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Epigenetic changes in childhood asthma: a path to precision medicine

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Abstract

The 2023 Global Initiative for Asthma (GINA) report highlights a significant rise in asthma rates particularly in low- and middle-income countries, with urbanization and exposure to environmental pollutants being key contributing factors. Children exposed to environmental influences throughout their critical developmental periods may experience epigenetic changes that could predispose them to asthma in the future. However, there are still issues implementing these findings in clinical settings, necessitating more research and technological advancements. The knowledge of epigenetics in childhood asthma might bridge the gap in knowledge of disease etiology and help the creation of precision medicine approaches. By integrating epigenetic indicators into diagnostic and therapy methods, clinicians can move closer to customized care, benefiting children with asthma. This review emphasizes the significance of epigenetic mechanisms in the development of pediatric asthma and the important associated genes like ORAI1, IL4, ADAM33, GSTM1, FLG, GATA3, STAT6, TNF, CD14, IKZF3, MUC5AC, and ORMDL3. We will also review the role of important epigenetic changes including non-coding RNAs, DNA methylation, and histone modifications in the pathophysiology of asthma. Furthermore, the potential of epigenetics as biomarkers for the diagnosis and prognosis of asthma and the therapeutic uses of epigenetic-based therapies such as DNA methyltransferase inhibitors and histone deacetylase (HDAC) inhibitors have been explored.

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Introduction

Childhood asthma is a serious respiratory condition predominantly affecting the airways, causing airway constriction and chronic inflammation interfering with normal respiratory function presenting clinically with chest tightness, coughing, wheezing, and dyspnoea[1]. According to the Global Initiative for Asthma's (GINA) 2023 report, urbanization, and environmental pollutants are recognized as the major causes of notable prevalence in many low- and middle-income nations[2]. It is worrisome to note that childhood asthma is one of the leading causes of school absences, emergency department admissions, and hospitalizations with the incidence of asthma increasing in developing countries[2,3].

Recent scientific explorations into the pathogenesis of asthma have revealed it to possess a very complex and multitiered foundation, influenced by genetic and environmental factors causing chronic airway inflammation, airway hyperreactivity (AHR), and irreversible airway remodeling, mucus hypersecretion, subepithelial fibrosis, and airway remodeling[3–5]. Asthma susceptibility has been linked to many critical genes, with important loci found on chromosomes 2, 6, 9, 15, 17, and 22. ORMDL3/GSDMB is the most prevalent gene found in these genomic areas, and it plays a crucial role in the etiology of asthma. This chromosome 17 gene has been closely linked to childhood asthma, suggesting that it plays a crucial role in the initiation and development of asthma in young people[6].

Epigenetics is defined as the study of the interaction of the environment and the functioning of the genome without changing the genome sequence[7]. The gene-environment interaction hypothesis holds that the functions of many known genes are determined by environmental factors and that epigenetic modification is an important mechanism underlying the interplay between environmental and genetic factors[5]. The three major types of epigenetic regulation include histone modifications, DNA methylation, and non-coding RNAs (ncRNAs), such as microRNAs[7,8]. Research reveals that epigenetic approaches targeting specific genes can identify potentially treat life-threatening illnesses like cardiovascular disease, cancer, neurodevelopmental, and neurodegenerative disorders. The astounding increase observed in the incidence, prevalence, and severity of asthma in the past few decades strongly substantiates the claim that environmental exposure plays a titular role in the pathogenesis of asthma, especially via their interactions with the genetic variants[4]. Despite ongoing research and an improved understanding, the prevalence of asthma has been rising in recent years with the absence of current epigenetic-based treatments.

This review explores the potential of epigenetic-based treatments for the condition. It gives a thorough summary of the state of research on the relationship between epigenetics and childhood asthma focusing on the processes of non-coding RNAs, histone modifications, and DNA methylation. This article also discusses the therapeutic potential of epigenetics, including the application of medicines that target enzymes like DNMT inhibitors and HDACs.

Functional characterization of predicted asthma genes

Many genes have been found to impact airway inflammation, remodeling, and immunological responses, and along with environmental stressors like pollution, tobacco smoke, and allergens, these genetic variants increase the incidence of asthma[9,10]. By understanding the epigenetic processes that control these genetic variations, they can be targeted for proper diagnosis, treatment, and prevention of childhood asthma. Table 1 lists the main genes linked to asthma and their roles in the underlying pathophysiology.

Table 1. Genes associated with asthma pathogenesis and their genetic variations.

Gene symbol	Gene function	Association with asthma pathogenesis	Etiology of genetic variations
ORAI1[11]	Calcium ion regulation, T-cell activation, cytokine production.	Variants linked to increased asthma susceptibility; especially, related to the immune response to allergens.	Genetic mutations and allergens can influence its expression and immune response.
IL4[12,13]	Promotes differentiation of T-helper cells, leading to Th2-mediated inflammation	IL4 drives IgE production and allergic responses, contributing to asthma; especially, allergic asthma.	Genetic mutations and environmental allergens like pollen and dust mites increase IL4 expression.
ADAM33[14]	Involved in airway remodeling and smooth muscle regulation	Contribute to airway hyperresponsiveness and remodeling features of asthma.	Genetic changes; tobacco smoke and air pollution can trigger ADAM33 activation.
GSTM1[15–17]	Detoxifies harmful substances like environmental pollutants	GSTM1 gene deletion is associated with asthma risk; especially, in children exposed to pollution.	Genetic deletion of GSTM1 and environmental pollutants (e.g. tobacco smoke).
FLG (Filaggrin)[18,19]	Maintains skin integrity and prevents allergens entering to the body	FLG mutations are linked to asthma; especially, in children with eczema, due to a weakened skin barrier.	Genetic mutations; allergens or irritants like harsh chemicals and pollution.
GATA3[20,21]	Transcription factor regulating Th2 differentiation.	GATA3 variants are associated with allergic asthma and Th2-mediated inflammation.	Genetic variants; and environmental allergens contribute to GATA3 overexpression.
STAT6[22]	Transcription factor helps in Th2 differentiation and cytokine production in allergic responses.	Variants increase susceptibility to asthma, especially in children with allergic tendencies.	Genetic variants; and environmental allergens like pollen can promote STAT6 activation.
TNF[23]	Pro-inflammatory cytokine, immune activation & airway inflammation.	Variants linked to asthma, particularly through increased airway inflammation and tissue remodeling.	Genetic mutations; air pollution and allergens exacerbate TNF expression.
CD14[24,25]	Receptor activates immune responses to environmental triggers, such as bacteria and allergens.	Variants in CD14 are associated with asthma, particularly in children exposed to environmental allergens.	Genetic changes; and environmental exposures (e.g., dust mites, mold) increase CD14-mediated immune activation.
IKZF3[26,27]	Regulates immune cell differentiation and activation.	Contribute to asthma susceptibility, influencing immune responses.	Genetic predisposition; environmental allergens.
MUC5AC[28]	Secreted protein involved in mucus production in the airways.	Overexpression of MUC5AC is associated with asthma and excessive mucus production.	Genetic variation; tobacco smoke and air pollution can upregulate MUC5AC production.
ORMDL3[29]	Regulates endoplasmic reticulum stress and inflammation. It plays a role in maintaining cellular homeostasis and regulating immune response.	Variants in ORDLM3 are associated with asthma; particularly, childhood asthma. The gene contributes to airway inflammation and immune response dysregulation by regulating cytokine synthesis and immune cell activation.	Genetic variations, incorporating single nucleotide polymorphisms (SNPs); and environmental factors (e.g. allergens) may influence gene expression and immune response.

Therapeutic potential of targeting epigenetic mechanisms in childhood asthma

The role of DNA methylation in immune regulation and airway inflammation

DNA methylation is an epigenetic process the refers to the addition of a methylgroup to DNA, which may regulate gene expression[30]. Around 1.5% of the genome contains 5-methylcytosine (5-mC), a change that occurs when a methyl group is introduced to the cytosine base's 5th carbon. Although more frequently found at CpG sites, 5-mC can exist at non-CpG sites; especially, in embryonic stem cells. Some CpG sites are unmethylated, but most are methylated because methylation inhibits transcriptional enzymes from linking to DNA, suppressing gene expression[31,32]. DNA methylation in adaptive evolution is closely associated with the potential ability to produce novel pathways with DNA methylation for phenotypic diversity.

Wang et al., pinpointed positive causal methylation sites related to asthma. The report identified three genes—ETS1, ITPKB, and JAK2, which had eight distinct DNA methylation sites. Two methylation sites, cg16265553 and cg13661497 downregulated ITPKB expression and inhibited JAK2 expression respectively[33]. This suggests that DNA methylation influences gene expression, which influences the risk of asthma. Potential drug therapies targeting CEP95, RBM6, ITPKB, ETS1, and JAK2 may be formulated for asthma.

A case-control study showed 81 regions that were differentially methylated in asthmatic patients. The authors reported 11 IgE-associated differentially methylated regions (DMR). The association of methylation changes of KLF 6 identifies novel genes and networks that are involved in the pathogenesis of asthma[34]. While Wang et al.[33] employed Mendelian Randomization (MR), Yang et al.[34] built on the understanding that the cause of asthma is associated with non-Mendelian inheritance. The potential of DNA methylation for treatment was highlighted in the use of classical Ayurvedic treatment which follows a holistic therapeutic approach rather than targeting any specific type of cell. Bhat et al.[35] reported that the signaling pathways of Neurotrophin TRK receptors, neurotrophin, ERBB, and epidermal growth factor receptors were enriched for differentially methylated genes in bronchial asthmatics. The Pulmo Seek model uses targeted DNA methylation sequencing with a blood-based test which is less invasive and a cost-effective strategy for identifying early-stage lung cancer. A similar, strategy in improving early diagnosis, and tracking the treatment's efficacy to manage asthma can be offered[36].

Histone acetylation and deacetylation: epigenetic control of airway inflammation

HDACs play a critical role in epigenetic control by modifying gene expression through chemical alterations that do not affect the underlying DNA sequence. These alterations may result in notable phenotypic shifts. Histone acetyl groups are eliminated by HDACs, which alters chromatin shape and gene activity. Deacetylation has a role in inflammation and many cellular processes like differentiation, proliferation, and gene expression[37]. These functions demonstrate the significance of HDACs in preserving cellular homeostasis and their potential as therapeutic targets[38]. A key function of histone acetylation and deacetylation is to control gene accessibility via modification of chromatin structure. A more relaxed chromatin structure caused by histone acetylation makes it possible for transcription factors to attach to genes and increase their expression[39]. Histone acetylation at loci such as IL-4 and IL-13 in asthma

exacerbates airway inflammation by promoting Th2-driven inflammation. On the other hand, chromatin condenses due to histone deacetylation, which inhibits gene expression[40]. Targeting histone-modifying enzymes may alter chromatin accessibility, which could help control immunological responses and inflammation in asthma.

An *in-vitro* demonstration in asthmatic mice demonstrated that histone hyperacetylation of ORMDL3 is associated with asthma and an increase in ORMDL 3 expression is associated with airway remodeling. A mouse model of asthma demonstrated that inhibiting p300 with C646, ORMDL3 expression, airway hyperactivity (AHR), and remodeling were decreased, indicating that p300 targeting might provide a treatment approach for childhood asthma[5]. A randomized controlled trial of increasing fruit and vegetable intake in asthmatic children did not impact asthma exacerbations over 6 months; however, a high F & V diet could modify histone modifications and related anti-inflammatory pathways. The authors found alterations in the HDAC activity of peripheral blood mononuclear cells (PBMC) and the expression of genes linked to G-protein coupled receptors (GPR41/43)[41].

A genome-wide mapping of histone modifications revealed that a considerable number of asthma-related single nucleotide polymorphisms (SNPs) were located on Th2 cell enhancers, a region in which the highest rate of H3K4 demethylation was measured in primary human CD4 + T-cell. In addition to the TH 2-associated cytokines IL-4, IL-5, and IL-13, the TH 9-associated cytokines IL-9, IL-10, and IL-21 are increased[42]. These studies suggest chromatin remodeling and histone alterations can provide therapeutic options for asthmatic children by providing a novel way to influence the underlying molecular mechanisms of asthma by altering the epigenetic regulation of gene expression. Normal gene expression patterns linked to inflammation and immunological responses may be restored by modifying histone modifications and the chromatin landscape; thus, alleviating the asthma symptoms and worsening of disease process.

Non-coding RNAs/microRNAs in the regulation of asthma-related inflammatory pathways

Long non-coding RNAs (lncRNAs), microRNAs (miRNAs), and circular RNAs (circRNAs) are examples of ncRNAs that do not code for proteins. These non-coding RNAs are important for the regulation of many biological functions. Studies have demonstrated the importance of ncRNAs in asthma as lncRNAs and miRNAs mostly regulate asthma gene expression. miRNAs such as miR-155 and lncRNAs affect immunological responses and increase airway hyperreactivity through transcriptional and post-transcriptional modulation of gene expression[43]. Children with asthma have distinct levels of miRNA and lncRNA expression compared to healthy controls, suggesting that these molecules may be used as diagnostic biomarkers and therapeutic targets[44,45] miRNAs are specifically linked to smooth muscle proliferation and airway inflammation.

Recent research has demonstrated the role of circRNAs in airway remodeling and smooth muscle cell proliferation; essential for the development of asthma. *In vitro* and *in vivo* models showed NORAD silencing decreased the levels of β-catenin and c-Myc.RCC2 upregulation abrogated the influence of NORAD downregulation on their expression levels in TGF-β1-induced BEAS-2B cells. These results suggested that the silence of NORAD inactivated the Wnt/β-catenin pathway by suppressing RCC2 in asthma[3]. A novel mechanism was suggested via which human bronchial epithelial (HBE) cells treated with exosomal lncRNA PAET accelerate DNA damage and contribute to PM2.5-induced pediatric asthma. lncRNA PAET was markedly elevated in exosomes produced from PM2.5-treated HBE cells in children with asthma which interferes with oxidative phosphorylation (OXPHOS) by increasing the m6A modification of COX4I1 mRNA through the regulation of METTL3 stability. Reduced COX4I1 expression and inhibition of OXOPHOS, in turn, raised reactive oxygen species (ROS) levels and caused DNA damage in recipient HBE cells[46].

How epigenetics triggers shape epigenetic modifications

Environmental exposures such as tobacco smoke, air pollution, vehicle exhaust, and pesticides, can significantly alter the epigenome and increase the risk of asthma in children (Table 2)[7]. These pollutants induce oxidative stress, altering miRNA expression, DNA methylation, and histone modifications later in life.

Epigenetic biomarkers for predicting childhood asthma: emerging approaches and applications

The role of epigenetics in disease has become a special focus of research. Epigenetic modifications profoundly affect gene expression and aberrant modifications have been linked to various diseases[7,38]. The rate at which environmental exposure brings changes in DNA sequences can explained by epigenetics[4]. Epigenetic modifications like ncRNAs, histone modifications, and DNA methylation are reversible, functionally relevant changes that do not impact the nucleotide sequence of the DNA[4,7,30].

DNA methylation: a predictive biomarker

In addition to being identified in several malignancies, aberrant DNA methylation patterns are increasingly becoming recognized as early markers of respiratory conditions including asthma. A DNA methylome analysis of PBMCs from 394 patients with mild-to-moderate asthma, showed that hypomethylation of the precortistatin (CORT) and IL-12 subunit β (IL12b) genes were associated with fewer hospitalizations and less use of oral corticosteroids, respectively, suggesting that these genes could be used as prognostic biomarkers[47]. DNA methylation might be a biomarker for IgE sensitization. The authors indicated IgE stratified analysis of replicated CpGs showed that DNA methylation signals in the nasal epithelium were mainly driven by IgE-positive subjects with asthma and not by IgE negative asthma subjects[30].

Histone modification as an epigenetic predictor

Histone modification changes are being studied as possible biomarkers for the early diagnosis of malignancies since they can significantly affect gene expression. Genes like ARDID5B, SENS1, and XPA are implicated in cellular senescence, cell cycle regulation, and DNA repair pathways, indicating their potential as biomarkers for Alzheimer's disease (AD)[5]. However, little is known about histone changes or modifications in asthma. The results of the previous

Table 2. Implications of environmental variables on childhood asthma and pertinent epigenetic initiatives[7].

Environmental trigger	Percentage of children affected	Epigenetic mechanisms involved
Passive smoking	20%–30%	DNA methylation of immune genes (e.g., AHRR, FOXP3), altered miRNA profiles.
Pollutants from air conditioners	~15%	Oxidative stress-driven histone modifications and DNA methylation.
Pollutants from refrigerators	10%–12%	Non-coding RNA dysregulation, DNA methylation of inflammatory pathways.
Mosquito repellent machines	~10%	Disruption of immune gene regulation via non-coding RNAs.
Vehicle emissions	20%–40%	Global hypomethylation, site-specific methylation (e.g., IL-4, IFN-γ genes).

Table 3. Techniques favoring the study of cellular diversity, enabling the analysis of heterogeneity in tissues, uncovering rare cell populations.

Technique name	Corresponding description
Single-cell RNA sequencing (scRNA-seq)	Efficient to measure the transcriptome of individual cells further cells are isolated, and RNA is reverse transcribed, and sequenced.
Single-cell DNA sequencing	First in hand to analyze individual cell genomes for mutations, copy number variations, and rearrangements.
Single-cell epigenomics	Studies gene regulation through chromatin accessibility (ATAC-seq), protein-DNA interactions (ChIP-seq), and DNA methylation profiling.
Spatial transcriptomics	Within the tissue architecture, this technique maps gene expression with spatial information.
Single-cell proteomics	Applying advanced mass spectrometry, protein expression, and modifications are measured, as methods like CyTOF.

study suggest that histone alterations might be promising as asthma biomarkers, but more substantial evidence is required to use it.

Non-coding RNAs: novel predictive biomarkers

Non-coding RNAs have been extensively studied as potential biomarkers in the context of different diseases. Recent animal and even human studies have revealed a potentially significant role of miRNAs in asthma pathogenesis[4]. Non-coding RNAs have been established to play an important role in gene expression control, either as transcriptional or post-transcriptional regulators. miRNAs can regulate key genes involved in the development of cancer, thus influencing tumor growth, invasion, and metastasis by increasing the activation of oncogenic pathways and limiting the expression of tumor suppressors[43].

Epigenetic-based therapeutic interventions in childhood asthma

HDAC inhibitors

Histone deacetylases (HDACs) are evolutionary conserved enzymes which operate by removing acetyl groups from histones and other protein regulatory factors, with functional consequences on chromatin remodeling and gene expression profiles[37]. A recent study demonstrated reduced oxidative stress, airway inflammation, and remodeling in an ovalbumin-induced asthmatic mouse model by HDAC inhibitors, curcumin (CUR), and sodium butyrate (SOB). This may be achieved by modifying the PI3K/Akt and HIF-1α/VEGF signaling pathways[48]. Li et al. also demonstrated reduced allergic airway inflammation and hyperresponsiveness in an allergic asthma model exposed to ovalbumin by HDAC8 inhibitors[49].

DNA methyltransferase (DNMT) inhibitors

DNA methyltransferase inhibitors have shown promising results by regulating immunological responses; especially, in treating cancer and respiratory conditions including COPD and asthma. DNMT inhibitors act by inhibiting DNA methyltransferases, enzymes that add methyl groups to DNA; thus, reactivating silenced genes, including those crucial for immune responses[50,51].

Future perspectives and approaches paving the way to precision medicine

The future of pediatric asthma treatment lies in leveraging advances in epigenetics for precision medicine. Key directions include the identification of personalized epigenetic biomarkers for early diagnosis and monitoring, allowing tailored treatments for individual patients. Targeting epigenetic modifications, such as DNA methylation, histone modification, and ncRNAs, offers potential therapies to reverse aberrant gene expression linked to asthma. The integration of epigenetic biomarkers into clinical practice could revolutionize asthma management. DNA methylation signatures, such as those identified in the ALOX5 gene, SOCS1, and RUNX3 offer the potential for stratifying patients into phenotypic subgroups and predicting therapeutic responses[51].

Early identification of such markers in cord blood or peripheral blood can guide the prevention of the same. It has been demonstrated that probiotics and omega-3 fatty acid supplementation during pregnancy lowers the risk by lowering inflammatory indicators and fostering immune balance in the fetus. The immune system is better able to tolerate and reduce epigenetic changes that lead to asthma when vaginal delivery is encouraged, which increases exposure to naturally occurring bacteria while lowering the need for antibiotics throughout infancy. Furthermore, asthma will be impacted by single-cell epigenomic approaches (Table 3), which will allow for more targeted treatments. Lastly, investigating how environmental influences and epigenetic pathways interact will result in the development of better preventative and therapeutic approaches.

Despite providing revolutionary insights, epigenetics still faces obstacles, such as the requirement for long-term research to prove causal links and the standardization of epigenetic analytic techniques. Due to genetic diversity, large-scale research is necessary to identify healthy biomarkers and validate therapies. The fundamental study is completed until clinical applications require overcoming ethical and legal barriers.

The clustered regularly interspaced short palindromic repeats (CRISPR) and CRISPR-associated protein 9 (Cas9) system are one of the most important strategies that contain palindromic repeats separated by short stretches of DNA called spacers. Spacers from foreign nucleic acids are incorporated to provide immunity against specific diseases[52]. The therapeutic application of CRISPR-Cas9 has raised great hope for curing diseases.

Conclusions

By examining the epigenetic alterations in childhood asthma, this review sheds light on the underlying mechanisms of the illness and the newer possibilities for precision therapy. These biomarkers have the potential for early diagnosis, risk assessment, and treatment of asthma; especially, DNA methylation, histone modifications, and ncRNAs. Epigenetic-based therapies can be made possible by advances in epigenomic technologies raising the prospect of individualized and focused treatments to enhance asthma control in children.

Author contributions

The authors confirm contribution to the paper as follows: study conception and design: Soni P; draft manuscript preparation, editing & revision: Soni P, D'Souza E (lead); compiled the predictive models for asthma exacerbations: D'Souza E. Both authors reviewed the results and approved the final version of the manuscript.

Data availability

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

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Conflict of interest

The authors declare that they have no conflict of interest.

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