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Review

Genetic and Epigenetic Factors in Risk and Susceptibility for Childhood Asthma

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Abstract: Asthma is a common respiratory disease that affects people of all ages, characterized by considerable heterogeneity in age, clinical presentation, genetics, epigenetics, environmental factors, treatment response, and prognostic outcomes. Asthma affects more than 330 million people worldwide, of which 33% are children under 14 years, and 27% are adults whose first symptoms occurred in childhood. However, the genetic and epigenetic mechanisms of childhood allergic diseases and asthma are still not fully understood. Here, we conducted a biomedical narrative review of genes associated with the risk, severity, and susceptibility of childhood asthma since it differs from asthma in adults regarding their pathophysiology, development, and outcomes. We also systematized the available information on epigenetic changes associated with childhood asthma.

Keywords: childhood asthma; genetic factors; epigenetics; GWAS

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1. Introduction

Asthma is a common respiratory disease that affects people of all ages. It is characterized by considerable heterogeneity in age, clinical presentation, genetics, epigenetics, environmental factors, treatment response, and outcomes [1]. Asthma affects more than 330 million people worldwide [1], of which 33% are children under 14 years of age, 27% are adults who had their first symptoms in childhood [2] and 40% are adults [3].

The clinical syndrome of childhood asthma is characterized by common symptoms, including wheezing, shortness of breath, chest tightness, and cough, combined with variable airflow limitation and bronchial hyperreactivity [1]. In contrast, the most common symptoms in adults with asthma are coughing (especially at night, during exercise, etc.), difficulty breathing, chest tightness, shortness of breath, and wheezing [3].

With the accumulation of epidemiological, pathogenetic, and clinical data, it became clear that asthma is not a single disease but a syndrome. In addition, the symptoms of asthma are associated with different (inflammatory) subtypes. Therefore, predicting childhood asthma's clinical course and evolution has important practical implications for patients, their parents, clinicians, and researchers [1]. Besides, the best way to study childhood-onset and adult-onset asthma is to look at them separately, as their pathophysiology, development, and outcomes may differ.

Early asthma studies used positional cloning techniques to look for risk or susceptibility genes in families. With the development of genome-wide association studies (GWAS), the discovery of new genetic biomarkers has become possible [4]. Advances in genome sequencing technology have allowed scientists to understand asthma's complexity more clearly, and GWAS has become one of the preferred research methods. Over the past ten

years, numerous alleles and loci have been identified as associated with asthma susceptibility, childhood asthma development, and asthma treatment response. Recent efforts to elucidate the mechanisms of asthma have focused on revealing epigenetics and environmental factors that influence gene expression without altering the DNA sequence at the molecular level [4].

Furthermore, asthma is common in families, determined by 55–74% genetic risk in adults [5,6] and almost 90% in children [7]. Higher estimates are typically found among boys than girls, with a ratio of up to 2:1, and in early-onset cases [8].

The rise in asthma cases worldwide over the past few decades clearly indicates that environmental factors are crucial for asthma development. Environmental risk factors for asthma are respiratory viral infections, tobacco smoke, animals (farm and domestic), microbial exposure, medications, air pollution, and other allergens [9–13]. In addition, all environmental exposures, especially those starting early in life, play a critical role in individual development and genetic responses and, thus, could lead to asthma [14].

We conducted a modified form of a narrative review, adhering to recent recommendations for writing a biomedical narrative review [15]. We searched through scientific databases and evidence from studies on childhood asthma regarding genetic and epigenetic factors. Initially, a comprehensive literature search was carried out in the bibliographic databases Medline (PubMed) and Scopus. Both MeSH (Medical Subject Headings) and relevant free-text terms were used, as follows: ("childhood asthma") AND ("genetic factors") AND ("epigenetics") AND ("GWAS"). Our search was confined to articles published up to September 2022. Relevant data were also derived from other papers identified using the search engine Google Scholar. Finally, references of retrieved publications were further hand-searched for supplements.

2. Genome-Wide Association Studies (GWAS) on Childhood Asthma

The Collaborative Study on the Genetics of Asthma (CSGA), one of the first studies to identify the critical loci corresponding to asthma, was published in 1997 [16]. This paper is the first attempt to consider whether different genes regulate the heterogeneity of asthma among distinct ethnic groups. The study analyzed asthma cases in sibling pairs with asthma from 3 different racial groups (African Americans, Hispanics, and Caucasians) and identified six loci: 5p15 and 17p11.1—qll.2 in African Americans, 2q33 and 21q21 in Hispanics, and 11p15 and 19q13 in Caucasians [16].

In 2007, a GWAS study found that several single nucleotide polymorphisms (SNPs) on chromosome 17q21 were associated with childhood-onset asthma and early-onset asthma [17]. This research group analyzed more than 317,000 SNPs in DNA from 994 children with asthma and 1243 controls. In addition, the study found that genetic variants that regulate *ORMDL3* gene expression are significant risk factors for childhood asthma [17].

In 2010, Sleiman et al. identified SNPs associated with childhood asthma in the previously established locus on 17q21 [18]. In addition, they found eight new SNPs related to childhood asthma at a novel locus on 1q31. One of them, rs2786098, was strongly associated with childhood asthma. The *DENND1B* gene in the 1q31 locus, expressed by dendric cells and natural killer cells, was also associated with susceptibility to asthma [18]. Other asthma studies provided information that the *dipeptidyl peptidase 10* (*DPP10)* gene had particular relevance to the risk of childhood asthma [19]. In 2010, Mathias et al. published a GWAS on two independent populations of African ancestry (asthmatic cases vs. controls and asthmatic subjects vs. family members) [20]. The study provided evidence for three SNPs in genes of potential biologic relevance to allergy and asthma, including rs1435879, mapping to the DPP10 gene on chromosome 2q12.3-q14.2.

Other studies linked the *CHI3L1* gene to a predisposition to asthma [21,22]. For example, the genotype and allele frequencies of rs4950928 of the *CHI3L1* gene in the Chinese Han children population showed a significant difference between asthmatic children and controls. However, for the rs12141494 SNP, no significant differences were found between the two groups [22].

The SNP allele frequencies in 24,000 asthma patients from the Transnational Asthma Genetic Consortium were analyzed to identify 22 genes associated with asthma [23]. The study found that the locus with the highest risk was 17q21 in the *GSDMB* and *ORMDL3* genes. In addition, the relationship of two SNPs, rs9273349 and rs9272346, in the HLA-DQ region was confirmed to relate to asthma [23]. These SNPs were found to be more strongly associated with asthma in children and early-onset asthma [17,24]. Ferreira et al. conducted a meta-analysis of European children, including 360,838 people (180,129 patients and 180,709 controls [25]. They detected 99 loci associated with asthma, atopic dermatitis/eczema, and hay fever. Two SNPs near *IL18R1* and in the *GSDMB* gene (17q21) were associated with childhood asthma.

Ferreira et al. and Pividori et al. compared 9,433 child cases of asthma, 21,564 adult cases of asthma, and 318,237 controls from the UK Biobank (UKBB) [25,26]. Pividori et al. identified 61 independent asthma loci, of which 23 were specific to childhood asthma, 37 were shared between children and adults, and only one was specific for adults [26]. In addition, Ferreira et al. reported 25 new loci linked with childhood asthma in/near genes *IRF4, NOD2, IL4R* and *IL2RA* [27].

Hayden et al. surveyed 10,199 adult smokers from the COPD Gene Study [28]. The GWAS showed that the availability of SNPs for childhood asthma increased the risk of developing chronic obstructive pulmonary disease (COPD) later in life. The study identified a significant association of genes *KIAA1958 (rs59289606), GSDMB, IL1RL1, IL13, LINC01149,* and *C11orf30-LRRC32* with asthma in children [28].

Other GWAS also confirm loci associated with genetic susceptibility to childhood asthma in *ORMDL3/GSDMB* (17q21), *HLA-DQ* (6p21), *IL1RL1* (2q11) and *IL18R1* (2q12), but also variants in *IL33* (9p24), *RAD50* (5q31) and *CDHR3* (7q22) [17,29–34]. In addition, the *ORMDL3* gene was associated with childhood-onset asthma, while the *HLA-DQ* gene was linked to asthma developed later in life. All these findings indicate that 38% of all cases of childhood asthma are the result of the combination of the identified genes [35].

A review published in 2019 summarized the GWAS and admixture mapping studies of asthma from the past two years [33]. Hernandez-Pacheco et al. identified new genes associated with asthma and confirmed previously identified ones. The authors also discussed the data on genetic variations of asthma susceptibility, asthma treatment response, and asthma predictive biomarkers. Moreover, they concluded that genetic information could be used to clarify the mechanisms of asthma development and evolution, to make a more accurate diagnosis and adequate treatment [33].

A search in PubMed and NHGRI-EBI GWAS Catalog revealed 15 GWAS studies involving asthma onset and related asthma traits, analyzed by MacArthur et al. [36]. Four of them concerned children [37–40], five adults [41–45], and another five studies identified genetic markers shared between children and adults [23,25,46–48]. Four-hundred fifty-one genetic variants (SNPs and short deletions/insertions) were associated with asthma and related traits by the GWAS.

A study by Schieck et al. on children with asthma showed that the disease affects more boys than girls [37]. Polymorphisms in the *DMRT1* gene were associated with the sex of asthmatic children, assessed in 703 children with asthma, where 65.3% of the participations were males and 658 non-asthmatic controls, where 49.7% were males [37]. *DMRT1* may play a role in developing sex-specific patterns of childhood asthma, but the mechanisms for these sex-specific differences are not yet elucidated.

More studies on childhood asthma included multi-ethnic asthma populations, but the presentation of non-European populations is not yet sufficient [49,50]. Most GWAS of childhood asthma have identified several risk alleles and loci, but most have been conducted on European descent. One recent study aimed to identify asthma susceptibility loci in Korean children [51]. They included 741 children with persistent asthma, 589 healthy children, and 551 healthy adults as controls. The results were validated using UK Biobank data. This GWAS identified an association between the *TNFSF15* gene and childhood

asthma in Korean children. The four identified variants of this gene were also associated with childhood asthma in the UK Biobank replication sample with the same effect [51].

All discussed genes identified by GWAS and important for childhood asthma are summarized in Table 1 [17–19,21–23,25,28–31,35,37,51]. Genes for childhood asthma severity or/and drug response [42,52–82] are presented in Table 2.

Table 1. Summary of genes with relevance significant to asthma in children identified by the GWAS.

Genome-Wide Association Studies				
Gene	**Locus/Chr. Region ***	**Function/Biomarker**	**Population**	**Ref.**
DENND1B	1q31	Involved in T cell receptor signaling pathway and positive regulation of T-helper 2 cell cytokine production	North American children of European ancestry	Sleiman et al., 2010 [18]
DPP10	2q14	Involved in positive regulation of protein localization to plasma membrane and proteolysis; IL-1 gene cluster	English and German; American Blacks, African Caribbean	Allen et al., 2003 [19]
ORMDL3 *GSDMB*	17q21	Acts upstream or within negative regulation of B cell apoptotic process;	Europeans, Asians, Hispanics,	Moffatt et al., 2007 [17] Moffatt et al., 2010 [29] Thomsen et al., 2015 [35] Demenais et al., 2019 [23]
CHI3LI	1q32.1	YKL-40 plays a role in the pathogenesis of autoimmune diseases;	Europeans, Hutterites, American, German	Ober et al., 2008 [21] Chen & Wang, 2017 [22]
HLA-DQ	6p21	MHC class II loci; involved in immunoglobulin production and immunoglobulin-mediated immune response	American Whites, Europeans	Li et al., 2010 [30] Thomsen et al., 2015 [35] Demenais et al., 2019 [23]
RAD50	5q31	Involved in DNA double-strand break processing; involved in mitotic G2/M transition checkpoint;	Northeastern Han Chinese,	Li et al., 2010 [30] Thomsen, 2015 [35]
IL13	5q31	Inflammation; involved in the positive regulation of macrophage activation	Northeastern Han Chinese, Europeans	Li et al., 2010 [30] Thomsen, 2015 [35]
CDHR3	7q22	Pronounced severe and early onset of disease; related to increased IL-17A response to viral infections;	Europeans	Bonnelykke et al., 2014 [31] Eliasen et al., 2022 [34]
IL1RL1 *IL18R1*	2q11 2q12	Encodes a protein in the Toll-like receptor superfamily/encodes the IL-18 receptor;	Icelanders, Europeans, East Asians	Moffatt et al., 2010 [29] Hayden et al., 2018 [28] Ferreira et al., 2017 [25]
IL33	9p24	Encodes IL-33, belongs to the IL-1 superfamily of proteins;	Europeans	Moffat et al., 2007 [17]

Table 1. *Cont.*

Genome-Wide Association Studies				
Gene	**Locus/Chr. Region ***	**Function/Biomarker**	**Population**	**Ref.**
IRF4 *NOD2* *IL4R* *IL2RA*	6p25 16q12 16p12 10p15	Involved in the regulation of T-helper cell differentiation and innate immune response; cytokine signaling in the immune system;	Europeans	Ferreira et al., 2017 [25]
KIAA1958 *IL1RL1* *IL13* *LINC01149*	9q32 2q12 5q31 6p21	Encodes a protein in the Toll-like receptor superfamily/encodes the IL-18 receptor; involved in positive regulation of macrophage activation;	Europeans	Li et al., 2010 [30] Hayden et al., 2018 [25]
DMRT1	9p24	Influence sex-specific patterns of childhood asthma; potential involvement in hormone or immune cell regulation;	Europeans	Schieck et al., 2016 [37]
TNFSF15	9q32	Not expressed in B and T cells; the expression of the gene product is inducible by TNF and IL-1 alpha;	Koreans, Asia	Kim et al., 2022 [51]

* https://omim.org/; https://www.ncbi.nlm.nih.gov/gene. Last accessed on 7 June 2023.

Table 2. Summary of some genes critical for childhood asthma severity or/and drug/treatment response.

Gene	**Locus/Chr. Region ***	**Association Effect (Pathogenesis, Function, Severity, Treatment)**	**Ref.**
ADBR2	5q32	Arg16-variant is associated with improved response to Beta-2 agonism; asthma severity;	Israel et al., 2000 [52] Litonjua et al., 2010 [53] Sood et al., 2018 [54] Scaparrotta et al., 2019 [55]
IL4	5q31	Encodes interleukin-4, associated with reduced forced expiratory volume in 1 s; associated with asthma severity;	Burchard et al., 1999 [56]
ALOX5	10q11	5-lipoxygenase, associated with improved response to ALOX5 inhibitor; worse lung function and asthma control;	Drazen et al., 1999 [57] Mougey et al., 2012 [58]
CRHR1	17q21	Intronic region of the corticotrophin-releasing hormone receptor 1 gene, response to inhaled corticosteroids;	Tantisira et al., 2004 [59]
CD14	5q31	Associated with asthma severity with modification from secondhand smoke; associated with asthma severity;	Choudhry et al., 2005 [60] Martin et al., 2006 [61]
ADAM33	20p13	Increased in severe asthma vs. mild asthma or no asthma; moderate and severe asthma;	Foley et al., 2007 [62]

Table 2. *Cont.*

Gene	Locus/Chr. Region *	Association Effect (Pathogenesis, Function, Severity, Treatment)	Ref.
ORMDL3 cluster	17q21	Association with exacerbations and poor asthma control on controller medication; response to treatment with inhaled corticosteroids; proinflammatory airway epithelial response;	Tavendale et al., 2008 [63] Bisgaard et al., 2009 [64] Berce et al., 2013 [65] Farzan et al., 2018 [66]
GLCCI1	7p21	Response to inhaled corticosteroids;	Tantisira et al., 2011 [67]
SPATS2L	2q33	Related to bronchodilator responsiveness; related to different ranges of asthma severity, age, and baseline;	Himes et al., 2012 [68]
ASB3	2p16	Modulates pulmonary function; bronchodilator response to inhaled β2-agonists;	Israel et al., 2015 [69]
IL1RL1	2q12	Response to inhaled corticosteroids; related to asthma susceptibility and severity;	Dijk et al., 2019 [70]
COL2A1	12q13	Response to inhaled corticosteroids; related to mild-to-moderate asthma;	Wan et al., 2019 [71]
MMP9	20q13	MMP-9 is released by inflammatory cells in response to allergen provocation in asthma, declining lung function;	Dragicevic et al., 2018 [72]
EDDM3B	14q11	Inhaled corticosteroids in pediatric asthma;	Levin et al., 2019 [73]
CRISPLD2	16q24	Associated with an adaptive response to asthma; a glucocorticoid responsive gene in airway smooth muscle cells;	Himes et al., 2014 [74] Almoguera et al., 2017 [42]
DNAH5	5p15	Associated with lung function or the presence/absence of COPD; moderate-to-severe persistent asthma;	Ramasamy et al., 2011 [75] Lee et al., 2014 [76] Mak et al., 2018 [77] Perez-Garcia et al., 2020 [78]
FCER2	19p13	Associated with response to inhaled corticosteroids; associated with asthma severity;	Lutz et al., 2015 [79] Wain et al., 2017 [80] Karimi et al., 2019 [81]
VEGFA	6p21	Associated with response to inhaled corticosteroids therapy severity of bronchial asthma;	Balantic et al., 2012 [82] Wan et al., 2019 [71]

* https://omim.org/; https://www.ncbi.nlm.nih.gov/gene. Last accessed on 7 June 2023.

3. Epigenetic and Childhood Asthma Development

In recent years, efforts to understand the etiology of childhood asthma have focused not only on genetics but also on epigenetics. Epigenetics is the inherited features that affect gene expression without changing the DNA sequence [83]. Epigenetic markers can be inherited by the next generation [84]. Epigenetic modifications may occur during prenatal development, childhood development, and adolescence. During these periods of life, people are most susceptible to various asthma-triggering factors [85]. Prenatal external environmental factors such as cigarette smoke, drugs, and alcohol and other postnatal factors such as air pollution, radiation, insufficient sleep, smoking, and improper diet may be the triggering factors for epigenetic changes [86,87]. We summarized some of these factors in Figure 1.

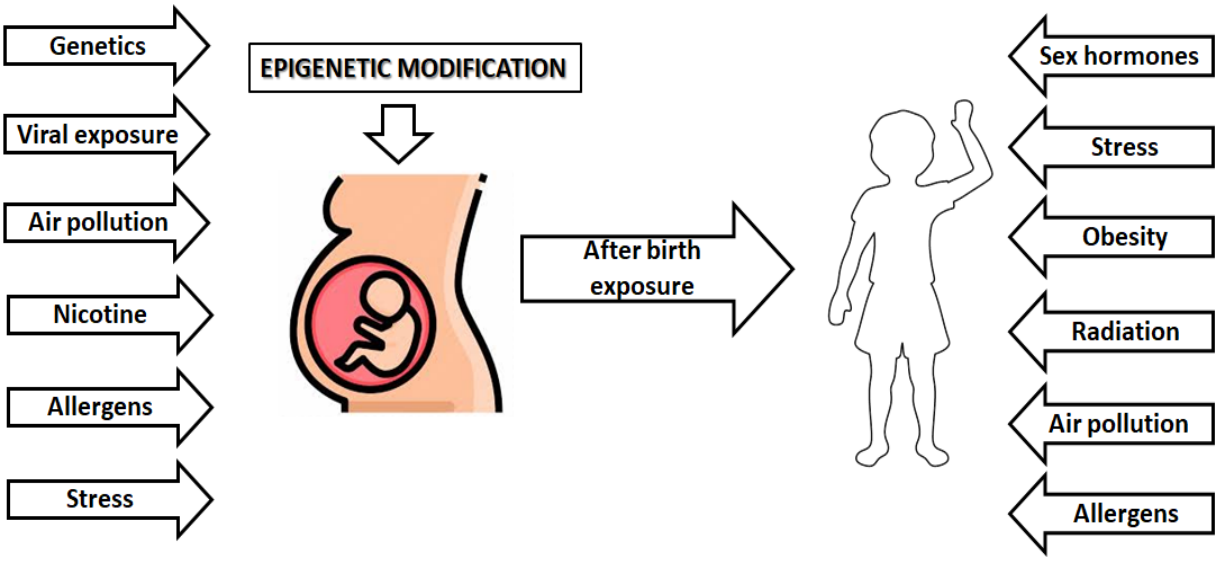

Figure 1. Some of the common risk factors associated with childhood asthma.

Obesity and childhood asthma are connected. Gene-environment interactions also influence both conditions. Because childhood obesity and asthma are significant pediatric health problems worldwide, they are included in the WHO Global NCD Action Plan 2023–2030 and the United Nations 2030 Agenda for Sustainable Development [86]. Furthermore, in recent years, obesity has been recognized as an independent risk factor for asthma development [88–90]. Obesity is associated with increased risk and morbidity in children with asthma compared to children with normal weight [91,92] (Table 3).

Moreover, in addition to the environmental factors, different patterns of epigenetic modifications have been identified associated with asthma, allergies, atopic dermatitis, and airway inflammation. Epigenetic regulation occurs through three main mechanisms: DNA methylation, histone modifications, and non-coding RNAs (microRNAs).

3.1. DNA Methylation and Studies of DNA Methylation and Childhood Asthma

The best-described mechanism in the literature is CpG-DNA methylation [85]. DNA methyltransferases added a methyl group to cytosine in a CpG dinucleotide, converting cytosine to 5′-methylcytosine. Over 80% of CpG dinucleotide sites are located outside of CpG islands [93]. Methylation of CpG islands near the promoters leads to transcription repression, while hypomethylation leads to genomic instability, upregulation of gene expression, and elevated mutation rates [94].

The associations between DNA methylation and diseases can be identified by an epigenome-wide association study (EWAS). In EWAS, where thousands of CpGs are being evaluated, multiple testing issues should be addressed to reduce false-positive findings [95].

EWAS are primarily cross-sectional studies and cannot differentiate whether epigenetic changes precede the disease or are a consequence of it. According to available data on childhood asthma, blood-based EWAS provides information mainly at the eosinophilic level. However, nasal epithelium EWAS provides information on methylation changes and regulatory perturbations of epithelial cells in the respiratory tract [96]. In addition, nasal epithelium EWAS was more reproducible in other cohorts than EWAS conducted in blood samples. All these data suggest that the methylation is tissue- and cell-specific [97]. Therefore, several EWAS studies and projects have attempted to describe the DNA methylation of different cell types and tissues of asthma patients [85,94,96,98].

A significant overlap of methylation changes was found in nasal and bronchial epithelial cells of children with asthma [96]. When conducting blood-based EWAS and nasal epithelium EWAS, genes such as *ACOT7*, *EPX*, *GJA4*, and *METTL* were found to be com-

mon [99]. This indicates that, except for the cell specificity of CpG methylation sites, there is also an epigenetic effect across tissues [100].

Recent studies by Xu [101] and Qi [102] focused on epigenetics and childhood asthma development in detail. The studies described gene/genetic variants associated with childhood asthma and epigenetic modifications connected with asthma development. All data discussed above [100,101,103–111] are systematized in Table 3 (modified from Qi et al., 2019).

Table 3. Summary of the major childhood asthma DNA methylation studies.

Gene/Candidate-Gene *	Ancestry	Tissue	Ref.
LMAN2; STX3; LPIN1; DICER1; SLC25A25;	European	Whole blood	Xu et al., 2018 [101]
ACOT7, EPX, GJA4 and *METTL1;*	American African	Nasal brush epithelial cells	Yang et al., 2018 [100]
ZFPM1; AP2A2; IL5RA;	European	Peripheral blood	Arathimos et al., 2017 [103]
CDHR3; CDH26; FBXL7;	Hispanic/Latino	Nasal brushes cells	Forno et al., 2018 [104]
EVL; NTRK1; SLC9A3; ACOT7;	Mixed ancestry	Nasal swab cells	Cardenas et al., 2019 [105]
CLNS1A, Mir_548; SUB1, LOC100129858; RUNX1; GPATCH2; WDR20; IL5RA; ACOT7; KCNH2;	-13 European cohorts; -3 mixed ancestry cohorts -1 African/American cohort	Whole blood	Reese et al., 2019 [106]
ORMDL3; CCL26	African American and European American	Bronchial airway epithelial cells	Nicodemus-Johnson et al., 2016 [107]
SMAD3; DDO/METTL24	European	Whole blood	Lund et al., 2018 [108]
CCL5, IL2RA, TBX21, FCER2, TGFB1, LIF, ADAM17, NHEJ1, AHR, PGDR, PI3K, GNA12 etc.	American cohort	Peripheral blood	Rastogi et al., 2013 [109]
ARG1, ARG2, IL6, iNOS	non-Hispanic white and Hispanic white ethnicity	Buccal cells/Nasal epithelium	Breton et al., 2011 [110]
KRT5, CRIP1, STAT5A	European	Bronchial epithelium	Stefanowicz et al., 2012 [111]

* Some genes were identified in more than one study.

3.2. Histone Modification and Studies of Histone Modification and Asthma

DNA condensation occurs with the help of core histones (H2A, H2B, H3, and H4) to form a chromatin structure [112]. Histone modifications are methylation, acetylation, phosphorylation, ubiquitination, sumoylation, and ADP-ribosylation. Disturbance in histone modifications has many clinical implications, leading to inflammatory responses by the immune system and the development of various diseases, including allergic asthma, rhinitis, atopic dermatitis, and allergies (Figure 2).

Histone modifications alter chromatin accessibility. For example, histone acetylation is carried out by the enzyme histone acetyltransferase (HAT), leading to a loose chromatin structure. This makes it available to transcription factors and activates gene expression. On the other hand, histone deacetylation is carried out by the enzyme histone deacetylase (HDAC), resulting in gene silencing and a lack of gene expression. These histone modifications are associated with the risk of asthma development or disease severity (in children and adults). They affect the gene expression of genes responsible for the differentiation and maturation of various immune cells, some of which are involved in asthma development [113].

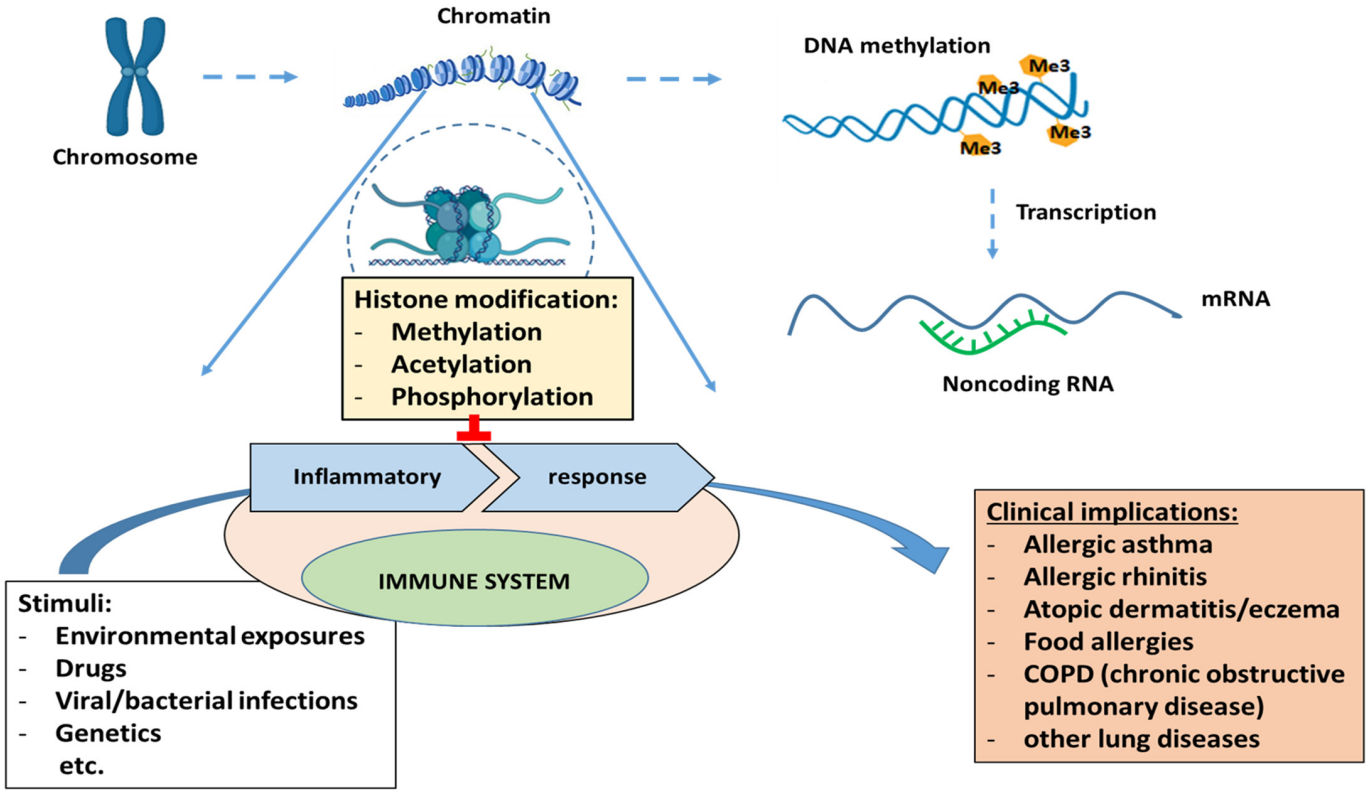

Figure 2. Clinical implications of epigenetic regulation (histone modifications, DNA methylation and non-coding RNAs).

HAT activity has been increased in adults [114] and children with asthma [115], and the ratio of HAT/HDAC changes also depending on the presence or/and severity of asthma.

To date, no publications discuss in detail the role of histone modifications in the development of asthma in children. Some studies have been conducted in animal models [116–119]. The results of other studies established the role of HDACs in T-cell development and asthma susceptibility. Their suppressed expression can lead to asthma and/or allergic airway diseases with varying severity, as well as resistance to corticosteroid therapy [114,120]. In HDAC1-deficient T-cell mice, there is an increased number of eosinophils and the production of Th2 cytokines, which is a prerequisite for asthma development [121]. These findings indicate that HDACs are essential in repairing airway epithelium, especially in airway remodeling observed in severe asthma [122].

A genome-wide histone modification study from 12 asthma patients and 12 controls identified 200 enhancer regions in three immune cell subpopulations (naive T cells, Th1 and Th2 cells). In addition, a selective enrichment in demethylation of the Lys at the fourth position of the N-terminal tail of histone 3 (H3K4me2) was shown. This marker indicates gene activation in promoters and enhancers of genes [123]. One hundred sixty-three regions were specific for the Th2 cells, 29 were specific for naïve T cells, and only 11 for Th1 cells.

A study of children with allergic asthma (n = 14) and controls (n = 18) identified a high level of histone acetylation (histone 3 at the *IL13* and *FOXP3* loci). The study also indicates a potential regulatory role of *IL13* acetylation on the amount of protein product [124].

Similarly, acetylation of histone H3 lysine 18 (H3K18) is related to increased expression of *STAT6*, *EGFR*, and Δ*Np63* [125]. The expression of epidermal growth factor receptor (EGFR) is vital for the proliferation, differentiation, and repair processes. It was increased in both healthy and damaged areas of the epithelium of pediatric and adult patients with asthma [125–128]. In addition, the signal transducer and activator of transcription 6 (STAT6) are also overexpressed in the epithelium of patients with severe asthma [129,130].

In a recent study, loss of HAT was found to be associated with a downregulation of the *ORMDL3* gene, which in turn led to the development of childhood asthma [131].

Some other studies have also identified a link between childhood asthma and histone modifications. For example, Wawrzyniak et al. found higher expression of histone deacetylases 1 and 9 in epithelial cells from 18 asthmatic patients and 9 controls [132]. In addition, increased expression of HDACs led to increased expression of *IL-13* and *IL-4*, which are critical genes for childhood asthma severity and treatment response.

It is well-known that prenatal and/or childhood exposure to environmental factors can influence the immune system and responses [133,134]. In addition, environmental factors can strongly induce epigenetic changes in immune cells, leading to the development of allergies/asthma [135,136].

In 2011, Brand et al. investigated epigenetic alteration in pregnant mice and offspring [137]. They demonstrated that changing H4 acetylation led to a childhood asthma phenotype.

Another research group evaluated the acetylation of histones H3 and H4 in the promoter regions of six immunoregulatory genes associated with childhood allergy in 173 placentas [138]. Three genes were found to be associated with high histone acetylation levels and risk of allergic sensitization—H3 acetylation in placentas at the *IFNG* and *SH2B3* genes and H4 acetylation at *HDAC4*. These data suggest that placental histone acetylation levels are associated with a reduced risk of allergen sensitization and have the potential to predict the development of childhood asthma/allergies.

Inhibition of HDAC activity has a preventive effect on epithelial barrier integrity in pediatric and adult patients with asthma [132].

To sum up, there is no doubt that histone modifications play a crucial role in the development and pathogenesis of asthma. However, more studies with larger cohorts are needed to obtain more accurate and transparent information about their contribution to immune-mediated and allergic diseases, such as asthma. Moreover, maternal asthma remains among the highest risk factors for childhood-onset asthma. Data show that epigenetic alterations may occur in the embryo of pregnant asthmatic women that may lead to severe asthma development in the offspring.

A summary of the studies on histone modification and childhood asthma [124,125,131,132,138] are presented in Table 4.

Table 4. Summary of the studies about the role of histone modification and childhood asthma.

Genes/Candidate-Genes *	Histone Modifications	Tissue	Ref.
IL-13, FOXP3	histone H3 acetylation	Peripheral blood	Harb et al., 2015 [124]
IL-4, IL-13	higher expression of HDACs 1 and 9	Bronchial epithelium	Wawrzyniak et al., 2016 [132]
STAT6, EGFR and Δ*Np63*	histone H3 acetylation	Bronchial airway epithelial cells	Stefanowics et al., 2015 [125]
IFNG, SH2B3 *HDAC4*	histone H3 acetylation histone H4 acetylation	Blood samples Placenta samples	Harb et al., 2019 [138]
ORMDL3	histone H3 acetylation	Bronchial epithelium	Cheng et al., 2019 [131]

* Some genes were identified in more than one study.

3.3. Non-Coding RNAs and Studies of Non-Coding RNA and Asthma

Non-coding RNAs, such as microRNAs (miRNAs, miRs), are single-strand RNAs of 21–25 nucleotides that regulate gene expression at the post-transcriptional level [139]. They act as dynamic regulators of gene networks by exercising control over the translation of many mRNAs by mRNA destabilization [140]. miRNAs play a significant role in biochemical pathways, cell signaling, cell and tissue development, and regulating pathological processes in various diseases. They have been identified as related to childhood/adult asthma, expressed in different tissues, including blood cells, airway epithelial cells, and

smooth muscle. They can also serve as potential biomarkers for diagnosis and therapy targets for asthma [141]. Differences in miRNA expression between asthmatic and healthy subjects were found [98]. Some asthma-related miRNAs may act on genes associated with respiratory tract function (i.e., miR-10, miR-140-3p, miR-708), and others may target genes related to immune system function (i.e., miR-21, miR-19a, miR-155, miR-210, miR-125b, miR-223) [142].

MiRNAs, such as miRNA-17-18-19-20, miRNA-26a/b, miRNA-27a/b, miRNA-125b, miRNA-155, and others, polarize macrophages as a reaction to specific environmental stimuli and signals toward an M1-phenotype (classically activated). Others as miRNA-21, miRNA-124, miRNA-223-3p, and miRNA-511-3p, e.g., polarize macrophages towards an M2-phenotype (alternatively activated) [143].

In a recent study, two miRNAs (miR-21 and miR-126) were found to be upstream-regulated in patients with asthma compared to controls [144]. Another study showed that miR-21 contributes to the production of eosinophils and proliferation [145]. MiRNA-21 is one of the most well-studied miRNAs in relation to asthma. In asthmatic patients, its high amount suppresses IL-12p35 and causes resistance to steroids [146]. IL-12p35 is predominantly produced by dendritic cells, monocytes, and macrophages and inhibits cytokine-induced STAT pathways and cell-cycle regulators. Serum miRNA-21 is related to asthma onset or allergies and could be used as a biomarker [146,147]. Both miRNA-21 and miRNA-146a were associated with increased levels of eosinophils and could be biomarkers for the eosinophilic endotype of asthma [148].

Another study identified increased levels of miRNA-155 and decreased levels of Let-7a in the blood of children with asthma (n = 100) compared to controls (n = 100) [149]. To distinguish the severity of the disease, different expression profiles of miRNA-155 and Let-7a were found [149]. MiRNA-155 plays a critical role in IL-33 regulation of airway inflammation in mouse models of asthma [150]. In addition, the Let-7 miRNA has been shown to target IL13 and exert anti-inflammatory effects in mice [151]. These data suggest that miRNA-155 could be one of the biomarkers suitable for childhood asthma diagnosis.

Another miRNA, miRNA-146, has also been studied in relation to asthma [152]. HLA-G variation in children also increased the risk of developing asthma, along with miRNA-152 [108]. In an examination of serum samples from 160 children in the Childhood Asthma Management Program (CAMP), 155 circulating miRNAs were detected [153]. Of these, eight were significantly related to PC20 (asthma test to determine the concentration of inhaled methacholine), but the most substantial relationship was with miRNA-296-5p. Two others, miRNA-30d-5p, and miRNA-16-5p, were found to be critical in the development of asthma via regulating airway smooth muscles [153].

MiRNAs may also be used as biomarkers to assess the risk of childhood asthma development or to predict the outcomes from treatment, as several studies showed [142,154–156]. All these findings demonstrated the importance of miRNAs in controlling inflammation, diagnosing disease severity, and treatment response in childhood asthma, as well as their potential use as disease biomarkers.

The miRNA studies associated with asthma [157–164] are summarized in Table 5.

Recently, our team also discussed the miRNA involvement in allergic rhinitis and mild asthma in adults as a part of united airway disease [165].

Our review paper has some limitations. First, we focused mainly on the GWAS outcomes related to the development and severe course of childhood asthma. We acknowledge that there are also numerous genes associated with asthma, including genes related to external risk factors and medications, responses to therapy, etc. Secondly, most of the cited studies have other limitations, such as a limited number of patients, some limitations in the design and methodology, or their failure to adjust the impact of different factors (i.e., environmental, etc.). Furthermore, new data is expected to be published since childhood asthma and overall asthma is a highly researched topic. We believe that this limitation is not fatal but a prospect for other reviews.

Table 5. Summary of some significant miRNAs' studies associated with asthma.

miRNAs	Level	Function/Role in Asthma	Tissue	Ref.
miR-21	increased	- eosinophilic accumulation - correlation with IL-13 - Th2 response - suppression of IL-12p35	bronchial epithelial cells	Lu et al., 2011 [157] Wu et al., 2014 [144] Pua et al., 2015 [145] Elbehidy R., 2016 [146]
miR-146	increased	- increase the eosinophilic level - anti-inflammatory - negative regulation of IL1β and COX2	blood samples, human ASM cells	Su et al., 2011 [152] Comer et al., 2014 [158] Hammad et al., 2018 [148]
miR-155	increased	- decreased level of Let-7a - regulation of IL-13 - in Th2 immune responses	blood samples	Zhou et al., 2016 [159] Karam et al., 2019 [149]
miR-19	increased	-mediate the production of IL-13 -targets mRNA of the TGFβR2 gene -regulation in responses of the Th2 cell	bronchial epithelial cells, airway T cells	Simpson et al., 2014 [160] Haj-Salem et al., 20015 [161]
miR-126	Increased	- increase AHR and immune migration - Th2 response - increase the eosinophilic level	bronchial epithelial cells, peripheral blood	Mattes et al., 2009 [162] Wu et al., 2014 [144] Tian et al., 2018 [163]
miR-15b, 126, -139, -142, -186 etc.		- lung function parameters in children	Blood samples	Kho et al., 2016 [164]

4. Conclusions

Recent efforts to elucidate the mechanisms of asthma have focused on elucidating epigenetics and environmental factors that influence gene expression without altering the DNA sequence at the molecular level. This biomedical narrative review summarized the available information on genes associated with risk and susceptibility to childhood asthma development. We also covered some of the epigenetic modifications associated with the development of children's asthma.

The accumulated data from GWAS on the numerous alleles and loci associated with allergies and asthma in children and adults made it possible to discover new genetic biomarkers for asthma that can be implemented in clinical practice.

Although histone modifications contribute to the development of childhood asthma, there is still a small number of studies in this area. Improving our knowledge in this area may lead to the discovery of effective diagnostic tools, therapeutic targets, and drugs for different types of asthma.

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