhood asthma in recent years, with the objective of understanding the disease's underlying molecular mechanisms and identifying prospective treatment targets. Childhood asthma is characterized by differences in the levels, activity, and interactions of proteins involved in the immune response, inflammation, and airway remodeling, according to proteomics studies. Asthma, for example, has been associated to greater levels of inflammation-related proteins including cytokines and chemokines, as well as changes in the activity of enzymes involved in airway remodeling such as matrix metalloproteinases.

Furthermore, proteomics has been used to explore the effects of environmental factors such as air pollution on asthma and to identify proteins that are affected by these factors, which may be biomarkers for asthma. In this article, we focus on the factors that affect asthma severity or drug treatment response. Although, there is a lack of proteomic data in asthmatic children leading to limited studies. A study (93) used unbiased proteome profiling of generated sputum supernatants to stratify 246 participants (with 206 asthmatic patients) to a greater degree than is currently attainable using granulocyte counts alone. The researchers utilized a technique called Topological Data Analysis (TDA) to build a network of patient clusters defined by shared airway proteomes, and they discovered that asthma severity increased across the network, with the most severe forms at the far-right end,

where neutrophilia was a prominent feature. A third of the asthmatics had the neutrophilic phenotype, associated with higher levels of sputum S100-A9 and matrix metalloproteinase-9 (MMP-9) proteins, and their symptoms were more likely triggered by dust or fungus. Consistent with the existing risk factors of asthma exacerbations, eosinophilia was linked to a higher prevalence of reported respiratory infections, the use of long-acting agonists, and GORD. The neutrophilic sub-phenotypes are predicted to have gene expression profiles caused by T2 cytokine IL13 downregulation. In contrast, the T2 cytokine IL5 mRNA is highly expressed in eosinophilic sub-phenotypes. Thymic Stromal Lymphopoietin (TSLP) was found to be present at low levels and not clearly distributed between sub-phenotypes, but eosinophils had some of the highest TSLP expression. The gene expression network revealed that IL2 activation increased from eosinophilic to neutrophilic sub-phenotypes, while *COL18A1*, a gene associated with atopy, decreased in neutrophilic sub-phenotypes. In the network, there was also an increase in the activation of virally induced transcription factors such as interferon alpha, KDM5B, and TNF from eosinophilic to neutrophilic end. The limitations include lack of validation of the individual biomarkers and subphenotypes in a different (validation) cohort to evaluate the repeatability within subjects in longitudinal research. Due to insufficient participant numbers in the sub phenotypes created by stratifying the extremely eosinophilic, neutrophilic, and atopic phenotypes, authors were unable to conduct the in-depth study of the phenotypes.

A recent study revealed IL-8 and IL-10 as indicators of bronchial inflammation and obstruction in the saliva of asthmatic children (94). Lipoxins (LXA4) and leukotrienes (LTB4) concentrations in sputum can be measured in children with severe asthma (SA), children with intermittent asthma (IA), and healthy controls (HC). One such study (95) used this approach known as induced sputum for 24 pediatric cohorts aged 6–12 years, 17 children had SA and control group consisted of 7 healthy children. Despite high dose inhaled glucocorticoid treatment, children with severe asthma (SA) exhibit lower amounts of the lipid mediator lipoxin A4 (LXA4) in their induced sputum samples than children with intermittent asthma (IA). They also discovered that leukotriene B4 (LTB4) levels were elevated in children with asthma, regardless of severity. The higher levels of LTB4 in the induced sputum samples reflect an imbalance in bioactive lipid mediators that leads to airway inflammation, possibly due to sustained recruitment of granulocytes inside the airways. Furthermore, the researchers discovered decreased expression of the LXA4 receptor, FPR2/ALXR, in induced sputum cells from children with SA, indicating a dysregulation of the LXA4 biosynthesis pathway. The researchers also found that granulocyte chemotactic ability is higher in induced sputum supernatants of children with SA than in children with IA, and that adding exogenous LXA4 at a nanomolar concentration resulted in a significant inhibitory effect of spontaneous granulocyte chemotactic activity. According to the findings, low levels of resolving LXA4 may interfere with leukocyte recruitment and trafficking, reducing the impact of chemotactic agents and encouraging the duration of airway inflammation. Also, in obese asthmatic children, there was a statistically significant negative connection between FEV1/FVC and sputum neutrophil gelantinase-associated lipocalin and matrix metalloproteinase-9 as shown by a study investigating the effect of obesity on airway and systemic inflammation (96). The study was limited to a

specific demographic of asthmatic children, it is uncertain whether the findings would apply to children with other demographics.

To summarize, proteomics is a promising method for studying childhood asthma since it uncovers fresh insights into the disease's underlying molecular processes and recommends innovative treatment choices. More research is needed, however, to fully understand the complex interplay of genetic, environmental, and epigenetic factors in asthma development and progression, as well as to produce more effective and safe asthma medications for children.

3.5.4 Metabolomics—The study of small molecule metabolites found in an organism or biological sample is known as metabolomics. Metabolomics can be applied to severe childhood asthma to discover specific metabolic pathways and chemicals that are altered in asthmatic children, which may provide insight into the underlying causes and processes of the disease. Metabolomics studies can be broadly classified into experimental (targeted and untargeted) and analytic studies. Untargeted metabolomic experimental procedures entail employing several analytical techniques to identify and quantify a wide range of small molecules in biological samples such as blood, urine, and exhaled breath. These procedures are not unique to any one collection of molecules and allow for the development of new and possibly important asthma biomarkers.

A study (97) sought to investigate the relationship between age and bronchodilator response (BDR), a measure of asthma control, in asthmatics aged 5 to 25 years from CAMP. The researchers employed metabolomic profiling, a method of identifying and measuring metabolites in biological samples, to investigate BDR in a group of asthmatics over three time points (n=560 with mean age of 8.8, n=563 with mean age of 12.8, and n= 295 with mean age of 16.8) spanning childhood, adolescence, and early adulthood. The study discovered that higher levels of 2-hydroxyglutarate may strengthen the inverse connection between age and BDR in asthmatic children, but higher levels of cholesterol esters, GABA, and ribothymidine may mitigate the age-associated BDR drop. The study was replicated in 320 Hispanic asthmatic children from Genetics of Asthma in Costa Rica Study (GACRS). Also, there may be a relationship between age and GABA and cholesterol esters, and that those with high levels of these metabolites may be able to slow the typical process of age-related BDR reduction. The interaction of 2-hydroxyglutarate with age may differ depending on gender. Another study, conducted by same authors, focuses on integrative omics study of 325 Hispanic/Latino asthmatic children (98) from Genetic Epidemiology of Asthma in Costa Rica Study (GACRS). The discovery cohort consisted of children who were 6-to-14 years of age with mild-to-moderate asthma. It uses a network technique to discover and integrate modules of highly coregulated genes and metabolites that correlate with lung function metrics such as FEV1 and the FEV1/FVC ratio, both of which are linked to the severity of childhood asthma. The study discovered that sphingolipids, lipids, and fatty acids were associated with BDR, and that this effect may be influenced in part by rs8079416, an SNP that regulates ORMDL3 expression. This was further replicated in 207 asthmatic children from CAMP and found consistent results.

A study conducted to find if breath-omics captures clinical/inflammatory phenotypes among 435 patients with asthma or COPD from BreathCloud, a multicenter cross-sectional study (99). The purpose of this study was to see if phenotyping chronic airway diseases solely through breathomics (analyzing exhaled volatile organic compounds (VOCs) with an eNose) provides combined asthma/COPD clusters that differ in terms of ethnicity, systemic eosinophilia, and systemic neutrophilia, FeNO, BMI, atopy, and exacerbation rate. The study discovered that eNose clusters identified in a mixed sample of asthma and COPD patients resemble previoxusly published clinical clusters observed in only asthma or COPD patients. Exhaled VOCs were also linked to systemic neutrophilic and eosinophilic blood counts in patients with chronic airway illness, with indications of a dose-dependent association. Systemic eosinophilia and neutrophilia, BMI, atopy, ethnicity, smoking pack-years, and ICS use appear to be the key independent drivers of the eNose signal in asthma and COPD.

Table 1 demonstrates a summary of various omic studies in pharmacogenetics of uncontrolled childhood asthma that are discussed in this review.

3. Conclusion

Uncontrolled asthma in children can be related to increasing number of genetic variants and epigenetic changes either in genes of pharmacological pathways or genes involved in pathophysiology of asthma. There is currently no single genetic variant that can be used as biomarker to predict therapeutic response for severe or uncontrolled asthma patients, although some SNPs have been largely linked with response to ICS (*LTBP1* with favorable ICS response, *GLCCI1* with decreased lung function with ICS). *ADRB2* is the most studied gene on pharmacogenetics of BDR (rs1042713 for efficacy of Salbutamol and Salmeterol). *ASB3* gene is associated with smooth muscle proliferation, and SNPs near genes *TBX3* and *EPHA7* are implicated in response to SABA.

Omics fields including pharmacogenomics, epigenomics, transcriptomics, proteomics and metabolomics are rapidly advancing that can aid in identifying novel asthma mechanisms and biomarkers to guide effective and safe management of asthma. Implementation of pharmacogenetic algorithms can improve therapeutic targeting in children with asthma, particularly with severe or uncontrolled asthma who typically have challenges in clinical management and carry considerable financial burden.

4. Expert opinion

To date, the pharmacogenetics of asthma has provided novel, detailed information about the biology, pathways, and mechanisms related to interindividual variability in drug response. These insights have largely come from studies of polymorphic genetic variation, although increasingly, studies involving other ‘omic disciplines have added to our understanding of this phenomenon. As outlined above, these newer studies include those related to transcriptomics, epigenomics, proteomics, and metabolomics, as well as integrative genomics and systems biology methods that combine multiple ‘omic subtypes together to improve the specificity and power of the biologic associations. What has yet to occur, however, is the formulation of a clinical biomarker test prognostic for asthma treatment

response that would represent true bench to bedside clinical implementation. For instance, in our experience to date, the SNP with the largest biomarker potential was *GLCCI1* rs37973, but that SNP explains only ~6% of the variability of ICS response.

So, how does this field get to clinical translation? In our opinion, there are several promising steps forward. First, given that single variants are not informative for assessing treatment response, genetic risk may be assessed through polygenic risk scores (PRSs), the weighted sum of a number of risk alleles. While most pharmacogenetic studies have focused on single highly-penetrant pharmacokinetic variants, polygenic risk may increase expressivity of monogenic variants (100). Moreover, the successful application of this approach to asthma as a disease supports its use for drug treatment response (101). With the increasing availability of whole genome sequencing, the establishment of polygenic risk score models promise to account for a greater proportion of the genetic variance explained. Pharmacogenetics-specific PRS models are under development (102).

Second, we mentioned other ‘omics contributing to asthma pharmacogenomic response, either alone or in combination. Because the effects of these other ‘omics are more proximate to the drug action and are quantitative traits, they have the potential to increase explanatory power as biomarkers. For example, Li, et al’s two miRNA model yielded an AUROC of 0.86 for ICS response, which is far greater than comparable SNP models to date.

Third, we have emphasized that asthma is being increasingly recognized as syndromic instead of one disease. As directly supported by biological observations, asthma is now felt to be best represented by a variety of subtypes, or more specifically, endotypes. Integrated into these endotypes are concepts outlined above, including T2 high and T2 low asthma, neutrophilic and eosinophilic asthma, and obese and non-obese asthma. Combinations of these factors, as well as other historical and demographic factors, generally yield about five total multifactorial endotypes. Given that the endotypic characteristics themselves lead to differences in treatment response, pharmacogenetic interrogation of the endotypes is warranted.

Finally, the immunologic underpinnings of asthma have led to the development of six current FDA approved asthma biologics which serve to target specific cytokines and pathways crucial to the pathogenesis of severe asthma. As with all other asthma therapies, there is heterogeneity of response to these biologics, with a good proportion of non-responders despite those individuals meeting current biomarker criteria for response to a particular biomarker. Better pharmacogenetic and pharmacogenomic biomarkers, based on the approaches mentioned above, are required to provide cost effective utility for these novel asthma therapies. Given this, the use of pharmacogenetics for asthma precision medicine remains feasible in the foreseeable future.

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Article highlights:

- Combining omics and clinical characteristics may be the most effective personalized medicine approach in asthma management.
- Single variant pharmacogenetic studies have been described for most commonly prescribed asthma medications like ICS (genes CRHR1, CHRM2, HSP8A, COL2A1, CYP3A4, GLCCI1, FBXL7, TBX21, CTNNA3, CRISPLD2, SPATA20, VEGF, TSC22D3) and bronchodilators (genes ADRB2, THRB, SPATA13-AS1, SLC22A15, NOS1, TBX3, EPHA7), however polygenic risk scores assessment may more accurately predict greater proportion of pharmacogenetic variance.
- Transcriptomics studies investigating the role of gene expression and genetics in asthma treatment response identified potential pharmacogenetic variants and candidate genes, such as CRISPLD2 and LTBP1.
- Proteomics studies in children with asthma have revealed variations in the levels, activity, and interactions of proteins involved in the immune response, inflammation, and airway remodeling.
- Metabolomics research has discovered that metabolites such as 2-hydroxyglutarate, cholesterol esters, GABA, and ribothymidine may influence the age-related reduction in bronchodilator response (BDR) in asthmatic children.Asthma is best represented as endotypes (like T2 high and T2 low asthma, neutrophilic and eosinophilic asthma, and obese and non-obese asthma), pharmacogenetic studies comparing these endotypes may reveal differences in treatment response.

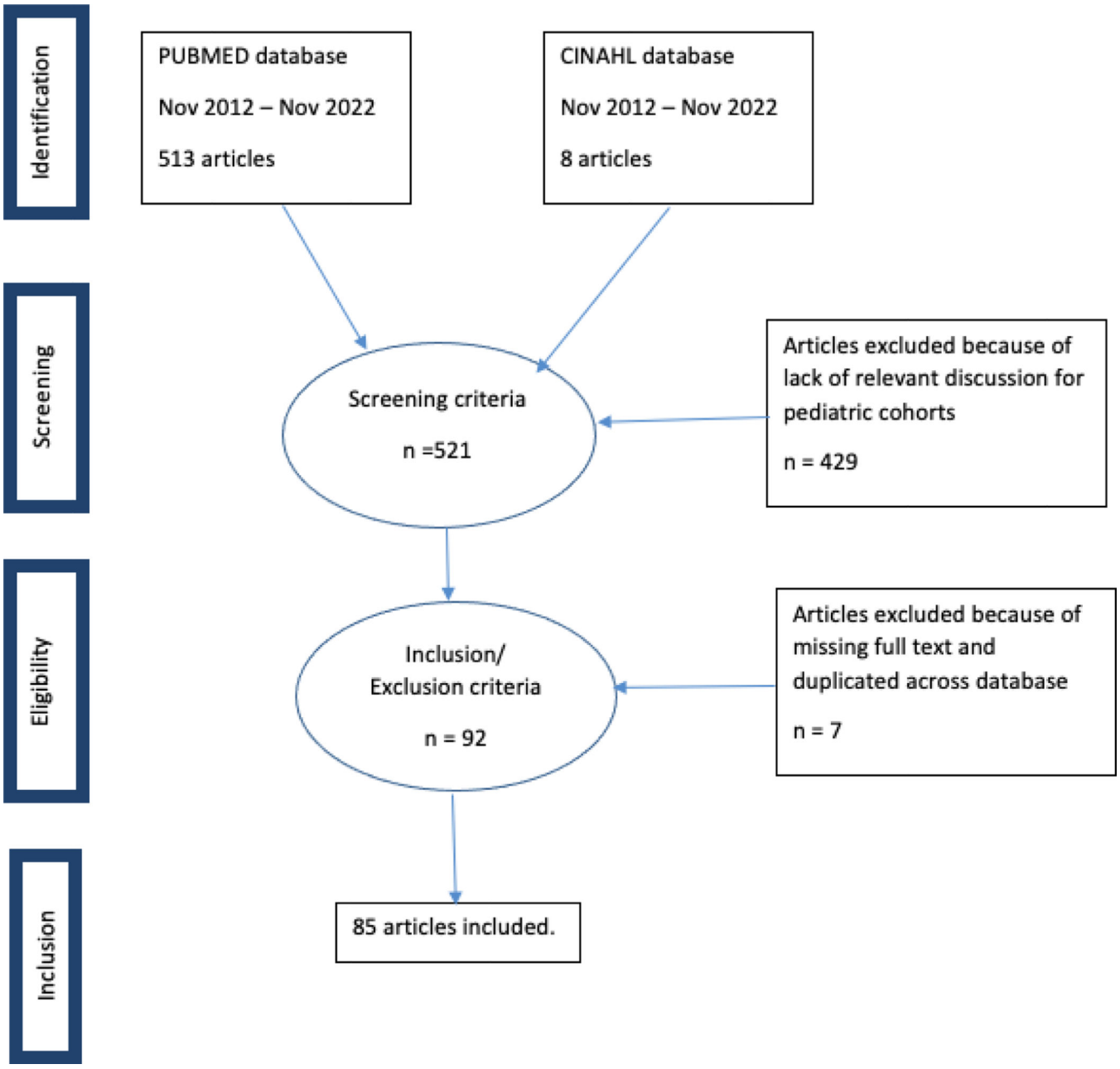

Figure 1.
Flow chart describing the article selection process.

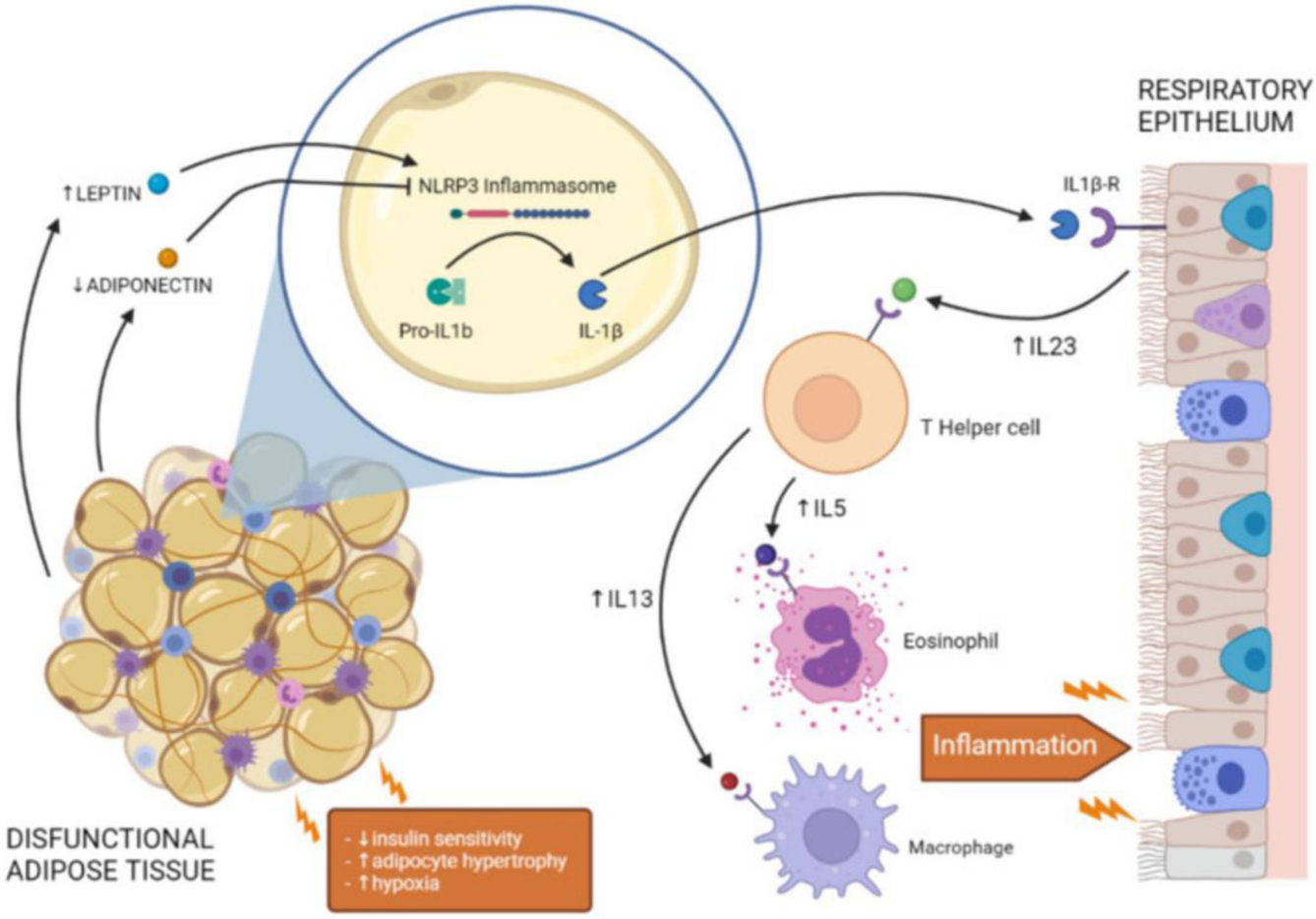

Figure 2.

Inflammatory effect of dysfunctional adipose tissue on respiratory epithelium in the lung. Insulin resistance, adipocyte hypertrophy and hypoxia modify adipokine secretion from adipose tissue promoting NLRP3 inflammasome activation and IL-1beta secretion. This in turn increases expression of proinflammatory cytokines including IL-23, IL-5, IL-3, promotes activity of immune cells like T helper cells, eosinophils, macrophages that eventually leads to lung inflammation.

Table 1

Studies in pharmacogenomics of uncontrolled pediatric asthma.

Topic	Genomics	Epigenomics	Transcriptomics	Proteomics	Metabolomics	References
1. Drug Class						
Corticosteroids	*CRHR1, CHRM2, HSP8A, COL2A1, HDAC1, CYP3A4, ZNF432, GLCCI1, FBXL7, CA10, SGK493, TBX21, CTNNA3, CRISPLD2, SPATA20, ST13, STIP1, ACOT4, FCER2, BRWD1, ORMDL3, ALG8, VEGF, NAPRT1, NR3C1, DUSP1, KLF15, PER1, TSC22D3*	-Hypermethylation of cg20434811, cg02822723, cg14066280, cg27254601, and cg23913400 -Hypomethylation of cg24937126 and cg24711626 -Hypomethylation of cg00066816 -Hypermethylation of cg04256470 -*VNN1* CpG4 promoter methylation	-miRNAs; hs-miR-155–5p and hs-miR-532–5p -miR-146b-5p, miR-206 and miR-720 -VNN1 mRNA expression −2484 cis-eQTL affecting 767 genes following dexamethasone treatment -Lower glucocorticoid receptor (GR) protein expression than good corticosteroid responder (GSR) lymphoblastoid cells - *CRISPLD2* mRNA and protein expression	-Higher levels of sputum S100-A9 and matrix metalloproteinase-9 (MMP-9) proteins -Lipoxins (LXA4) and leukotrienes (LTB4) concentrations -Lipid mediator lipoxin A4 (LXA4), FPR2/ALXR induced sputum samples		Genomics: 24–33 Epigenomics: 82–86 Transcriptomics: 87–89 Proteomics: 93–96
Bronchodilators	*ADRB2, THRB, ASB3/SOCS, SPATA13-AS1, SLC22A15, SPATS2L, RNFT2, NOS1, TBX3, EPHA7*				-Higher levels of 2-hydroxyglutarate -Higher GABA and cholesterol esters - sphingolipids, lipids, and fatty acids were associated with BDR, and that this effect may be influenced in part by rs8079416, an SNP that regulates ORMDL3 expression	Genomics: 34–42 Metabolomics: 97–98
Leukotriene modifiers	*MRPP3, GLT1D1, ALOX5, LTC4S, LTA4H, MRP1, CYSLTR2, PTGDR −441C*					Genomics: 43–47
Biologics	*POU2F1* for Mepolizumab *CCL23, SIGLEC8, PTGDR2, CACNG6, IDO1*, and *HSD3B7* for Lebrikizumab		-Serum periostin levels for Lebrikizumab response			Genomics: 48–49 Transcriptomics: 90–91

Topic	Genomics	Epigenomics	Transcriptomics	Proteomics	Metabolomics	References
2. Multiancestry Association Studies	*NFKB1, SLC39A8, FCER2, APOBEC3B, APOBEC3C, RNFT2, NOS1, TPST2, VCAMP1, EXTL2, PANK1*					Genomics: 31, 41, 51–52, 54
3. Obesity related Asthma	*SMAD3, ACOXL, MYL6, ERBB3, COL16A1, UNC13D, POU2F1, TBL1XR1, ADRB2, NR#C1, TNF* alpha gene complex, *VDR*	-DNA methylation *CCL5, IL2RA, TBX1* -Promoter methylation of *FCER2, TGFB1*		-Sputum neutrophil gelantinase-associated lipocalin and matrix metalloproteinase-9		Genomics: 60, 63, 68, 70 Epigenomics: 71 Proteomics: 96