Asthma exacerbations: the genes behind the scenes

Short Title: **Omics of asthma exacerbations**

Herrera-Luis E[1], Forno E[2], Celedón JC[2], Pino-Yanes M[1,3,4†*]

[1]Genomics and Health Group, Department of Biochemistry, Microbiology, Cell Biology and Genetics, Universidad de La Laguna (ULL), La Laguna, Tenerife, Spain

[2]Division of Pediatric Pulmonary Medicine, UPMC Children's Hospital of Pittsburgh, University of Pittsburgh, Pittsburgh, Pennsylvania, U.S.A.

[3]CIBER de Enfermedades Respiratorias, Instituto de Salud Carlos III, Madrid, Spain

[4]Instituto de Tecnologías Biomédicas (ITB), Universidad de La Laguna (ULL), La Laguna, Tenerife, Spain

Corresponding author:

Dra. María Pino-Yanes
Genomics and Health Group. Department of Biochemistry, Microbiology, Cell Biology and Genetics
Universidad de La Laguna (ULL)
Apartado 456, 38200, La Laguna, Tenerife, Spain
E-mail: mdelpino@ull.edu.es

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ABSTRACT

The clinical and socioeconomic burden of asthma exacerbations (AEs) represents a major public health problem. In the last four years, there has been an increase in ethnic diversity in candidate-gene and genome-wide association studies (GWAS) of AEs, which in the latter case has led to the identification of novel genes and underlying pathobiological processes. Pharmacogenomics, admixture mapping analyses, and the combination of multiple “omic” layers have contributed to prioritizing genomic regions of interest and/or understanding the functional consequences of genetic variation. Despite this, the field still lags behind the genomics of asthma, where a vast compendium of genetic approaches has been used (e.g., gene-environment interactions, next-generation sequencing, or polygenic risk scores). Furthermore, the roles of the DNA methylome and histone modifications in AEs have been scarcely investigated, and microRNA findings remain to be validated in independent studies. Likewise, the most recent transcriptomic studies highlight the importance of host-airway microbiome interaction in the modulation of AEs risk. Leveraging -omics and deep-phenotyping data from sub-types or homogenous subgroups of patients will be crucial to overcome the inherent heterogeneity of AEs, and boost the identification of potential therapeutic targets and the implementation of precision medicine in clinical practice for AEs.

KEYWORDS: Asthma exacerbations. Genomics. Epigenetics. Transcriptomics.

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RESUMEN

La carga clínica y socioeconómica de las exacerbaciones asmáticas (EA) representa un importante problema de salud pública. En los últimos cuatro años, ha aumentado la diversidad étnica en los estudios de asociación de genes candidatos y del genoma completo (GWAS) de las EA, lo que en este último caso ha llevado a la identificación de nuevos genes y procesos fisiopatológicos subyacentes. La farmacogenómica, los análisis de mapeo de por mezcla y la combinación de múltiples capas "ómicas" han contribuido a priorizar regiones genómicas de interés y/o comprender las consecuencias funcionales de la variación genética. A pesar de esto, el campo todavía está en desarrollo en comparación con la genómica del asma, donde se ha utilizado un amplio compendio de enfoques genéticos (por ejemplo, interacciones gen-ambiente, secuenciación de nueva generación o puntuaciones de riesgo poligénico). Además, el papel de la metilación del ADN y las modificaciones de las histonas en las EA se han explorado escasamente, y los hallazgos relacionados con los microARNs aún no se han validado en estudios independientes. Asimismo, los estudios transcriptómicos más recientes destacan la importancia de la interacción entre el microbioma de las vías respiratorias y el huésped en la modulación del riesgo de las EA. La integración de datos ómicos y de fenotipado profundo de subtipos o subgrupos homogéneos de pacientes será crucial para superar la heterogeneidad inherente de las EA e impulsar la identificación de dianas terapéuticas potenciales y la implementación de la medicina de precisión para las EA en la práctica clínica.

PALABRAS CLAVE: Exacerbaciones asmáticas. Genómica. Epigenética, transcriptómica.

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ABBREVIATIONS

AEs	Asthma exacerbations
AUC	Area under the curve
ChIP-Seq	Chromatin immunoprecipitation sequencing
COPD	Chronic obstructive pulmonary disease
CpG	Cytosine-phosphate-guanine
DMRs	Differentially methylated regions
DNAm	DNA methylation
eQTM	Expression quantitative trait methylation
eQTL	Expression quantitative trait loci
EWAS	Epigenome-wide association study
FeNO	Fractional exhaled nitric oxide
FEV_1	Forced expiratory volume in one second
GxE	Gene-environment
GWAS	Genome-wide association study
GWIS	Genome-wide interaction study
ICS	Inhaled corticosteroids
LABA	Long-acting beta2-agonists
lncRNA	Long non-coding RNA
miRNA	Micro-RNAs
mRNA	Messenger RNA
OCS	Oral corticosteroids
PGWAS	Pharmacogenomics GWAS
PGWIS	Pharmacogenomics GWIS
PRS	Polygenic risk score
TNF	Tumor necrosis factor
UK	United Kingdom
US	United States
WGCNA	Weighted gene co-expression network analysis

DEFINITIONS

- Candidate-gene association study: Statistical approach that interrogates the association of genetic variation with a trait of interest, analysing genomic regions selected based on a biological hypothesis.
- Genome-wide association study (GWAS): Agnostic scan of genetic variation across the genome for association with a trait of interest.
- Genome-wide interaction study (GWIS): Agnostic scan of the interaction between genetic variation across the genome and a factor of interest (e.g., environmental or genetic factors) on a phenotype under study.
- Admixture mapping: gene mapping approach that investigates whether chromosomal ancestry (local ancestry) is associated with a trait of interest, allowing the detection of genomic regions harbouring genetic variants that exhibit ancestry differences.
- Next-generation sequencing (NGS): high-throughput technology that allow determining the DNA sequence of single DNA molecules in parallel. These methods involve DNA fragmentation, DNA sequencing, and mapping to an organism's reference genome to detect the genetic variation of a given sample.
- Whole exome sequencing (WES): next-generation approach that allows detecting genetic variation in the genomic protein-coding regions (exons).
- Whole genome sequencing (WGS): next-generation approach that determine the DNA sequence in the entire genome.
- Epigenome-wide association studies (EWAS): agnostic scan of epigenetic markers, usually DNA methylation, across the genome for association with a trait of interest.
- Transcriptome-wide association studies (TWAS): agnostic gene-based scan of gene expression across the whole genome for association with a trait of interest.
- Proteome-wide association studies (PWAS): agnostic scan of protein expression for association with a trait of interest.
- Metabolome-wide association studies (MWAS): agnostic scan of metabolite levels for association with a trait of interest.
- Quantitative trait locus (QTL): position of the DNA sequence where genetic variation is associated with a quantitative trait, such as DNA methylation (methylation quantitative trait locus, meQTL), gene expression levels (expression quantitative trait locus, eQTL), splicing ratios of transcripts (splicing quantitative trait locus, sQTL), protein levels (protein quantitative trait locus, pQTL) or metabolite levels (metabolic quantitative trait locus, mQTL).
- Expression quantitative methylation (eQTM): position of the DNA sequence where methylation levels are associated with gene expression levels.

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INTRODUCTION

Asthma exacerbations (AEs) are episodes of worsening symptoms requiring a change in treatment. AE events can be severe, and while multiple criteria have been used in the literature [1], a common definition comprises asthma-related hospitalizations, emergency department (ED) visits, and the use of systemic (oral, intramuscular, or intravenous) corticosteroids. However, this definition should be regarded cautiously because it often relies on a subject's self-report without incorporating other clinical or physiological parameters capturing the underlying pathophysiology of the episode [2].

AEs are a major public health problem and a priority in asthma research. Each year, approximately 75,000 people are hospitalized, and 15,000 people die from asthma in the United Kingdom (UK) [3]. In the United States (US), there are ~170,000 asthma-related hospitalizations, 1.8 million ER visits, and ~4,000 asthma-related deaths per annum. In fact, yearly asthma healthcare expenditures amount to £1.1 billion in the UK [4] and $50.3 billion in the US [5]. Indirect asthma costs, such as work and school absences, further increase the economic impact of asthma [5]. Moreover, AEs affect the quality of life of individuals with asthma [6,7] and their caregivers [8]. Although several studies have found an association between AEs and lung function decline [9–13], infants with a reduced airway calibre may also be at higher risk of loss of lung function and AEs [14,15]. In fact, the baseline airway wall area percent, an indicator of airway remodelling, is associated with the annual rate of future AEs and long-term decline in lung function [16,17].

To date, the best predictor of AEs is having had one within the last year [18–20], highlighting the key roles of genetic factors and/or early-life determinants. In addition, identifying clinically relevant biomarkers or predictors of AEs is crucial to guide the reduction and prevention of AEs. AEs are likely due to the complex interplay of genetic, environmental, and behavioural factors [18,21–23]. In fact, risk factors for AEs

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comprise allergen, air pollution or tobacco exposure, viral infections, psychological stress, treatment adherence, obesity, or genetic factors, among others [18].

Ethnic differences in the patterns of AEs are evidenced worldwide. In the US, African Americans and Puerto Ricans exhibit higher rates of AEs [24–28], while in Europe, AE rates are higher in Southern European countries [29]. African Americans are also more likely to have longer lengths of stay in intensive care units compared with Europeans [30]. In fact, African ancestry has been associated with AEs among African Americans [31] and other individuals of African descent in the US [32]. However, this association has not been validated for the number of exacerbations [33] or in Puerto Ricans [34], a recently-admixed population with up to ~25% African ancestry [34,35]. More recent findings suggest that the association of African ancestry and asthma re-admissions in African Americans may be mediated by disease management and socioeconomic factors [36].

A detailed description of genetic association studies of AE published until 15th November 2018 was previously reported by Herrera-Luis et al. [16]. Gautam et al. [37] reviewed the transcriptomics of asthma susceptibility, disease severity, and AEs prior to 2022, but no extensive summary of epigenetic studies of AEs has been published. In this review, we discuss the latest findings from -omics studies of AEs, assess methodological challenges, and propose future directions in this research field. For that purpose, we provide an update on the state of the art of the genomics and transcriptomics of AEs from the aforementioned dates to 1st October 2022 and review the epigenetic articles of AEs ever published.

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LITERATURE MINING

Literature mining of genomic, epigenetic, and transcriptomic studies of AEs was conducted in PubMed [38] applying the following search terms: (Transcriptomics [Title/Abstract] OR Candidate gene [Title/Abstract] OR polymorphism [Title/Abstract] OR SNP [Title/Abstract] OR Genetics [Title/Abstract] OR GWAS [Title/Abstract] OR EWAS [Title/Abstract] OR epigenetic [Title/Abstract] OR methylation [Title/Abstract] OR histone [Title/Abstract] OR micro RNA [Title/ Abstract] OR mRNA [Title/ Abstract] OR transcriptomics [Title/ Abstract]) AND (asthma with exacerbations [Title/Abstract]). We excluded manuscripts reporting 1) reviews, editorials, or opinion articles, 2) findings in animals or cell lines, or 3) no data on -omics or candidate-gene associations with AEs.

GENETIC ASSOCIATION STUDIES

The genetic determinants of AEs have been thoroughly investigated using hypothesis-driven approaches to select genomic regions of interest [1] (**Figure 1A**). However, candidate-gene association studies are hampered by non-reproducibility across studies and a low likelihood of identifying true biological risk variants because of the polygenic structure underlying complex human traits [39]. Conversely, genome-wide association studies (GWAS) allow for agnostic interrogation of genetic variation across the genome for association with a trait. These hypotheses-free strategies can uncover novel pathogenic mechanisms, potentially leading to new therapeutic targets [40] (**Figure 1B**). Most genetic association studies have investigated single nucleotide polymorphisms (SNPs), which are base substitutions at a single position in the genome sequence. Although rare genetic variation (<1% minor allele frequency) may be implicated in the pathophysiology of AEs, whole-genome or exome association studies are yet to be conducted for AEs (**Figure 1C**).

In populations resulting from the admixture of two or more ancestral populations, admixture mapping analysis can be an alternative strategy to avoid the high penalty of statistical significance in GWASs, particularly in genetically complex populations often underrepresented in biomedical research [41–43]. Briefly, differences in the number of copies of alleles inherited from distinct ancestral populations at a given locus, or "local ancestry", can be leveraged to distinguish candidate regions where local ancestry is associated with a trait of interest (**Figure 1D**). Genetic variants within the biologically plausible candidate region are then interrogated for association with the trait to identify causal variants that usually evince distinct allele frequencies between ancestral populations [41,42,44].

Since the most frequently used approaches to identify susceptibility alleles for AEs are biased to uncover variants with modest effect sizes (i.e., candidates gene studies) or located in non-coding regions of the genome (i.e., GWAS), it is imperative to comprehensively assess the functional impact of genetic variation [1,45]. In this context, investigating the effect of variants on different -omic layers (**Figure 1E**) has become easier, given the availability of multiple free tools online (e.g., see [46–49]).

Candidate-gene association studies. Most candidate-gene association studies of AEs focused on polymorphisms in genes previously implicated in asthma or in viral pathways [1], such as the Interleukin 33 (*IL33*) [50], vitamin D receptor (*VDR*) [54], or *SERPINE1* gene encoding for the plasminogen activator inhibitor-1 (*PAI-1*) [52] (**Table 1**). For instance, adding several asthma-related variants at *SPATS2L* and *IL33* that were associated with ED management failure to ED-related clinical scores improved the predictive capability for ED management failure compared with the clinical model alone (area under the curve [AUC]: 0.82 *vs.* 0.79, $p = 0.0004$) [50]. Moreover, an expression quantitative trait loci (eQTL) analysis of respiratory syncytial virus (RSV)-related genes narrowed down the modulatory effect of RSV infection on a *CEACAM3* locus for AEs [53]. Likewise, a candidate-gene association study of six genomic

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regions harbouring genes whose combined sputum gene expression signature exhibited predictive capability for exacerbations uncovered a *DNASE1L3* locus for AEs associated with *DNASE1L3* transcript expression levels in asthma-related tissues [56].

The first GWAS of asthma revealed variants at chromosome 17q12-21 with larger effects on asthma in children than adults [64], whose effects may be intensified by early-life and passive tobacco smoke exposure [65,66]. As expected for the most consistently replicated signal for asthma across populations, genetic variation and gene-by-environment (GXE) interactions for chromosome 17q12-21 have been investigated in relation to AEs [1,67]. More recently, the effect of *GSDMB* SNP rs7216389 on AEs was found not to be modulated by prenatal second-hand smoke exposure in Danish children [68]. Several 17q12-21 variants are associated with expression levels of nearby genes in bronchial epithelial cells and located within binding sites for Interferon regulatory factors, suggesting effects through antiviral pathways [59], consistent with previous GxE evidence on asthma susceptibility [67].

Two recent studies of Korean subjects with asthma revealed genetic associations for AEs in *NLRP4* and *OXSR1* that differed by smoking status [51,62]. NLRP4 is a regulator of the inflammasome acting as an inhibitor of type I interferon signalling, tumor necrosis factor (TNF)-α and IL-1β-mediated NF-κB activation [69]. Conversely, *OXSR1* encodes an oxidative stress responsive kinase that participates in ion transport and cell volume homeostasis [62]. In fact, *OXSR1* expression was increased by smoke exposure and glucocorticoid treatment in various airway cell types [62].

In the reviewed period, four candidate gene studies have explored susceptibility variants for response to inhaled corticosteroids (ICS) [60,61,63,70], long-acting beta2-agonists [55], or montelukast [58] using AEs as a clinical endpoint. Four of them assessed asthma-related genes: *IL1RL1* [60] and *CRHR1* [61] for ICS, *ADRB2* [55] for LABA, and *LTA4H* [58] for montelukast response. The other two combined or integrated multiple omics to prioritize candidate genes [63,70]. Hernandez-Pacheco et

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al. [57] identified a member of the family of latent-transforming growth factor-beta binding proteins (*LTPB1*) as differentially expressed after glucocorticoid exposure in several transcriptomic datasets from airway smooth muscle cells and peripheral blood mononuclear cells. Within *LTBP1*, two polymorphisms associated with AEs exerted ethnic-specific effects [70]. Kan et al. [63] leveraged a previous GWAS of change in forced expiratory volume in one second (FEV_1) after ICS treatment ($p<1\times10^{-4}$), chromatin immunoprecipitation sequencing (ChIP-Seq), and transcriptomics to develop a multi-omics integrative score that prioritized a locus harbouring a member of the family of inhibitor of apoptosis proteins (*BIRC3*) near glucocorticoid receptor-binding sites. The *BIRC3* locus was significantly associated with AEs -despite ICS use- in Hispanics/Latinos, African Americans, and Europeans [63].

GWAS. Six non-pharmacogenomic GWAS of AEs were published in the reviewed period (**Table 2**). An asthma-related *HLA-DQB1* locus was associated with AEs in British adults and Hispanic/Latino children, possibly through regulatory effects over HLA genes [71]. In European children, a study comparing participants with AEs and individuals without asthma revealed a novel genome-wide signal at *FUT2/MAMSTR*, along with several previously asthma-related loci, as expected of such a comparison strategy [74]. Interestingly, the epistasis of a functional *FUT2* SNP with an *ABO* SNP increased the risk of respiratory infection with *Streptococcus pneumoniae* [74].

Most genetic association studies of AEs have been conducted in Europeans [16], but recent substantial efforts have increased ethnic diversity and representation [72,73,75–77]. As a result, the largest GWAS meta-analysis of severe AEs in Hispanics/Latinos children (n=4,010) uncovered a genome-wide significant association in *LINC03033,* a long non-coding RNA (lncRNA) that participates in myofibroblasts differentiation and airway remodelling [72]. The risk allele for AEs was associated with higher DNA methylation (DNAm) levels at *LINC03033* in nasal epithelium, which in turn was

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associated with higher expression of *KCNJ2-AS1* [72], also overexpressed in atopic asthma [84]. Another recent GWAS compared asthma cases with AEs to controls without asthma to overcome the reduced statistical power derived from the complex genetic structure in recently-admixed populations in order to identify genetic signals for asthma with AEs in Hispanic/Latino and African American children [73]: a genome-wide significant locus nearby lncRNA *LINC01913* was associated with asthma with severe exacerbations, possibly through *LINC01913* expression in lung and DNAm of *PKDCC* in blood. While *LINC01913* function remains unknown, PKDCC is involved in lung development and mediates various homeostatic cellular processes [73]. Likewise, an intronic variant in the *MYT1L* gene, encoding for a regulator of proteins of the nervous system, was associated with the annual number of AEs in Koreans [75]. More recently, a multi-ancestry meta-analysis of GWAS of AEs identified two suggestive variants associated with blood DNAm or expression levels of genes participating in inflammation and host defence (*VCAM1*, *EXTL2*, and *PANK1*) [76].

Pharmacogenomic GWAS (PGWAS) of AEs have identified susceptibility variants for response to ICS [1,77,80,82,85] and LABA [79]. Genomic regions harbouring the loci suggestively associated with AEs in children receiving ICS are implicated in response to viral infections (*APOBEC3B/APOBEC3C* [77]), baseline lung function (*CACNA2D3* [86]), bronchodilator responsiveness (*CACNA2D3* [87]), or the Wingless/integrase 1 signalling (*WNT5A*) pathway [80]. Moreover, two studies considered AE despite ICS use as a secondary outcome to validate genetic associations for ICS response at *EDDM3B* [78] and *ROBO2* [81]. While the *EDDM3B* and *APOBEC3B/APOBEC3C* variants exerted similar effects across several ethnic backgrounds [77,78]), *CACNA2D3/WNT5A* and *ROBO2* loci exhibited effects specific in children of European descent [80,81].

In addition, a recent study in older adults of European ancestry with asthma treated with ICS uncovered 152 suggestive associations for AEs defined using diagnosis

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codes, and a genome-wide signal for oral corticosteroid (OCS) use nearby *PTCHD4,* which encodes a regulator of hedgehog signalling previously associated with airway disease [82]. Furthermore, a genome-wide interaction study (GWIS) of age on AEs despite ICS use found genome-wide significant signals in genes implicated in angiogenesis, lung function and chronic obstructive pulmonary disease (COPD) (*THSD4*), inflammatory and immune processes, and glucocorticoid response (*HIVEP2*) [83]. Moreover, the only multi-ancestry meta-analysis of GWAS of AEs despite LABA use discovered suggestive associations within genes previously implicated in lung function (*TBX3* [88]) and response to short-acting beta2-agonists (*EPHA7* [89]).

As previously indicated, some studies aimed to shed light into the role of genetic variation by assessing their functional and biological impact. For instance, *CACNA2D3/WNT5A* and *ROBO2* variants were associated with the expression of proteins involved in asthma pathophysiology in plasma [80,81]. Gene-level analysis stratified by smoking status in Koreans revealed that significant genes in non-smokers were enriched for T-cell immune responses and DNA/RNA modifications, while tissue development and apoptosis were the most important processes in smokers [75].

Genetic variants associated with AEs despite ICS use in European adults are enriched in genes implicated in protein and fatty acid metabolism, toll-like receptor signalling, antigen cross-presentation, or vesicular transport [82]. Among European children treated with ICS, genetic variants associated with AEs were enriched in asthma-related genes that showed differential expression under trichostatin A exposure [80]. Trichostatin A is an antifungal antibiotic with histone deacetylase activity that has been shown to reduce airway inflammation and hyperresponsiveness [90]. Interestingly, histone deacetylase participates in the regulation of corticosteroid sensitivity [91]. Overall, these findings support further investigation of the therapeutic potential of trichostatin A in asthma.

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Admixture mapping. Admixture mapping studies have identified genetic variants associated with asthma, IgE levels, bronchodilator response, and lung function [42,94], but only two admixture studies of AEs have been published (**Table 3**). The only admixture mapping of AEs independent of treatment conducted in Hispanics/Latinos revealed significant associations for AEs with Indigenous American ancestry at chromosomal regions 5q32, 13q13-q13.2, and 3p13. The 5q32 SNP rs1144986 (*C5orf46*) was significantly and consistently associated with AEs in Mexican Americans and Puerto Ricans, but was not validated in non-Hispanics/Latinos. The risk allele of rs1144986 was associated with altered *DPYSL3* DNAm levels and lower gene expression of *SCGB3A2* in blood. While *DPYSL3* may be involved in airway remodelling, *SCGB3A2* is an upstream regulator of TGFβ-mediated antifibrotic processes in the lung [92].

Another study investigated the association of local ancestry with response to different step-up regimens including ICS in 516 subjects with asthma of African descent [93]. The primary outcome was a composite score comprising AEs, a 31-day difference in annualized asthma-control days, and a 5% difference in percent predicted FEV_1. African ancestry at 12q24.22-q24.23 was associated with better responsiveness in children that transitioned from low-dose ICS to the quintuple dose of ICS compared to those who received 100 µg fluticasone plus salmeterol. Moreover, African ancestry at chromosome 22q12.1 was associated with better responsiveness in adults that transitioned from low-dose ICS to the quintuple dose of ICS compared with those who received 2.5 times the ICS dose. Analysis of genetic variants within these regions revealed one SNP that was consistently replicated for association with AEs in African Americans treated with ICS [93].

EPIGENETICS

The three main epigenetic mechanisms that can act synergistically to regulate gene expression are DNAm, histone modifications, and non-coding RNAs such as micro-RNAs (miRNA). However, histone modifications have been investigated for asthma [95] but not for AEs.

DNAm. DNAm consists of the addition of a methyl group to a cytosine, often within 5′-cytosine-phosphate-guanine-3′ dinucleotide sequences (or CpG sites). DNAm levels have been associated with disease risk and health outcomes, including asthma and allergy [96]. Most CpGs in the human DNA methylome are hypermethylated and located in regions of low CpG density but CpG-rich regions, known as CpG islands, are often hypomethylated. While promoter DNAm usually leads to reduced gene expression, gene body DNAm is associated with active transcription [97].

Although DNAm is the most extensively studied epigenetic mechanism, only one targeted DNAm study of AEs [98] and one epigenome-wide association study (EWAS) [99] of AEs as a proxy of treatment response have been published (**Table 4**). Curtin et al. [98] found that increased cord blood DNAm of the *IL2* promoter was associated with AEs and hospitalizations for asthma or wheezing later in childhood. On the other hand, Wang et al. [99] conducted a multi-ancestry EWAS meta-analysis of peripheral blood CpG markers and AEs despite ICS treatment. Hypomethylation of cg00066816 upstream of *IL12B*, which encodes for a subunit of the heterodimeric IL-12, a pro-inflammatory cytokine involved in Th1 and Th17 signalling [100], was nominally associated with the absence of asthma-related ED visits or hospitalizations in the previous year in children on ICS. In a secondary analysis, 13 CpGs were differentially methylated in subjects who received OCS bursts in the past year despite ICS use. Although functional effects of DNAm over blood gene expression were explored, the CpG-gene pairs were not consistently replicated across studies [99].

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miRNAs. miRNA are post-transcriptional regulators that exert their effects by binding to the 3′ untranslated regions of mRNAs, leading to mRNA deadenylation and subsequent degradation. These small non-coding molecules are implicated in the regulation of multiple cellular processes and have recently gained attention in allergic and chronic lung diseases [101–103].

To our knowledge, seven studies have addressed the role of miRNAs in AEs, including three studies in blood, three in serum, and one in induced sputum (**Table 5**). All studies focusing on circulating miRNAs applied single marker approaches, while the study that performed miRNA profiling in induced sputum carried out a systems biology approach. Specifically, Gomez et al. [109] conducted a weighted gene co-expression network analysis (WGCNA) of miRNA and mRNA expression levels in induced sputum from 61 subjects with asthma. The analysis of 221 miRNAs revealed a 12-miRNA module directly correlated with asthma hospitalizations. In their cluster analysis, high expression levels of these 12 miRNAs were associated with neutrophilic inflammation, low T2 biomarkers, and airflow obstruction. Notably, the sputum 12-miRNA module correlated with mRNA modules implicated in the TLR9/Th17 signalling pathway and endoplasmic reticulum stress. One of the miRNA associated with high sputum neutrophil counts in response to ozone exposure, hsa-miR-223-3p, acted as a regulator of both of these two mRNA modules [109].

Midyat et al. [104] reported that 10 of 739 tested miRNAs were differentially expressed by asthma and AE severity in children. Another study found that miR-1 is downregulated in acute-stage asthma and predicted asthma attacks with an AUC of 0.90, significantly higher than the AUC from asthma-related cytokines (e.g., IL-4 or IL-5) ($p<0.05$) [105]. Analysing animal models and primary human endothelial cells, miR-1 has been implicated in the regulation of airway eosinophilia through the inhibition of eosinophil binding to the endothelium by promoting RNA-induced gene silencing of eosinophil trafficking genes [106].

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In a six-week longitudinal study, 3 of 7 circulating miRNAs tested were significantly lower during an AE episode than a follow-up visit: miRNA-126a, miRNA-16, and miRNA-21 [108]. Furthermore, miRNA-21 and miRNA-126a expression levels were positively correlated with FEV_1%, whereas miRNA-21 levels were higher in participants with atopy or FeNO levels >25 parts per billion. MiRNA-126a and miRNA-21 are both considered promoters of Th2-mediated allergic inflammation [101,111], and miRNA-21 is a systemic oxidative stress marker dysregulated in the airways and/or blood in atopic dermatitis and allergic asthma [101].

In an analysis of subjects with frequent exacerbations and infrequent/no exacerbations, 20 of 649 tested blood miRNAs were differentially expressed by asthma [110]. In the COPDGene study, 5 of these 20 miRNAs were associated with COPD exacerbations, supporting some overlap in the pathogenesis of COPD and asthma. The gene targets of these 4 miRNAs participate in PI3K-Akt and MAPK signalling pathways [110], which are relevant in Th-2 inflammation and asthma pathogenesis [102].

Only one study has investigated the role of miRNAs in response to treatment using AEs as a clinical endpoint. In particular, miRNA profiling of serum samples was conducted in 153 children with asthma after randomization to ICS [107]. In univariate logistic regression models, 12 of the 125 tested serum miRNAs were significantly associated with OCS bursts in the previous year. Moreover, the combination of a clinical score for exacerbations along with 3 of these 12 miRNAs (miR-146b, miR-206, and miR-720) suggested a higher predictive capability for AEs compared with clinical score alone (AUC: 0.81 *vs*. 0.67) [107]. Of note, miR-146b-5b and miR-206 serum levels have been associated with asthma and COPD [103], as well as with baseline FEV_1/FVC in individuals with asthma [112].

TRANSCRIPTOMICS

Studies of transcriptomics and AEs prior to 2022 were recently reviewed by Gautam et al. [37]. Such studies have identified distinct AE-related gene expression signatures implicated in innate and adaptative immunity, viral and non-viral exacerbations, and revealed genes implicated in frequent exacerbations (*TNFR2*) and in AEs triggered by colds (genes implicated in *SMAD3* signalling pathways). Only one single-cell RNA-sequencing study in the context of AEs has been conducted, highlighting the implication of several cytokines and intracellular transduction regulators in multiple cell types in this trait [113].

Two transcriptomic studies of AEs have been published in the reviewed period. One focused on the interaction of transcriptional and bacterial networks in nasal epithelium on the risk of AEs in children [114]. Specifically, the risk of AEs increased along with the expression of genes implicated in *SMAD3*-related cell differentiation in a context of high abundance of a bacterial network dominated by *Veillonella, Streptococcus, Neisseria,* and *Haemophilus* and/or reduced abundance of a bacterial network dominated *Staphylococcus* [114]. Another study aimed to understand the pathophysiological factors underlying frequent exacerbations using transcriptomic data from bronchial biopsies. *CEACAM5,* encoding for a cell surface glycoprotein upregulated by interferon-gamma [115], was the only transcript differentially expressed in subjects with frequent exacerbations compared with those with infrequent exacerbations. However, no differential expression was found when subjects with persistent frequent exacerbations were compared with those with persistent infrequent exacerbations. An analysis of several gene signatures for viral infections and type 1 and type 2 inflammatory pathways revealed that subjects with frequent exacerbations had higher expression of those signatures than those with persistent frequent exacerbations [116].

CONCLUSION AND FUTURE DIRECTIONS

AEs constitute a major burden on individuals with asthma and their caregivers, healthcare systems, and society as a whole. Although preventing AEs is key in clinical practice, risk stratification of patients with AEs is challenging due to the inherent heterogeneity of the biological mechanisms underlying these events. Despite this, -omic studies have identified genes and biological processes associated with AEs and proposed potential therapeutic targets. These results need to be validated in independent cohorts and experimental studies, and much work remains to be done compared to -omics findings in other respiratory traits, such as asthma [37], or COPD [117–119].

Perhaps because of the heterogeneity of AEs, specific phenotyping approaches have been successful in identifying novel susceptibility variants [58,74,120]. Despite the increased statistical power derived from a large sample size, future studies should also consider analyzing subtypes or homogenous groups of individuals exposed to similar exacerbation triggers, which would allow the characterization of GxE interactions, almost unexplored in AEs [1]. An alternative approach to boost statistical power in recently admixed populations is to leverage local ancestry into GWAS models to increase the resolution of causal variant(s) identification [121]. Pointedly, differences in the definition of AEs, trigger agents, or clinical characteristics of individuals with asthma may have reduced statistical power in several GWASs [76,77,79,80,122]. This could also account, at least partially, for the lack of replication of SNPs associated with AEs across independent populations [76].

A combination of genetic variants into a single score of risk burden or polygenic risk score (PRS) for AEs is not feasible without additional risk stratification that also considers clinical and environmental parameters. Recently, multi-ancestral PRS for

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asthma developed using lasso sum [123] or Bayesian regression [124] have captured the risk of asthma, although other studies have failed to achieve this [125,126]. PRS incorporating DNAm or gene expression data may better capture environmental influences in order to improve risk stratification [127]. The extent to which methylation risk scores (MRS) or transcriptome risk scores (PTRS) may contribute to risk prediction is still to be determined, though promising findings have been published for other respiratory traits [128,129]. Within this context, it will be crucial to evaluate the predictive power of biomarkers in populations not included in the discovery phase or training datasets [130].

Similarly, the severity and number of AEs have a prognostic capability in risk-stratification [131], but only one GWAS of the annual number of exacerbations has been conducted [75], and no study has assessed temporal distance among events and/or the time-to-first exacerbation. Moreover, although bioinformatic tools have been used to evaluate the functional impact of potential susceptibility variants, many of these resources do not include data from tissues/cells obtained from asthma patients, across several asthma-relevant tissues, or diverse ethnic backgrounds. In this sense, experimental studies are required to understand the biological role of identified genes and establish their prognostic value to adequately implement precision medicine in patient risk stratification and prioritize potential therapeutic targets.

The role of rare variants in AEs has been poorly investigated, despite the fact that they may underlie ethnic/racial differences in the burden of AEs or interact with environmental exposures to modulate AEs. Furthermore, although ethnic diversity has increased in genetic studies of asthma, particularly for Hispanic/Latino populations, large-scale genome-wide studies of Asian and African-descent populations have not been implemented.

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The contribution of the DNA methylome to AEs remains largely unexplored [99]. Thus, a priority in asthma epigenetics is to investigate the role of DNAm as a mediator of environmental effects or as a consequence of AEs, not only at the CpG level, but at differentially methylated regions (DMRs). Future research should also focus on the role of genetically-regulated DNAm and epigenetically-regulated gene expression. Furthermore, it will be key to consider that hypomethylation states in previous EWAS of asthma in blood were largely driven by a lower eosinophil count in blood [132], which is why specific cell types [132,133] or cell-type deconvolution algorithms to discern cell-type specific DNAm signals using whole-blood data [134] are gaining interest. Moreover, histone modifications have been implicated in asthma susceptibility and severity, ICS response, and immune responses to viral infections [95,135], yet little is known about histone modifications and AEs.

Most epigenetic asthma studies have focused on miRNAs in blood and serum, and validation of their findings is needed to exclude spurious results due to differences in sample processing [136,137]. Despite this concern, many miRNAs have been consistently implicated in chronic respiratory or allergic diseases, highlighting their potential as possible therapeutic targets (e.g., miR-206 and miRNA-21) [101–103]. Other plausible candidates to participate in AEs are miRNAs involved in airway inflammation or respiratory infections [101,102,138]. Undoubtedly, further exploration of the role of the miRNAome and its interaction with other -omics layers in the upper and lower airways is required to determine the role of altered miRNA expression in AEs.

Transcriptomic studies conducted in the reviewed period highlight important host-microbiome interactions in the upper and lower airways and open new directions for future research. Although McCauley et al. [114] found that the interaction of host gene expression levels and microbial networks in the upper airways promote AEs, the causative direction of those relationships is unclear. Still, they proposed several

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plausible candidate genes that could be evaluated in other cohorts. Interestingly, among individuals with frequent AEs, Hoda et al. [116] found increased *CEACAM5* expression, which is also promoted by the interferon gamma [115].

Although there has been recent progress in genomic studies of AEs, the role and the interaction of different -omic layers in the modulation of the risk of AEs remain largely unexplored. In many cases, novel findings remain to be validated in independent populations, and their prognostic potential is unclear. Moving forward, multi-ethnic cohorts with better phenotyping of clinical and environmental characteristics, careful phenotyping approaches, evaluation of longitudinal exacerbation data, and combination or integration of different -omics layers of data will be crucial to identify accurate biomarkers of AEs for precision medicine.

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CONFLICT OF INTEREST

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TABLES

Table 1. Main findings and characteristics of candidate-gene studies for AEs conducted from 15th November, 2018 to 1st October, 2022.

rsID (Gene)	Subjects	Phenotype	EA/EG	Effect size (95%CI) or (SE)	P	PMID [reference]
rs295137 (*SPATS2L*)	491 European children with moderate-to-severe asthma presenting to the ER	Hosp/active asthma management ≥8 h in ER after OCS/return visit within 72 h for one of events after presenting to the ER	T	OR: 1.77 (1.17, 2.68)	0.006	30644648 [50]
rs7037276 (*IL33*)			T	OR: 0.55 (0.33, 0.90)	0.02	
rs1342326 (*IL33*)			C	OR: 0.52 (0.32, 0.86)	0.01	
rs16986718 (*NLRP4*)	1-year longitudinal study of 1,454 Korean subjects with asthma, including 955 never-smokers	Number of ER visits/Hosp/OCS/rescue bronchodilator/increase of asthma medication	G	Increased annual exacerbation episodes	0.001	30526007 [51]
		≥2 exacerbations events vs one/none		OR: 2.56 (NA)	6.7×10^{-5}	
		SNP x pack/years on exacerbations		NA	0.014	
rs1799768 (*SERPINE1*)	265 subjects (48% European, 43% African/African American) with poorly controlled asthma enrolled in a randomized clinical trial of soy isoflavones.	OCS	4G4G/4G5G vs 5G/5G	IRR: 2.57 (1.09-6.07)	0.031	30707970 [52]
		Soy isoflavones intake×SNP on OCS		NA	0.005	
		Number of OCS events/person-year		RR: 0.28 (0.12, 0.59)	<0.001	
rs7251960 (*CEACAM3*)	Discovery: 456 Taiwanese children with asthma Replication: 844 children with mild-to-moderate asthma recruited in the United States	Discovery: Nocturnal wheezing/ cough or wheezing/dyspnea in the last 2 weeks. Replication: Asthma-related limitation of activity/wheezing-induced nocturnal awakenings at least once a month in the last 2 months	CT/TT vs CC	$OR_{Discovery}$: 2.58 (1.65, 4.03) $OR_{Replication}$: 1.53 (1.03,2.31)	3.12×10^{-5}; 0.035	32606071 [53]
		RSV x SNP on exacerbation.		NA	0.03	
rs1544410 (*VDR*)	657 Australian children (64.2% European) presenting to the ER with acute asthma/wheezing/ bronchiolitis	Exacerbation severity Z-scores	TT vs CC	Increased severity scores	0.005	32380236 [54]
rs2228570 (*VDR*)		Exacerbation severity Z-scores	AA vs GG	Increased severity scores	0.001	
		Lifetime Hosp for acute respiratory illnesses	AG vs GG	Increased severity scores	0.011	
ADRB2 variants	832 children with asthma	Hosp/ER visits/OCS in the last 6-12 months despite ICS plus LABA use	Arg16/Gln27 vs Gly16/Glu27	1.40 (1.05,1.87)	0.022	34128573 [55]
			Arg16/Gln27 vs	1.43 (1.05-1.94)	0.023	

			Gly16/Gln27			
rs67622929 (*DNASE1L3*)	Discovery: 1,002 African American subjectss with asthma. Replication: 2,181 Hispanic/Latino children with asthma	Hosp/ER visits/OCS in the last 12 months	C	$OR_{Discovery}$: 1.48 (1.18,1.87) $OR_{Replication}$: 1.18 (1.01,1.37)	7.9×10^{-4}; 0.03	33035569 [56]
rs11681246 (*LTBP1*)	2,681 European children 1,347 Hispanic/Latino or African American children with asthma	Hosp/ER visits/OCS in the last 6-12 months despite ICS use	G	OR: 0.72 (0.63, 0.83)	3.28×10^{-6}	32786158 [57]
rs76390075 (*LTBP1*)			C	OR: 0.40 (0.26, 0.63)	6.76×10^{-5}	
rs2660845 (*LTA4H*)	Patients with asthma. Discovery: 523 Europeans with early-onset asthma R_1: 2,514 Europeans with early-onset asthma R_2: 486 Hispanic/Latino children R_3: 71 African American children	Hosp/ER visits/OCS in the last 6-12 months despite montelukast use	G	$OR_{Discovery}$: 2.92 (1.04,8.18) OR_{R1}: 1.02 (0.87,1.19) OR_{R2}: 1.04 (0.78,1.39) OR_{R3}: 0.27 (0.09,0.80)	0.041 R_1: 0.833 R_2: 0.788 R_3: 0.019	34550981 [58]
rs2517955 (*PGAP3*)	3-year longitudinal study of 273 non-Hispanic white adolescents and adults with asthma	Number of asthma-related ER visits/Hosp in 3 years	C	β: 1.05 (NA)	0.0034	32795586 [59]
rs1031458 (*GSDMB*)			G	β: −0.77 (NA)	0.028	
rs3902920 (*GSDMB*)			T	β: −0.88 (NA)	0.012	
rs13431828 (*IL1RL1*)	2,412 European, Hispanic/Latino or African American children	Hosp/ER visits in the last 6-12 months despite ICS use	C	OR: 1.32 (1.08, 1.62) OR: 1.31 (1.07, 1.59)	0.02 0.02	31755552 [60]
rs242941 (*CRHR1*)	European adult patients with asthma ($n_{Discovery}$=597; $n_{Replication}$: 9,842)	Hosp/ER visits/OCS despite ICS use	A	$RR_{Discovery}$: 6.11 (NA) $RR_{Replication}$: 1.16 (NA)	<0.005; 0.004	33428814 [61]
rs1134481 (*TBXT)*			T	$RR_{Discovery}$: 0.36 (NA) $RR_{Replication}$: 1.02 (NA)	<0.005; 0.563	
rs37973 (*GLCCI1*)			G	$RR_{Discovery}$: 1.88 (NA) $RR_{Replication}$: 0.82 (NA)	<0.005; <0.005	
rs1384006 (*OXSR1*)	1-year longitudinal study of 1,454 Korean subjects with asthma, including 955 never-smokers	Number of ER visits/Hosp/OCS/rescue bronchodilator/increase of asthma medication	C	Increased annual exacerbation episodes	0.004	34983467 [62]
		≥2 exacerbations events vs one/none		OR: 0.36 (0.18, 0.72)	0.004	
rs9665961 (*BIRC3*) *	5,710 European adults, 166 European children, 854 Hispanic/Latino children and	Hosp/ER visits/OCS in the last 6-12 months despite ICS use/8% decrease in FEV_1 in patients after 6	A	OR: 0.81 (NA)	3.77×10^{-4}	34971648 [63]

	493 African American children with asthma	weeks of ICS therapy

*A total of 35 SNPs in linkage disequilibrium ($r^2 \geq 0.8$) were significantly associated with AEs on the sample size weighted meta-analysis based on p-values. For visual clarity, the most significant variant in the meta-analysis is shown here, accompanied by the odds ratio corresponding to the largest cohort contributing to the rs9665961 genotype data on the multi-ancestry meta-analysis. Abbreviation: β: Regression coefficient; CI: Confidence interval; EA/EG: Effect allele/genotype; ER: Emergency room; FEV_1: Forced expiratory volume in the first second; Hosp: Hospitalizations; ICS: Inhaled corticosteroids; IRR: Incidence risk ratio; LABA: Long-acting beta2-agonists; NA: Not available; OCS: Oral corticosteroids use; OR: Odds ratio; RR: Relative risk; R_n: Replication study (number $_n$); RSV: Respiratory syncytial virus; SE: Standard error of the beta coefficient; SNP: Single nucleotide polymorphism; P: P-value.

Table 2. Main findings and characteristics of genome-wide approaches to study the genetic factors involved in AEs conducted from 15th November, 2018 to 1st October, 2022.

Type of study	rsID (Gene)	Subjects	Phenotype	EA	Effect size (95%CI) or (SE)	P	PMID [reference]
GWAS	rs56151658 (*HLA-DQB1*)	Discovery: 34,167 white British adults with asthma Replication: 2,645 Hispanic/Latino children with asthma	ER/Hosp/OCS	A	$OR_{Discovery}$: 1.36 (1.22, 1.52) $OR_{Replication}$: 1.19 (0.99, 1.42)*†	3.11×10^{-8} 5×10^{-3}*	32890573 [71]
GWAS	rs2253681 (*LINC03033*)	4,010 Hispanic/Latino youth with asthma	ER/Hosp/OCS	A	OR: 1.55 (1.34,1.79)	6.3×10^{-9}	33093117 [72]
GWAS	rs4952375 (*LINC01913*)	Children with asthma. Discovery: 3,310 Hispanics/Latinos; replication: 1,043 African Americans.	ER/Hosp/OCS	A	$OR_{Discovery}$: 1.37 (1.20,1.55) $OR_{Replication}$: 1.53 (1.12 ,2.08)	1.24×10^{-6}; 7.43×10^{-3}	32841424 [73]
GWAS	rs721992318 (*GSDMB*)	Discovery: 2,866 European children experiencing severe AE between ages 2 and 6 years, and 65,415 non-asthmatic controls. Replication: 1,118 children.	Discovery: Asthma with Hosp; Replication: Asthma	T	OR: 1.65 (1.56,1.75)	1.6×10^{-68}	33328473 [74]
	rs696733010 (*CDHR3*)			A	OR: 1.41 (1.32,1.51)	2.1×10^{-23}	
	rs107163018 (*HLA-DQA1*)			C	OR: 1.25 (1.18,1.32)	8.0×10^{-14}	
	rs34093366 (*IL33*)			G	OR: 1.37 (1.26,1.49)	1.6×10^{-13}	
	rs134232666 (*IL33*)			C	OR: 1.31 (1.22,1.40)	1.7×10^{-13}	
	rs1018962918 (*IL1RL1*)			C	OR: 1.40 (1.27,1.54)	7.7×10^{-12}	
	rs104382818 (*WDR36*)			C	OR: 1.20 (1.14,1.27)	1.0×10^{-10}	
	rs2054118 (*IL13*)			A	OR: 1.21 (1.13,1.29)	1.0×10^{-8}	
	rs281379 (*FUT2/MAMSTR*)			G	$OR_{Discovery}$ 1.18 (1.11,1.25) $OR_{Replication}$: 1.43 (1.16,1.79)	2.6×10^{-9}; 1.1×10^{-3}	
GWAS	rs10519519 (*MYT1L*)	1-year longitudinal study of 20 non-smoking and 188 smoking Korean patients with asthma	Annual rate of episodes of increased dyspnea, wheezing, or coughing with a >20%decrease in FEV_1	A	β: 0.60 (0.11)	8.32×10^{-7}	35606283 [75]

GWAS	rs12091010 (*VCAM1/EXTL2)*	Discovery (4,989 subjects with asthma): 53.1% Europeans, 23.2% Hispanics/Latinos, 13.3% Singaporean Chinese, and 10.3% African Americans. Replication: 36,477 European and 1078 non-European asthma patients	ACC/ER/Hosp/OCS/SA	T	$OR_{Discovery}$: 0.82 (0.75–0.90) $OR_{Replication}$: 0.89 (0.82–0.97)	9.05×10^{-6}; 5.35×10^{-3}	35754128 [76]
	rs943126 (*PANK1*)	Children with asthma. Discovery: 854 Hispanic/Latino, 493 African Americans. Replication: 1,697 Europeans	ER/Hosp/OCS despite ICS use	C	$OR_{Discovery}$: 0.85 (0.78,0.92) $OR_{Replication}$: 0.92 (0.86,0.98)	3.10×10^{-5}; 1.30×10^{-2}	
PGWAS (ICS)	rs5995653 (*APOBEC3B/APOBEC3C)*	Children with asthma. Discovery: 854 Hispanic/Latino and 493 African Americans. Replication: 1,697 Europeans	ER/Hosp/OCS despite ICS use	A	$OR_{Discovery}$ 0.76 (0.62,0.93) $OR_{Replication}$: 0.66 (0.56,0.79)	4.80×10^{-6}; 7.52×10^{-3}	30697902 [77]
	rs62081416* (*L3MBTL4/ARHGAP28)*	854 Hispanic/Latino and 493 African American children with asthma		A	OR: 2.44 (1.63,3.65)	1.57×10^{-5}	
PGWAS (ICS)	rs3827907 (*EDDM3B*)	Patients with asthma. Discovery: 244 African Americans. Replication: African Americans (n_{R1}=803 and n_{R2}=563) and Latinos (n_{R3}=1,461)	Discovery: SNPxICS adherence on change in ACT score over 6 weeks of ICS treatment. Replication 1: SNPxICS adherence on time to ER/Hosp/OCS. Replication 2-3: SNPxICS use on ER/Hosp/OCS	C	$Coef_{Discovery}$12.35 (NA) $Coef_{R1}$: -0.07 (NA) $Coef_{R2}$: 0.15 (NA) $Coef_{R3}$: 0.96 (NA)	7.79×10^{-8}; 0.023; 0.029; 0.041	30367910 [78]
PGWAS (LABA)	rs1947048 (*EPHA7*)	1,425 children and young adults with asthma (23% Hispanic/Latino, 10.4% African American, 32.5 Singaporean Chinese)	ER/Hosp/OCS despite LABA use	G	OR: 2.50 (1.69, 3.69)	4.36×10^{-6}	33706416 [79]
PGWAS (LABA)	rs6489992 (*TBX3*)			A	OR: 1.77 (1.40, 2.23)	4.96×10^{-6}	

PGWAS (ICS)	rs67026078 (*CACNA2D3*/*WNT5A*)	Children with asthma. Discovery: 2,681 Europeans. Replication 1: 538 Europeans. Replication 2: 854 Hispanic/Latinos, 493 African Americans, 426 Singaporean Chinese	ER/Hosp/OCS/SA despite ICS use	C	$OR_{Discovery}$: 1.50 (0.93, 2.43) OR_{R1}: 1.83 (1.16, 2.90)	4.22×10^{-6}; R_1; 0.01; R_2: NS	33303529 [80]
PGWAS (ICS)	rs1166980 (*ROBO2)*	Children with asthma. Discovery: 166 Europeans. Replication 1: 2,681 Europeans. Replication 2: 854 Hispanic/Latinos, 493 African Americans	Discovery: ≥8% in FEV_1 after 6 weeks of ICS treatment Replication: ER/Hosp/OCS/SA despite ICS use	G	$OR_{Discovery}$: 7.01(3.29, 14.93)	4.61×10^{-7}, R_1-R_2: NS	34442380 [81]
PGWAS (ICS)	rs72891545‡ (*ROBO2)*	Discovery: 2,681 Europeans	ER/Hosp/OCS/SA despite ICS use	A	OR: 4.79 (2.36, 9.73)	1.44×10^{-5}	
PGWAS (ICS)	rs138717703 (*RBMXP1/PTCHD4*)	European adults with asthma ($n_{Discovery}$= 5,710; $n_{Replication}$=1,141)	OCS despite ICS use	G	$OR_{Discovery}$: 1.73 (1.39, 2.16) $OR_{Replication}$: 1.48 (0.75, 2.90)‡	7.91×10^{-7}; 5.78×10^{-4}	35501119 [82]
PGWAS (ICS)	rs77506063 (*RBMXP1/PTCHD4*)			C	$OR_{Discovery}$: 1.73 (1.39, 2.16) $OR_{Replication}$: 1.48 (0.75, 2.90)‡	7.91×10^{-7}; 5.78×10^{-4}	
PGWAS (ICS)	rs145325916 (*RBMXP1/PTCHD4*)			C	$OR_{Discovery}$: 1.74 (1.40, 2.16) $OR_{Replication}$: 1.27 (0.66, 2.42)‡	6.18×10^{-7}; 3.56×10^{-3}	
PGWAS (ICS)	rs116023293 *(HNRNPA3/P4 PTCHD4)*			G	$OR_{Discovery}$: 1.74 (1.40, 2.16) $OR_{Replication}$: 1.27 (0.66, 2.42)‡	5.28×10^{-7}; 3.56×10^{-3}	
PGWIS (Age; ICS)	rs34631960 (*THSD4*)	1,321 adult and child Europeans with asthma	SNPxAge use on ER/Hosp/OCS	C	$OR_{Discovery}$: 2.33 (1.61, 3.38) $OR_{Replication}$: 1.82 (1.23, 2.7);	7.08×10^{-6}; 2.97×10^{-3}	32119686 [83]

PGWIS (Age; ICS)	rs2328386 (*HIVEP2*)		T	$OR_{Discovery}$: 0.33(0.2, 0.55) $OR_{Replication}$: 0.51(0.34, 0.77)	1.86×10^{-5}; 1.49×10^{-3}

*rs56151658 was not available in Hispanics/Latinos. The results for the most significant proxy in Latinos (r^2=0.71) are shown (rs9275356). †Effect size from the largest replication cohort is shown. ‡The genetic variant was identified using a candidate-gene approach using the GWAS summary statistics. Abbreviations: ACC: Acute asthma care; ACT: Asthma Control Test; Coef: Interaction coefficient estimate; CI: Confidence interval; EA: Effect allele; ER: Emergency room visits; FEV_1: Forced expiratory volume in the first second; Hosp: Hospitalizations; GWAS: Genome-wide association study, ICS: Inhaled corticosteroids; LABA: Long-acting beta-agonists; OCS: Oral corticosteroids use; NA: Not available; NS: Non-significant; PGWAS: Pharmacogenomic GWAS (asthma treatment considered is shown within parenthesis); PGWIS: Pharmacogenomic genome-wide interaction study (tested environmental variable and asthma treatment considered are shown within parenthesis); R_n: Replication study (number $_n$); SA: School absences; SE: Standard error of the beta coefficient; SNP: Single nucleotide polymorphism; P: P-value.

Table 3. Main findings and characteristics of the admixture mapping studies of AEs conducted from 15th November, 2018 to 1st October, 2022.

rsID (Gene) Chromosomal band	Subjects	Phenotype	EA	OR (95%CI)	P	PMID [reference]
rs1144986 (*C5orf46*) 5q32	Patients with asthma. Discovery: 625 Mexican Americans. R_1: 1,124 Puerto Ricans R_2: 1,001 African Americans, 1,250 Singaporeans, and 941 Europeans.	ER/Hosp/OCS	G	Discovery: 0.43 (0.28, 0.66) R_1: 0.79 (0.62, 1.00)	$9.45x10^{-5}$; $4.94x10^{-2}$; NS	36180068 [92]
rs5752429 (*TPST2*) 2q12.1	Discovery: 266 adolescents/adults of African-descent ancestry Replication: 222 African Americans	Discovery: Better response to 5xICS vs 2.5xICS Replication: ER/Hosp/OCS despite high ICS use	A	Discovery: 0.21 (0.09, 0.52)* Replication: 2.28 (1.33, 3.90)	6×10^{-4}; 0.003	34762840 [93]
rs73399224 (*RNFT2*) 12q24.22	Discovery: 250 children of African-descent ancestry Replication: 379 African Americans	Discovery: Better response to 5xICS vs 100 µg fluticasone plus salmeterol Replication: ER/Hosp/OCS despite ICS use	G	Discovery: 0.17 (0.07, 0.42)* Replication: 1.97 (1.07, 3.64)	8.0×10^{-5}; 0.03	

Table 4. Main findings of the studies of DNAm in AEs.

Biological sample	Subjects	Phenotype	CpG	Gene/Nearest Gene	Regression coeficient (95%CI)	P	PMID [reference]
Cord blood	303 children recruited by a birth cohort in Manchester (UK)	Asthma-related hospitalizations or ER after the first year of life	Promoter site 1	*IL2*	1.07 (1.01,1.14)	0.03	23414538 [98]
		Asthma/wheeze-related hospitalization after the first year of life			1.12 (1.04,1.20)	0.002	
Blood	394 children treated with ICS (57.4% Europeans, 42.6% Hispanic/Latino)	Asthma-related hospitalizations or ER in the past year despite ICS use	cg00066816	*IL12B*	−3.10 (NA)	0.002	31187518 [99]
			cg00557354	*ARHGEF7*	−3.49 (NA)	0.001	
			cg04256470	*CORT, CENPS*	3.62 (NA)	<0.001	
		OCS use in the past year despite ICS use.	cg09495977	*HTRA3*	−2.42 (NA)	0.017	
			cg12333095	*ANKRD13A*	−3.48 (NA)	0.001	
			cg13818573	*C1QL1*	−3.59 (NA)	<0.001	
			cg21589280	*DDAH1*	−3.06 (NA)	0.003	
			cg03080985	*SH3BGRL2*	−3.07 (NA)	0.003	
			cg04330449	*NEUROG1*	−2.64 (NA)	0.009	
			cg05307923	*ADARB2*	−2.57 (NA)	0.011	
			cg08724517	*MAP9*	2.95 (NA)	0.004	
			cg11665562	*PSMC1*	−3.25 (NA)	0.001	
			cg14269514	*OAZ3, MRPL9*	−3.11 (NA)	0.002	
			cg24322623	*MYOD1*	−2.96 (NA)	0.004	

Abbreviations: CI: Confidence interval; ER: Emergency room visits; ICS: Inhaled corticosteroids; OCS: Oral steroid bursts; NA: Not available; P: P-value; UK: United Kingdom.

Table 5. Main findings and characteristics of miRNA studies in the context of AEs.

Biological sample	miRNA profiling	Subjects	Phenotype	Main findings	PMID [reference]
Whole blood	Human MicroRNA v2.0 Assay Pool (Illumina).	Children with (n=100) and without asthma (n=100) recruited at a Turkish hospital	Asthma severity (GINA, 2008) and AEs severity	Increased expression of 10 miRNAs was associated with asthma severity and exacerbations severity: HS_108.1, HS_112, HS_182.1, HS_240, HS_261.1, HS_3, HS_55.1, HS_91.1, hsa-mir-604, and hsa-mir-638.	26422695 [104]
Peripheral blood	q-PCR	Children with acute-stage asthma (n=100) and healthy children (n=100) recruited at a Chinese hospital	Acute asthma attacks (not defined)	miR-1 expression levels were reduced in acute-stage asthma compared with controls. miR-1 expression levels improved prediction of acute asthma attacks compared with IL-4, IL-5, IL-8, and TNF-α in the same population.	30046607 [105]
Serum	q-PCR	Subjects with (n=59) and without asthma (n=11) recruited in the United States	Lifetime and past 12 months frequency of asthma-related hospitalizations	miR-1 levels were inversely correlated with sputum eosinophilia and asthma-related hospitalization frequency, and positively correlated with lung function and ACT scores.	32035607 [106]
Serum	q-PCR	European children with asthma from CAMP: 38 with and 115 without exacerbations	OCS bursts in the past 12 months following randomization with ICS	Increased expression of 12 miRNAs was associated with OCS bursts: miR-206, miR-146b-5p, miR-222-3p, miR-409-3p, miR-223-5p, miR-126-5p, miR-339-3p, miR-30e-3p, miR-126-3p, miR-342-3p, miR-454-3p, and miR-720. A clinical and 3-miRNA model (miR-146b, miR-206, and miR-720) showed higher AUC for prediction of OCS use compared with the clinical model in the same population (AUC: 0.81 vs 0.67).	29940952 [107]
Serum	q-PCR	6-week longitudinal study of 21 adults with asthma recruited at a Polish hospital	Admission for an unplanned visit due to worsened symptoms of asthma accompanied by a decrease in ventilatory parameters	Reduced levels of miRNA-126a, miRNA-16, and miRNA-21 during the exacerbation compared with the follow-up visit.	31743969 [108]
Induced sputum	Nanostring nCounter array v3.0a	Subjects with (n=62) and without asthma (n=9) recruited in the United States	Asthma-related hospitalizations in the past 12 months	A 12 miRNA.WGCNA module was directly correlated with asthma hospitalizations. Ten of these miRNA correlated significantly and consistently with sputum neutrophils, longer duration of asthma, decreased quality of life, impaired lung function, and/or increased BDR. The miRNA module correlated with a mRNA module enriched in genes participating in TLR/Th17 signalling and endoplasmic reticulum stress.	32255668 [109]

Whole blood	Small-RNA sequencing	Costa Rican children with asthma (n_{FE}=183; n_{IF}=168) from GARCS	≥3 events of asthma-related ER/AC visits and/or hospitalizations in the last 12 months (frequent exacerbations, FE) compared with no or infrequent exacerbation (IF)	5 miRNA (miR-451b, hsa-miR-142-5p, hsa-miR-6739-3p, hsa-miR-7-5p, and hsa-miR-4433b-5p) were downregulated in FE compared with IF. 15 mIRNA (hsa-miR-93-3p, hsa-miR-766-3p, hsa-miR-331-3p, hsa-miR-532-3p, hsa-miR-664b-3p, hsa-miR-296-5p, hsa-miR-6515-3p, hsa-miR-4286, hsa-miR-1296-5p, hsa-miR-29b-2-5p, hsa-miR-500b-5p, hsa-miR-500a-5p, hsa-miR-642a-5p, hsa-miR-103a-2-5p, and hsa-miR-550a-3p) were upregulated in FE compared with IF. miR-532-3p, miR-296-5p, miR-766-3p, miR-7-5p, and miR-451b also showed significant association with COPD exacerbations.	35447890 [110]

Abbreviations: AC: Acute care; AUC: Area under the curve; CAMP: Childhood Asthma Management Program; COPD: Chronic obstructive pulmonary disease; ER: Emergency room; FE: Frequent exacerbations; GARCS: Genetics of Asthma in Costa Rica Study; GINA: Global Initiative for Asthma; ICS: Inhaled corticosteroids; IF: No or infrequent exacerbations; mRNA: Messenger RNA; OCS: Oral corticosteroids; q-PCR: Real-time quantitative polymerase chain reaction; RNA: Ribonucleic acid; Th17: T helper 17 cells; TLR: Toll-like receptor; WGCNA: Weighted gene co-expression network analysis.

Table 6. Main findings and characteristics of transcriptomic studies of AEs conducted in 2022 (up to 1st October, 2022).

Biological sample	RNA profiling	Subjects	Phenotype	Main findings	PMID [reference]
Nasal blow	RNA-seq (NextSeq 500 platform)	208 children with asthma from United States	OCS/Hospitalization	Increased *SMAD3* expression among children with altered abundance of the two bacterial network was associated with increased exacerbation risk.	35149044 [114]
Bronchial biopsies	GeneChip® Human Genome U133 Plus 2.0 Array (Affymetrix).	317 participants with severe asthma from Europe	≥2 events of systemic corticosteroids use vs (frequent exacerbators, FE) <2 events (infrequent exacerbators, IE)	*CEACAM5* expression was increased in FE compared with IE. Higher expression scores for viral infection gene signatures, type 1, T-helper type-17, and type 2 activation pathways in FE compared to IE. Higher expression scores of type 2, type 1 and steroid insensitivity pathway signatures in persistent FE compared to persistent IE.	35474304 [116]

Abbreviations: FE: Frequent exacerbators; IE: Infrequent exacerbators; OCS: Oral corticosteroids use; RNA-seq: RNA sequencing.

Figure 1.

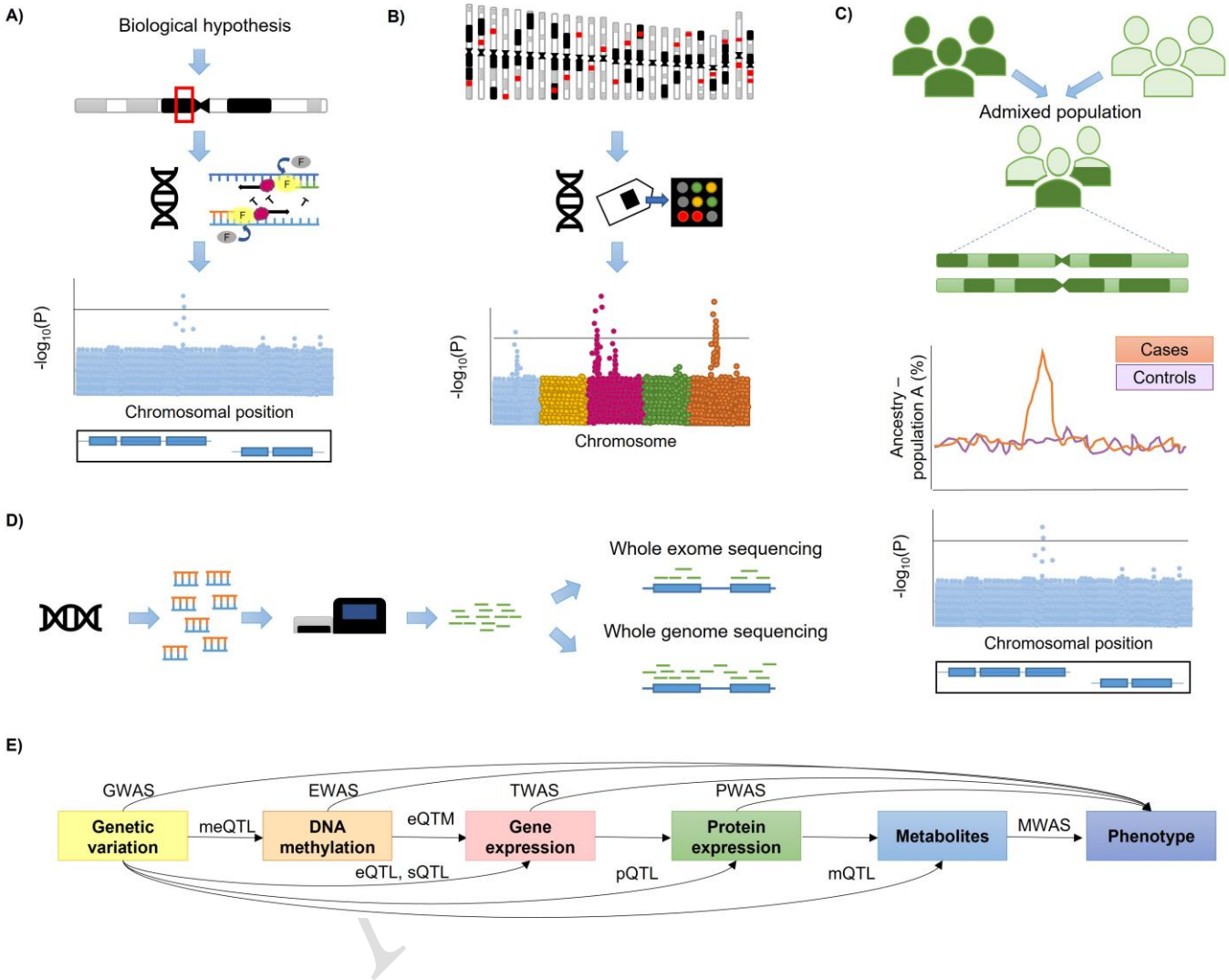

FIGURE LEGENDS

A) Candidate-gene association study. A biological hypothesis is used to prioritize genomic regions that will be genotyped, and genetic variants within the regions will be tested for association with the trait of interest. **B) GWAS**. Genetic variation is profiled via genome-wide genotyping arrays and evaluated for association with the trait of interest**. C) Theoretical framework of admixture mapping.** The genomes of the admixed individuals are composed of mosaics of ancestral blocks derived from ancestral populations. The association of local ancestry and a trait of interest is evaluated in order to prioritize genomic regions where genetic variants will be assessed for association with the trait of interest. **D) Next-generation sequencing (NGS) approaches.** The DNA is fragmented and sequenced, then reads are mapped to the reference genome. While whole exome sequencing (WES) focuses on genomic protein-coding regions (exons), whole genome sequencing (WGS) determines genetic variation in any part of the genome. **E) Combination of different -omic and clinical layers to understand the biological mechanisms underlying a trait of interest.** The association of genetic variation with a specific trait, DNAm, gene expression, protein expression or metabolites is assessed by GWAS, epigenome-wide association studies (EWAS), transcriptome-wide association studies (TWAS), proteome-wide association studies (PWAS) or metabolome-wide association studies (MWAS), respectively. Moreover, a regulatory genetic variant can exert effects as methylation quantitative trait locus (meQTL), expression quantitative trait locus (eQTL), splicing quantitative trait locus (sQTL), protein quantitative trait locus (pQTL) and/or metabolic quantitative trait locus (mQTL). Moreover, methylation levels at a specific chromosomal position may regulate gene expression levels (eQTM).

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