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Review Article

Asthma: Why Pharmacogenomics Cannot Deliver a Decisive Prognosis

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Abstract

In its "multifactorialness, asthma, as a condition, has continued to see a marked increase in prevalence. Even though this may be tied to the population explosion that is witnessed in the world, the multifactorial nature of the condition makes it an ever-present issue in the world today. The condition's prognosis is not tied to how very developed a certain country is; as such, it is necessary to approach it as a global phenomenon affecting all and sundry. This, therefore, requires an increase in the research into its existential prevalence. Health research foray into pharmacogenomics has shown great promise in tackling many genetically induced medical conditions. Thus, even though the process is financially demanding, its promise should not be downplayed. The simple question that this inquiry seeks to underscore is, why is pharmacogenomics stunted in dealing decisively with the asthmatic condition in individuals, ergo ensuring that we still have this as an issue? We might say that it is because it is multi-factorial, a combination of genetic and environmental factors. However, this clause is not as simple as it presents itself. Therefore, the inquiry still stands. This research seeks to bring to the fore the most recent advancement in that which pertains to the asthmatic condition, including the pharmacological breakthroughs that have been witnessed. However, the above-stated inquiry as to pharmacogenomics and its failure in dealing decisively with the asthmatic condition remains.

Abbreviations

FEV_1: Forced Expiratory Volume in 1 second; FVC: Forced Vital Capacity; PEF: Peak Expiratory Flow; CXR: Chest X-Ray; FeNO – Fractional exhaled nitric oxide; a marker of Type 2 (eosinophilic) inflammation. TNF-α: Tissue Necrosis Factor Alpha; IL (interleukins): Broad group mediating immune responses (e.g., IL-4, IL-5, IL-13); CXCL1 (GRO-α), CXCL2 (GRO-β), CXCL5, CXCL6, CXCL8 (IL-8): Major neutrophil chemoattractant; MCP (CCL2): Monocyte Recruitment; HLA-DQ: Human Leucocyte Antigen- DQ; SMAD3: TGF-β Signaling Protein; Chr 17 (ORMDL3 / GSDMB): Chromosome 17 and its attendant proteins; Chr 22 (IL2RB): Chromosome 22; TSLP: Epithelial Alarmin; ADAM33: Airway Remodeling and Bronchial Hyperresponsiveness; HBEC: Human Bronchial Epithelial Cells (key disease drivers); IL5RA: Eosinophil Survival and Activation; APA2: Adaptor Protein Involved in Immune Signaling; ADRB2: β_2-Adrenergic Receptor; CpGs: DNA Methylation Sites; DNMT1: DNA Methyltransferase (maintenance methylation); MBD2: Methyl-DNA Binding Protein; TET enzymes: DNA Demethylation; PM20D1: Epigenetically Regulated Metabolic Gene; p300 / CBP: Histone Acetyltransferases (HATs); KAT2A: HAT is Involved in Transcription Activation; SMYD3: Histone Methyltransferase; HDAC1: Histone Deacetylase, Inflammation Regulation; SIRT (sirtuins): NAD^+-Dependent Deacetylases, Steroid Sensitivity; METTL3 / WTAP: m^6A "writers"; YTHDF1 / YTHDFs: m^6A "readers"; IGF2BPs (e.g., IGF2BP2): m^6A readers, mRNA stabilization; FTO: m^6A "eraser."

Introduction

Asthma, as a chronic inflammatory condition, is marked by a varied repertoire of symptoms ranging from wheezing, dysnea, orthopnea, cough, confusion, etc. The way in which these symptoms presents itself can lead to a misalignment of diagnosis [1]. It is properly referred to as an obstructive respiratory disease (in line with others such as Chronic obstructive pulmonary disease and bronchiectasis). Even in its being obstructive, the fact about the condition is that it is the body's response to certain environmental triggers, such as allergens, air pollution, tobacco smoking, viral infections, etc. This goes to imply that it is somewhat an immune reaction (the body's defense) to ensuring homoeostasis in the face of an offending agent. This reaction leads to inflammation, bronchoconstriction, and mucus filling. These, therefore precipitates the symptomatic visuals of what is presented. The developmental presentation of asthma is seen in children, and it may or may not manifest with other conditions that are tied to atophy such as eczema and hay fever [2].

Asthma can also be considered a disease with different phenotypes that are marked with distinctively defined inflammatory and molecular endotypes whose presentation is characterized by a robust airway inflammatory response and hyperactivity [3]. Therefore, we can categorize this condition as phenotypic and endotypic in its orientation. The phenotypic categorization includes

1. Allergic Asthma (AA)
2. Eosinophilic asthma
3. Aspirin exacerbated respiratory disease (AERD)
4. Neutrophilic asthma
5. Obesity associated asthma
6. Exercise-induced bronchoconstriction [4]

The inflammatory endotypic categorization includes:

A. High T2 asthma

B. Non-T2 asthma [5].

To properly diagnose this condition, it is important to obtain the patient's history and embark on certain respiratory examination especially Spirometry, which measures the FEV_1, FVC, and the FEV_1/FCV ratio), the PEF (which measures the maximum speed of expiration), a bronchodilator reversibility test (that occurs alongside spirometry), Fractional exhaled Nitric Oxide (which measures the eosinophilic inflammation of the airways) and others like CXR.

Methodology

This review adopts a comprehensive narrative approach to examine the intersection of pharmacogenomics, epigenetics, and asthma pathophysiology. The inquiry is structured around a central question: why pharmacogenomics has not yet delivered a decisive prognosis for asthma despite significant advances in genetic and molecular understanding. To address this, we systematically synthesized evidence from peer-reviewed literature published between 2000 and 2025, focusing on key databases such as PubMed, Scopus, and Web of Science. Inclusion criteria prioritized studies involving genome-wide association studies (GWAS), epigenetic modifications (e.g., DNA methylation and histone acetylation), and their impacts on asthma phenotypes, drug responses (e.g., to inhaled corticosteroids and beta-agonists), and clinical outcomes. Grey literature, including conference abstracts and preprints from medRxiv, was also consulted to capture emerging trends. The narrative synthesis involved thematic analysis to identify gaps, such as the underrepresentation of epigenetic-drug interactions in diverse populations and the challenges of translating polygenic risk scores into personalized prognostic tools. No formal meta-analysis was performed due to heterogeneity in study designs and endpoints; instead, qualitative integration highlights translational barriers and proposes future directions for integrating multi-omics data in asthma management.

Pathophysiology

The pathophysiology of asthma is properly tied to the respiratory epithelium- the pseudostratified ciliated columnar (PCC) epithelium (with goblet cells). In the presence of a trigger that is consistent and unabating, there are marked changes to the PCC epithelium and also the goblet cells therein. These changes include:

I. Shedding of the epithelium, beginning from the cilia,

II. Hyperplasia of the goblet cells with the thickening of the basement membrane

The above two will therefore occasion the other presentable changes that are seen, which include:

I. Ciliary dysfunction (this arises as a result of epithelial shedding, in which case a bloated responsiveness is seen, which includes the loss of barrier function - thereby allowing the ease of access to allergens; loss of enzymatic functioning that aids in the breakdown of inflammatory mediators; and exposure of the sensory nerves that will enable reflex neural effects on the airway [6])

II. Mucus plugging

III. Bronchospasms,

IV. Airway obstruction and remodeling.

What is being said is that in asthma, it is the obstruction to ventilation that is the real danger. Although it is of note that the remodeling that is seen in asthma is very much reversible.

The pathophysiology of asthma also takes into cognizance the fact that it can also be atopic or non-atopic. Therefore, in elaborating a pathophysiology of asthma, we define it according to

A. Non-atopic (Inflammatory) pathophysiology and

B. Atopic pathophysiology

Atopic pathophysiology

This pathophysiology generally starts in the child or the adolescent. It is linked to externally provoked triggers and is traceable to familial connections of atopy, such as eczema and rhinitis [7,8]. This is marked by the circle of initial sensitivity with the IgM approach, accompanied by a second wave of allergen attack marked by a more robust IgG approach to the offending agent. This is typical of the type I hypersensitivity reaction, which is mediated by IgE. This is seen in more of the asthmatic conditions. Thus, when there is an exposure to an offending agent such as house dust mites, pollens, dander

from domesticated animals, tobacco smoke, and fumes, etc., there is an initiation of the proceedings that culminates in what is seen as the aforementioned "presentational" changes that define the airway, leading to airflow obstruction. The pathophysiology of this form has its triggers more externally than internally.

The circle of its pathophysiology, therefore, at the point of the offending agent or trigger, the airway epithelial cells release innate cytokines (IL 25/33) which are not of the class of the Th2. These local cytokines induce APC cells, and these cells elicit a differentiation of the naive T cells. This leads to the production of Th2 cytokines (IL4/5/9/13). IL-4 enables the production of IgE, which binds to the mast cells awaiting a second wave of offence from the allergen. In the second wave of offense, there is mast cell degranulation [3]. This leads to the release of mediators like Histamine (this causes bronchoconstriction, vasodilation), Heparin (which contributes to the edema that is seen in bronchi), and TNF-alpha (that recruits other immune cells). After degranulation, mast cells yet enables the synthesis of other mediators like the leukotrienes, prostaglandins, and other cytokines (this is what is referred to as mast cell activation). The recruitment of these mediators that are newly synthesized leads to heightened responsiveness or hyperresponsiveness from the airway to the allergen.

Non-atopic (inflammatory) pathophysiology

This is also known as the IgE-independent, and the inflammatory changes that mark the non-atopic are different from that which is seen in the atopic. And the reason this is subnamed inflammatory is that, rather than the eosinophils that define the immune response to the atopic, it is neutrophils that combat the offending agent, and the offending agent is more internally orchestrated (as seen in and by infections) [7] than externally. The age group of patients that fall into this class is adults. That is to say that the non-atopic is linked to the adult onset of asthma.

In this, it is the infection that is the major trigger to the immune response, and the cytokines that are released due to the infection are IL-6/8/17 and TNF-alpha by the respiratory epithelium. These cytokines (IL-6 promotes local inflammation while IL-8 enables neutrophil chemoattraction, TNF-alpha, amplifies the action of the other cytokines, and also contributes to airway remodeling, when there is persistence, IL-17 contributes to AHR) enable the recruiting of the neutrophils, which then exacerbate the system as seen by AHR, and the eventual "presentational" changes that are witnessed.

In sum, the evidential properties of what is presented as a case of asthma are the same for both atopic and non-atopic kinds.

Endotypic classification of asthma

There are three types to this classification, and they, as earlier noted, are Th2 low and Th2 high.

1. High-Th2 inflammation – It includes AA, eosinophilic asthma, and AERD [3].

Even though it is seen in the adult population, this endotype has been described in children with mild, moderate, and severe asthma and is characterized by a high degree of atopy, increased eosinophils (in sputum and serum), high levels of T2 cytokines (IL-4, IL-5, and IL-13), and early signs of airway remodeling [9]. In this endotype, IL-4 plays a key role in the Th2 differentiation. Cytokines IL-5 and IL-9 are more for differentiation, activation, and survival of eosinophils, and IL-13 induces goblet cell hyperplasia, mucus hypersecretion, airway hyperresponsiveness (AHR), and early signs of airway remodeling [3]. This endotype shows a good response to steroids.

2. Non-Th2 inflammation - Neutrophilic, pauci-granulocytic, and obesity-associated asthma are defined under non-Th2 inflammation. It includes non-Th2 cytokines - IL-17, IL-8, and IL-6, and noninflammatory endotypes where structural abnormalities and neuroinflammation are predominantly found [10]. The subendotypes include:

a. Neutrophilic asthma (NA) is identified as the activation of Th17 cells, associated with an altered innate immune response [10]. The NA is characterized by the following:

   a. Adult onset, which is usually after 12 years

   b. Fixed airway obstruction (marked by low-forced expiratory volume 1 [FEV1]).

   c. Low postbronchodilator response to β2 agonists

   d. Low FeNO (biomarker of eosinophilic asthma), low periostin levels (indicator of IL-13 inflammatory activity), and low prostaglandins (PGE2)

   e. Less response to methacholine bronchial provocation tests

   f. Corticosteroid unresponsiveness

   g. Th17 cytokine milieu - IL-6, IL-8, IL-21, IL-23, IL-17 A/F, IL-1 B, TNF-a, and TGF-B

   h. Chemoattractant chemokines - CXCL1 (Gro-a), CXCL2 (Gro-b), CXCL5, CXCL6, CXCL8 (IL-8), and MCP [10].

b. Severe pauci-granulocytic asthma has no cellular inflammation on biopsy, but thickening of the sub-epithelial basement membrane and inflammation are present in the small airways [10].

c. Mixed granulocytic asthma (MGA) - More severe asthma (T2 high and T2 low) with poor lung function and frequent exacerbations [10].

According to P. Pignatti, et al. based on research done

on MGA shows that it is more akin to the eosinophilic and neutrophilic asthma. Their data showed that.

Asthmatics with mixed granulocytic phenotype are older, have higher sputum cell counts, and a lower prevalence of nasal polyposis than eosinophilic subjects. They had higher blood eosinophils and lower GERD prevalence than neutrophilic patients. Lung function variables and treatment with inhaled corticosteroids were not significantly different [11].

Genotyping asthma's endotypic classification

In a study done by S.F Thomsen, to show the risk or chances of an individual ending up as an asthmatic. It was realized that the highest risk is contained in that of the monozygotic twin, as seen in the Table 1.

Whilst it stands that the 5% with no family history, who turn out to be asthmatic, can be related either to the non-atopic or the atopic (in which case it is going to be idiopathic), the increasing nature of the percentage is closely linked to familial connection. It underscores the point that asides the 5% with no familial connection, the bulk of the risk is upon those who have familial links. If it is familial, then we can trace it down the genetic expression of the family to which the asthmatic belongs [12].

According to Moffatt, et al. reeling off the research done in 2010 known by the Genome Wide Association (GWA) study to identify the genetic associative markers of asthma, the genes of susceptibility are identified on the following chromosomes: chromosomes 2 (*IL1RL1/IL18R1*), 6 (*HLA-DQ*), 9 (*IL33*), 15 (*SMAD3*), 17 (*ORMDL3/GSDMB*), and 22 (*IL2RB*) [13]. However, the *ORMDL3* gene, in particular, was associated with childhood onset, whereas the *HLA-DQ* gene was related to later-onset asthma [12]. These nucleotide polymorphisms (single-nucleotide polymorphism, SNP), for asthma, show the association in those who have asthma in relation to these genes that have been singled out. In reference to the above-listed genes, many have been linked to the cytokines that are seen to be operational in the body of the asthmatic when there is a trigger. Therefore, these Genetic polymorphisms in genes including alarmin cytokines (TSLP and IL-33), type 2 cytokines (IL-4, IL-13), and other inflammation-related proteins (HLA, ADAM33), and the vitamin D receptor have been shown to enhance or reduce the risk and severity of asthma in individuals [14]. There are yet other genes like the APA2, IL5RA etc as seen in the table below that indicate a high genetic susceptibility to asthma. As to Table 2, the researches were done at varied times, and these results were put forward as collated by Douglas da Silva Lima, et al.

Table 1

Affected relative	Person's own risk of asthma (%)
No family history	5
Uncle/nephew/niece	10
Half sibling	10
Full sibling	25
One parent	25
Dizygotic twin	35
Two parents	50
Monozygotic twin	75

Table 2 shows the Characteristics of DNAm studies on asthma, demonstrating heterogeneous techniques applied among the trials [15].

What is being alluded to is that these genes are inherited by the individual. Another very important point to decipher is how they are expressed, that is to say, does the existence of these genes in the individual mean that he/she must be asthmatic? Epigenetics provides a little insight into this.

It should be noted by the side, yet very importantly, that the role of polymorphisms in what pertains to the genes cannot be overlooked in what pertains to drug administration. A good instance is highlighted in reference to the standalone use of SABA (short-acting beta agonist -salbutamol) and LABA (long acting Beta agonist - femeterol). It has been noted that there have been exacerbations of the symptoms presented owing to the polymorphism in the ADBR2 gene. While these drugs can be used for immediate relief, they are not advised for long-term use. The polymorphism of the ADBR2, particularly with the Arg16 homozygotes, will enable a downregulation and a desensitization when SABA or LABA is used [16]. Therefore, in practice, owing to the high cost of genetic sampling, and seeing that there are persons with these variants who are unaware of this, SABA and LABA are used for immediate remedy and not for continued usage. Rather, ICS (inhaled corticosteroids) are used.

The role of epigenetics

From all that has been detailed so far, it is obvious that we have singled out genetics as a major player in what pertains to the condition of asthma. Another major player in this is epigenetics. Simply put, epigenetics refers to an alteration in the expression of a DNA sequence that is of itself not altered in structure (an alteration that is fostered by external influence upon the DNA structure). Since the asthmatic patient (as in all human persons) is in steady interaction with the external world, it goes without saying that Epigenetic regulation plays a critical role in asthma pathogenesis, influencing gene expression through DNA methylation, histone modifications, and RNA modification [17]. The onset and clinical progression of asthma are strongly connected to environmental exposures and genetic susceptibility [18,19] which are heritable. Environmental and genomic aspects, as well as aberrant immune maturation early in life, may engage the disease outbreak [20]. To the three elements of epigenetics - histone modification, DNA methylation, and RNA modification, there are activities of writers and erasers, and these determine the eventual outcome of what is expressed by these proteins. For instance, RNA modification, writers like METTL3 deposit m6A, erasers such as FTO remove these marks, and reader

Table 2

Author	Patients	Sample	Main Results
Reese, et al. 2019	*n* = 1299; Age = 7-17 years old	Whole blood	Identified epigenetic variations related to asthma in newborns and children.
Cardenas, et al. 2019	*n* = 1083; Age = 12 to 65 years old	Nasal swab cells	285 CpG sites associated with asthma.
Arathimos, et al. 2017	*n* = 1529; Age = 7.5 years and 16.5 years	Peripheral blood	IL5RA and AP2A2 gene methylation related to asthma at 16.5 years old.
Popovic, et al. 2019	*n* = 136; Age = 6 to 18 months	Saliva	PM20D1 gene hypermethylation is associated with early childhood wheezing.
Yang, et al. 2018	*n* = 78; Age = 10 to 12 years old	Nasal epithelia	186 genes related to atopy, asthma, immunity, airflow obstruction, and epigenetic regulation.
Ning, et al. 201934	*n* = 182; children. 3 to 14 years old	Peripheral blood	ADAM33 polymorphism is correlated with increased susceptibility to asthma.
Nicodemus-Johnson, et al. 2016	*n* = 115; adults. 26 to 52 years old	Airway epithelial cells	Regulatory locus associated with asthma risk and epigenetic signatures of specific asthma endotypes.

proteins like IGF2BPs and YTHDFs interpret them to regulate RNA stability and the expression of inflammatory mediators [21]. RNA modifications, notably m6A, play a pivotal role in governing immune responses, as alterations in RNA modification regulators within immune cells can influence the expression of genes involved in immunity, inflammation, and pathogen defense. This mechanism contributes to the post-transcriptional control of gene expression in asthma pathogenesis [22]. Table 3 expresses the means by which epigenesis induces the asthmatic outcome.

Table 3 showcases writers and erasers of the three elements involved in epigenetics that pertain to the regulation or induction of asthma. The right regulation of these writers and erasers is key to determining the outcome of these proteins. This study, summarized by the table above, highlights the central role of epigenetically important regulators classified as writers, erasers, and readers of histone, DNA, and RNA modifications in asthma pathogenesis. Dysregulation of histone acetyltransferases (e.g., p300/CBP) and deacetylases (e.g., SIRT1–SIRT7) alters chromatin accessibility, leading to pro-inflammatory gene expression. DNA methylation enzymes such as DNMT1 and DNMT3A, along with demethylases like TET1 and readers like MBD2, modulate immune gene profiles. Additionally, m6A RNA modifiers METTL3/14 (writers), FTO (eraser), YTHDF, and IGF2BP2 proteins (readers) emerge as pivotal regulators affecting asthma susceptibility and severity by influencing inflammatory pathways, immune response modulation, and airway remodeling [21]. Another protein of note is the SMAD3 (SMAD Family Member 3), which is a protein-coding gene located at chromosome 20p13. It plays an important role in immune response regulation and acts together with other proteins to promote fibrosis regulation [45]. The hypermethylation (a dysregulation) of the SMAD3 gene promoter is associated with asthma, particularly in children of asthmatic mothers [15]. A study by DeVries, et al. [46] has shown that children from asthmatic mothers had the SMAD3 gene methylated at birth. The methylation profile was analyzed from cord blood samples of children from three different cohorts [15].

Maintenance below the normal biologic threshold is the core of what occurs in epigenetics. Therefore, the summary of the above is that when there is a dysregulation (leading to the over shooting to the threshold) of these writers and erasers, then the expression of the proteins is tilted away either slightly or elaborately. If the assault is sustained from the environment, then the outcome that was once indefinite assumes a definite core. This protein dysregulation to the elements of epigenetics, is a pivotal aspect in what relates to the expression of asthma, as these proteins are innate regulators against hypersensitivity and hyperreactivity that define the pathophysiology of asthma. Thus, even when there is a genetic susceptibility, these regulators are so important in either ensuring no expression or partial or full expression of the asthmatic condition. More to this, pharmacotherapeutic activity on these proteins working on these genes has been shown to produce hopeful displays in relation to this condition. For instance, the IL5RA gene (Interleukin 5 Receptor Alpha sub-unit) is found on the human chromosome 3. Hypomethylation of the IL5RA gene in Airway Epithelial Cells (AECs) and eosinophils has been shown to be a potential therapeutic target for asthma [15]. This epigenetic finding allowed the study and incorporation of the monoclonal antibody Benralizumab [47] (Anti-IL-5Ra) in clinical practice, a drug that binds to IL5RA, inducing a reduction in exacerbations and improvement in lung function in patients with severe asthma [48].

It is worthwhile noting that even with the definiteness of the knowledge that arises from epigenetics, some aspects yet remain grey to human knowledge. For instance, some exposures to allergens can promote healthier airway development even in the presence of a genetic predisposition to the disease [15], while in other instances, it does not. Also, children from a farm environment who are frequently exposed to allergens, bacteria, fungi, and others from diverse microbiomes, and the consumption of unprocessed cow milk, may develop a strong protective barrier against asthma and allergy. Indeed, children from rural areas have shown a prevalence of allergic diseases lower than that of children from urban environments [15].

Future angles: Why personalised medicine (pharmacogenomics) cannot deliver a decisive prognosis?

A decisive prognosis will ensure that the instances of morbidity associated with asthma are dealt with. That is to say that with a decisive prognosis, morbidity is further

Table 3

Modification type	Role	Examples	Function	References
Histone Modification	Writer	p300/CBP	p300 and CBP are histone acetyltransferases that, with increased expression in asthma, likely activate pro-inflammatory genes, contributing to chronic airway inflammation	[23]
		KAT2A	KAT2A plays a crucial role in acetylating lysine 18 on histone 3, a modification that is found to be elevated in the epithelial cells of individuals with asthma	[24]
		SMYD3	SMYD3 was found to be upregulated at the mRNA level in airway fibroblasts from asthmatic individuals, suggesting its involvement in asthma-related epigenetic dysregulation	[25]
	Eraser	HDAC1	HDAC1 was significantly increased in bronchial epithelial cells (HBECs) of asthmatic patients	[26]
		HDAC2	Patients with mild asthma exhibit a slight decrease in HDAC2 activity in bronchial biopsies and alveolar macrophages.	[27]
		HDAC3	HDAC3 regulates NF-κB activity in asthma by deacetylating specific lysine residues, suppressing inflammation. HDAC3 deficiency in macrophages reduces inflammatory gene expression, underscoring its role in controlling asthma-related inflammation	[28]
		SIRT1	Both protective and deleterious roles in asthma	[29]
		SIRT2	SIRT2 exacerbates asthma-associated inflammation by driving Th2 cell responses and macrophage polarization	[30]
		SIRT3	Song, et al. found that decreased Sirt3 expression in asthmatic mice contributes to increased apoptosis, oxidative stress, and inflammation.	[31]
		SIRT6	Jang, et al. found that Sirt6 is upregulated in asthmatic mice.	[32]
		SIRT7	Fang, et al. found that increased SIRT7 expression in airway smooth muscle cells regulates TGF-β1-induced cell proliferation and migration, highlighting its role in asthmatic airway remodeling.	[33]
DNA modification	Writer	DNMT1	DNMT1 maintains DNA methylation patterns, and reduced levels are associated with increased Socs3 expression, promoting inflammation in asthma	[34]
		DNMT3a	Dnmt3a regulates Th2 responses by modulating IL-13 gene methylation; loss of Dnmt3a decreases methylation, enhancing IL-13 expression and asthma-associated lung inflammation	[35]
	Reader	MBD2	MBD2 is an epigenetic reader protein recognizing methylated CpG sites, suppressing SOCS3 expression, and promoting Th17 cell differentiation. Elevated MBD2 drives neutrophilic inflammation, contributing to severe asthma. a	[36]
	Eraser	TET1	Reduced TET1 promoter methylation (cg23602092) in nasal cells correlates with childhood asthma and traffic-related air pollution, altering TET1 expression and 5hmC. TET1 modulates DNA methylation and epigenetic regulation in asthma	[37]
RNA modification	Writer	WTAP	WTAP was demonstrated to be abnormally expressed in asthma patients WTAP knockdown relieves asthma progression by regulating the m6A levels of AXIN1 in a YTHDF2-dependent manner	[38,39]
		METTL3	METTL3 regulates Th2 cell differentiation in T2 asthma by modulating SOX5 m6A methylation in bronchial epithelial cells. This mechanism may offer a potential target for preventing and managing T2 asthm.a	[40]
	Reader	YTHDF1	YTHDF1, highly expressed in airway epithelial cells of allergic and asthmatic individuals, enhances CLOCK translation in an m6A-dependent manner. This triggers NLRP3 inflammasome activation and IL-1β secretion, promoting inflammatory responses in the airways.	[41]
		YTHDF2	m6A-YTHDF2 regulates macrophage polarization by inhibiting M1 and promoting M2 phenotypes through NF-κB, MAPK, and STAT pathways, playing a key role in asthma subtypes and targeted therapy	[42]
		IGF2BP2	IGF2BP2 promotes asthma by stabilizing Tsc1 mRNA, which helps macrophages adopt the M2 phenotype	[43]
	Eraser	FTO	FTO plays a pivotal role as an eraser of m6A modifications in asthma by regulating the stability of mRNA transcripts such as IKBKB, leading to the activation of the NF-κB pathway and contributing to inflammation and epithelial barrier dysfunction	[44]

reduced till it comes to a permanent stop. However, it is already evident that asthma is a genetic (we are referring to gene polymorphism) + environment + epigenetic control issue. Speaking in terms of an interaction between the three agents, it is clear that the genes have a markedly higher risk of tunneling the individual down that asthmatic black hole. With a percentage of about 35-70%, as seen in Table 1, genetics plays a fundamental role in the emergence of asthma in the individual. However, one cannot rule out the role of the environment that has about 20-40% input in what relates to an asthmatic emergence. The last agent- epigenetics, plays a mediatory role (in addition to its element of chance it harbours), and this is why an exact figure/percentage of its influence cannot be ascertained. Herein lies the difficulty in bringing in personalised medicine into the foray. This is because asthma is not a single-gene disorder, as we find in sickle cell disease (SCD). It is multifactorial. More to this, as in other diseases, it is influenced heavily by an interaction with the environment in which the individual inhabits. But more to be considered is the fact that epigenetics plays a huge mediatory role in all, and its role is so delicately bound to the element of chance, which can and has shown itself to be reversible. Without the role of epigenetics, the definitive dawn of its onset will be determined by the environmental factors or triggers. But epigenetics' input to the asthmatic condition is so vital to its onset that it shows itself to be the true instigator of the onset of the asthmatic condition. I want to hypothetically propose that the input and contribution of epigenetics to the asthmatic condition is not understood; research focuses on this agent for the sake of ensuring that the aspect of chance in its operation is gotten rid of. To this, a better understanding is what is required.

Personalized medicine (pharmacogenomics) has indeed made inroads into the production of a note of finality on what pertains to asthma, as can be instanced via the interleukin (IL)-

4 and IL-13 pathway (that is to say the gene-regulated cytokine pathway) which mediates Th_2 lymphocyte-mediated allergic inflammation by binding and activating a common sub-unit of the IL-4 receptor, the IL-4α receptor sub-unit [49]. Now, in recent clinical trials, a molecular inhibitor of the IL-4α receptor subunit, pitrakinra, and a monoclonal antibody, dupilumab, are effective in preventing loss of symptom control in asthma sub-populations characterized by increased blood or sputum eosinophils. Both biologic drugs block the IL-4α receptor sub-unit (encoded by *IL4RA*), resulting in dual inhibition of a shared IL-4 and IL-13 proinflammatory pathway [49-50]. Other drugs in this category include: Omalizumab (which targets the IL-4/13 IgE elicited pathway), mepolizumab and reslizumab (which target the IL-5 gene), etc., in addition to the older drugs (SABA, LABA, ICS) that have been used for asthma. Drugs are aimed at correcting an anomaly to ensure that the pathology in the pathophysiology is erased, leaving one with a normal functioning physiology. The advent of these drugs is an attestation of the work of pharmacogenomics in relation to asthma. However, these drugs cannot work on the premise of the idiopathic nature of chance. What is being alluded to here is that part of what pertains to asthma is chance, one that is contained in epigenetics. I mean, how can it be that in the event of a hypomethylation, there is either the individual being induced towards the asthmatic condition or being protected against it? It would seem like even though there are advancements made in getting to a decisive treatment for this condition by means of pharmacogenomics, attaining a decisive end to it all appears to be a herculean task. And this is due to the happenstance to which epigenetics reeks.

In avoidance of pessimism, it is to be noted that with more advancement in health technology, better ways would be found to approach this issue with a more robust framework, for future advances in pharmacogenomics research will depend on a continued collaborative effort to recruit and analyze larger, comprehensively characterized asthma populations from different racial and ethnic groups representative of different ancestral backgrounds [49]. To arrive at this, the formation of an "asthma phenotype index", considering molecular and clinical criteria, with predictive values of management would be relevant for asthma diagnosis and modulated treatment [52]. Other positive outlooks would delve into the characterization of epigenetic alterations with a homogeneous approach and standardized techniques for disease outbreak and progress [19]. New studies in the areas of genomics, biochemistry, and genetics can facilitate the understanding of how epigenetic mechanisms influence the evolution of these patients, promoting safer and more economical clinical approaches [15]. The future of pharmacogenomics and its contribution to delivering a decisive prognosis of asthma lies in understanding the operation and biological mediation of epigenetics in all relates to asthma.

Conclusion

Asthma's manifold causative agents are not to be handled in an isolated manner; nonetheless, looking at it from the sub-cellular arena, it is an issue of threshold. This is because we have already seen how dysregulation of these proteins (epigenetics) would lead to a variant expression (although not in all cases). And these proteins have their own isolated frame from which they operate. It is more or less like a symphony, with each person playing or singing his part without reference to the other, thereby producing a coordinated sound. Every sub-cellular proteinous element also engages in this; we refer to asthma as a threshold problem because there can be varied assaults, but if that threshold is not reached, then all is maintained according to the status of normalcy. And even if the threshold is met in one, a counter-regulatory effect has the propensity to make it silent (ensuring that the threshold is not met), thereby ensuring that the individual does not express the symptom. In other aspects, it is that the development process for those who have atopic asthma can focus on the regulations that are to be found in place. Thus leading to the fact of an eventual non-show of the asthmatic symptoms as the child or adolescent becomes an adult. The difficulty of pharmacogenomics in the asthma problem is the individuality in operations on these subcellular elements. It thus calls for a more robust approach as science advances. But for now, all that can be said is that since the human person is in constant rapport with the environment, asthma (especially the atopic) has all the underpinnings of the type 1 hypersensitivity reactions; there is a need for better sensitization to the effects of pollution in the environment. More to this, since it is reversible in its effect, management of the condition is primary to survival.

Author contributions

The author stands as the sole proprietor of the conceptualization, literature review, manuscript drafting, critical revision, and final approval of the manuscript.

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